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INTERNATIONAL NETWORK OF CLINICIANS FOR ENDOCRINOPATHIES IN THALASSEMIA AND ADOLESCENT MEDICINE (ICET-A)

Acute and chronic complications in hemoglobinopathies: The Equality Plus Project (4th Part)

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Abstract

The management of patients with hemoglobinopathies is very complex, requiring a multidisciplinary approach. Nevertheless, physicians in many disciplines may care for these patients and should be familiar with their potential acute and chronic complications. Having a good understanding of the mechanisms and management may improve the patients' quality of life and reduce premature mortality of sufferers. The aim of this short review is to provide an update on acute and chronic complications in children, adolescents and young adults affected by SCD and TDT.

Key words: Hemoglobinopathies, acute and chronic complications, Equality Plus project.

Introduction

Overall, 5% of the global population are carriers for hemoglobinopathies, with 40% of them being represented by HbS (1). The burden of this and other hemoglobin disorders is expected to increase in the coming decades because of the reductions in infant mortality in many low-income countries and the increasing migration from high- to low-HbS-frequency areas worldwide (2). The prognosis for transfusion-dependent β-thalassemia (TDT) has dramatically improved in the

last two decades. However, many transfusion-dependent patients continue to develop progressive accumulation of iron. This can lead to tissue damage and eventually death, particularly from cardiac disease. and fatal arrhythmias. Osteoporosis, bone pain and bone changes, bile stone formation, increased risk of viral hepatitis, cirrhosis, growth retardation, hypogonadism, diabetes mellitus, and hypothyroidism are the other common complications (3).
Common acute complications in patients with sickle cell disease (SCD) are acute pain events, acute chest syndrome and stroke; chronic complications (including chronic kidney disease) can damage all organs (4).
The management of patients with hemoglobinopathies is very complex, requiring a multidisciplinary approach. Nevertheless, physicians in many disciplines may care for these patients and should be familiar with their potential acute and chronic complications. Having a good understanding of the mechanisms and management may improve the patients' quality of life and reduce premature mortality of sufferers.
The aim of this short review is to provide an update on acute and chronic complications in children, adolescents and young adults with SCD and TDT.

A. Transfusion-dependent β-thalassemia (TDT):

1. The complications of thalassemias

Main clinical complications in thalassemic patients are due to medullary / extramedullary hematopoiesis, transfusion with immune/ non immune, and iron overload / chelation therapy (5).
The most common disease-related complications were osteoporosis, extramedullary hematopoeisis (EMH), hypogonadism, and cholelithiasis, followed by thrombosis, pulmonary hypertension (PHT), abnormal liver function, and leg ulcers. Hypothyroidism, heart failure, and diabetes mellitus were less frequently observed. On multivariate analysis, older age and splenectomy were independently associated with an increased risk of most disease-related complications (6).
A multicenter cross-sectional study was conducted in patients with thalassemia aged ≥ 18 years old in Thailand. They defined disease-related complications as follow up.

1) Pulmonary hypertension defined as the presence of clinical suspicion of pulmonary hypertension and a right ventricular systolic pressure > 36 mmHg by trans-thoracic echocardiography.
2) Heart failure that was defined as the presence or the history of signs and symptoms of heart failure according to the Framingham criteria.
3) Diabetes mellitus was defined as the fasting plasma glucose 126 mg/dl.
4) Extramedullary hematopoiesis was defined as the presence of clinical signs and symptoms or evidence of extramedullary hematopoiesis by ultrasonography, computed tomography scan (CT scan) or magnetic resonance imaging (MRI).
5) Gallstones were defined as the presence of gallstones in the gallbladder by ultrasonography.
6) Hypothyroidism was defined by the presence of elevation of serum TSH more than the upper limit and the level of free T4 that was lower than normal range.
7) Osteoporosis was defined as the presence of pathological fracture or the bone mineral density T-score < 2.5 SD.
8) Thrombosis was defined by the presence of clinical signs and symptoms of thrombosis or the evidence of thrombosis by computed tomography angiogram (CT angiogram), computed tomography scan (CT scan), venography, angiography, doppler ultrasonography, or magnetic resonance imaging (MRI).
9) Infection was defined as the history of infections or the presence of clinical signs and symptoms of infections which were confirmed by the isolation of pathogens from blood, pus, stools, cerebrospinal fluid (CSF) or other body fluids.
10) Leg ulcers were defined by the presence of chronic venous ulcers on the legs.

In this study, the prevalence of thalassemia-related complications was 100% in patients with TDT and 58.8% in patients with non-transfusion-dependent thalassemia (NTDT). Disease-related complications are more prevalent in patients with TDT than patients with NTDT. Splenectomy and advanced age were important risk factors for developing major complications in both groups (7).

a. Transfusion complications:
Transfusion policies and complications are critical to quality of life and survival in thalassemia. Transfusion reactions are hemosiderosis, hemolytic transfusion reactions, and infections. Hemolytic transfusion reactions (acute, delayed), febrile non-hemolytic, allergic, transfusion, transfusion-related acute lung injury, post-transfusion purpura, transfusion-associated GVHD, hypotensive reactions, and transfusion–associated dyspnea.
Alloimmunization and autoimmunization are a serious adverse consequence of transfusion therapy. The incidence of autoantibody and alloantibody in patients with thalassemia major change 10-19% and 5-6.5% respectively. Prospective studies indicate that antigen matching for Cc, Ee, D, and K reduces alloimmunization. Molecular red cell phenotyping of donors and recipients may increase the efficacy and efficiency of red cell matching and decrease blood inventory requirements (8, 9).

b. Hemosiderosis or Iron Overloading:
The predominant mechanisms driving the process of iron loading include increased iron burden secondary to transfusion therapy in TDT and enhanced intestinal absorption secondary to ineffective erythropoiesis and hepcidin suppression in transfusion dependent thalassemia NTDT. Different organs are affected differently by iron overload in TDT and NTDT owing to the underlying iron loading mechanism and rate of iron accumulation (10).

c. Cardiac complications:
Despite the advances in the management of thalassemia major, heart disease remains the leading cause of mortality in patients afflicted with this disorder. Cardiac involvement in thalassemia encompasses a spectrum of disorders including myocardial dysfunction, arrhythmias, pulmonary hypertension, and peripheral vascular disease. The myocardium is particularly susceptible to complications from iron loading in thalassemia major.
Atrial fibrillation is the most frequently encountered iron-related arrhythmia. Monitoring of myocardial iron content is mandatory for clinical management of cardiac risk. T2* cardiac magnetic resonance measures myocardial iron and is the strongest biomarker for prediction of heart failure and arrhythmic events (11, 12).

d. Cholelithiasis and hepatic complications:
This complication has been reported in 10-57% of TDT and NTDT patients. Pathogenesis of cholelithiasis is multifactorial. The main contributing factor is deemed to be precipitation of bilirubin in the bile as a result of increased hemolysis. Iron deposition within gallbladder is also involved in the development of cholelithiasis The role of ineffective erythropoiesis has also been suggested in the formation of gallstones (13).
The life-long need for transfusion renders patients vulnerable to transfusion-transmitted viral infections such as HIV, HBV, HCV. HCV has emerged as the major risk in the last decades. HCV is the main risk factor for liver fibrosis in TDT patients. Excess liver iron is now clearly recognized as a cofactor for the development of advanced fibrosis and cirrhosis in patients with HCV infection (14).

e. Bone and skeletal complications:
Thalassemia bone disease is a composite of not only multiple hormonal deficiencies but also multi-organ diseases. Bone disease is composed of a complex piecemeal of risk factors that include genetic factors, hormonal deficiency, marrow expansion, skeletal dysmorphism, iron toxicity, chelators, and increased bone turnover.
Clinical presentations include growth impairment, rickets-like features, back pain, spinal deformities, any sign of nerve compression, severe osteoporosis, and fragility fractures. The reported frequency of osteoporosis, even in well treated TDT patients varies from 13.6% to 50% with an additional 45% affected by osteopenia (15, 16).

f. Hypercoagulability:
Venous thromboembolic events, such as pulmonary embolism, deep venous thrombosis, and portal vein thrombosis, have been observed in adult thalassemia patients, mainly in NTDT. The observation that thrombotic events are more frequent in NTDT and TDT patients who have undergone splenectomy strongly supports the procoagulant activity of circulating damaged red blood cells. Thrombosis is one of the most important complications after splenectomy and requires fast diagnosis, effective therapy and good follow-up. In a retrospective study was reported a larger prevalence of venous thromboembolic events in NTDT patients (29%) than in TDT (2%) (17, 18).

g. Neurologic complications:
Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity. Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are mainly attributed to DFO neurotoxicity (19).

h. Ocular complications:
Ocular complications such as retinopathy, crystalline lens opacification, color vision deficiency, nyctalopia, depressed visual field, reduced visual acuity, reduced contrast sensitivity been reported in TDT patients. These complications may be a result of anemia, iron overload in the body tissue, side effects of iron chelators, and the complications of orbital bone marrow expansion (20).

i. Oral and Dental complications:
The main oral manifestations of thalassemia are class II malocclusion, maxillary protrusion, high caries index, severe gingivitis (21).
We investigated the periodontal status and the iron accumulation in gingival tissues of TDT patients. The periodontal tissues are affected by iron accumulation as well as hepatic, cardiac, and endocrine tissues in TDT patients (22).

l. Endocrine comllications:
TDT patients frequently develop severe endocrine complications mainly due to iron overload, anemia, and chronic liver disease, which require prompt diagnosis, treatment and close follow-up by specialists.

i) Hypogonadism
The most common endocrine complication documented in TDT patients is hypogonadotropic hypogonadism which increases with age and the associated comorbidities. It has been proved to be the result of hemosiderosis of the gonadotrophin cells of the pituitary gland. Gonadal damage may occur especially in patients with severe iron. The prevalence and severity of hypogonadism in thalassemia major varies among studies, depending on the age group studied, genotype of thalassemia, extent of transfusion, age at the beginning and type of iron chelation therapy.
Hormone replacement therapy (HRT) with sex steroids aims to relieve symptoms and signs of androgen or estrogens deficiency, using convenient and effective formulations of testosterone or estrogen/progesterone. The type of HRT, dosage, and route of administration are extremely complex in patients with thalassemia because of the chronicity of treatment and because many physical and psychological changes take place during the treatment period. Early diagnosis and treatment are crucial for normal pubertal development and to reduce the complications of hypogonadism (23, 24).

ii) Diabetes mellitus
Diabetes is an important complication of TDT patients. The mechanisms of abnormal glucose homeostasis are complex and multifactorial.
The usual symptoms of polyuria, polydipsia, and weight loss, have been reported to occur in 94.5% of patients with TM and diabetic ketoacidosis (DKA) has been reported to be the presenting manifestation of diabetes in 13.8% to 31.1% of patients. However, in our personal experience, diabetic ketoacidosis is rare (25).
Management of DM should be individualised. The first line treatment in all TM patients with glucose disturbances should be an intensification of iron chelation therapy to achieve a negative iron balance. Moreover, an individualized patient-tailored therapeutic approach is recommended with subcutaneous insulin therapy or anti-hyperglycemic drugs, after a careful consideration of drug contraindications and interactions (26).
Compared to the general diabetic population, there is no marked difference in the monitoring of glycaemia control in thalassaemic patients. All patients with DM should regularly be monitored for the development of complications. Kidney function and imaging of the fundi should be carried out to evaluate the presence and degree of diabetic complications. With regard to macrovascular complications of diabetes, they include ischemic heart disease, cerebrovascular disease, and peripheral vascular disease (25).
A recent study by *Pepe et al.* (26) showed that DM in patients with TM significantly increases the risk for cardiac complications, heart failure, hyperkinetic arrhythmias and myocardial fibrosis. Moreover, these patients with clinical diabetes are at a high risk for additional complications such as thyroid dysfunction or hypogonadism and should be strictly monitored (25).
The credibility of Hb A1c as a gold standard for

the measurement of control of diabetes in TM patients has been questioned because the hemoglobin composition of patients' erythrocytes is considerably modified, due to regular and frequent transfusions (25).

iii) Growth hormone deficiency

The diagnosis of growth hormone deficiency (GHD) is generally straightforward in children as growth retardation is present. However, in adults the diagnosis of GHD is often challenging. GHD in adults is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance and cardiac capacity and altered lipid metabolism with increase in adiposity (27).

In patients with chronic diseases, the clinical evaluation of GHD is difficult because signs and symptoms may be subtle and nonspecific, and universal provocative testing in all patients is difficult because the approach is cumbersome and expensive.

At present, GH stimulation test should be indicated in presence of the following clinical and laboratory parameters: Short stature (Height standard deviation scores <–2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF-1 level <–2 standard deviations. Very low IGF-1 levels, especially in those patients with childhood-onset GHD, in the presence of pituitary iron deposition and/or atrophy are highly suggestive of GHD (11).

In adult TM patients, with normal liver function, an IGF-1 level <50th percentile should be taken in consideration as a cut-off level for the GH assessment (28).

iv) Hypothyroidism

The frequency of primary hypothyroidism in TDT patients, in different reports, ranges from 4% to 29 %, based on the level of FT4/T4 and TSH. An assessment of thyroid function is generally recommended after the age of 10 years. The etiology of thyroid disorders in TDT patients is substantially different from that in the general population; transfusional iron overload and increased iron uptake from the gastrointestinal tract, as a result of ineffective erythropoiesis accompanied by anemia and hypoxia, are implicated in over 90% of morbidity and mortality in patients with TDT (29).

Doctors caring for TDT patients most commonly encounter subjects with subclinical primary hypothyroidism in the second decade of life. Secondary hypothyroidism is uncommon. There is very little evidence for the presence of autoimmune thyroiditis.The severity of the clinical manifestations generally reflects the degree of thyroid dysfunction and time needed for the development of hypothyroidism (29).

In patients with a TSH >10 mUI/L, thyroxine therapy (L-T4) is considered reasonable due to the systemic adverse effects of primary hypothyroidism Current guidelines do not recommend routine thyroid hormone substitution in subjects with normal FT4 levels and a TSH between 4.5 and 10 mUI/L.

However, the term subclinical hypothyroidism implies that patients should be asymptomatic (although symptoms are difficult to assess), especially in patients with chronic disease. Thyroid function tests on a 4–6 months interval are recommended to monitor treatment based mainly on serum TSH level (29).

v) Adrenal insufficiency (AI)

The diagnosis of adrenal insufficiency (AI) is relatively simple when glucocorticoid secretion is profoundly depressed.

However, AI can present a difficult diagnostic challenge, especially when adrenal insufficiency is partial. This is a particularly important issue as acute crises may occur during stress periods in undiagnosed patients (30).

Recently, a significant prevalence of "biochemical" central adrenal insufficiency (CAI), ranging from 15% to 53.6 %, has been reported in children, adolescent and adults with TDT (12).The pathophysiological basis of "*biochemical*" AI in TDT has not yet been well-defined. Chronic transfusions induce iron overload in several organs, including adrenal and pituitary glands. Furthermore, the adrenal glands might also be directly affected by iron toxicity (30).

Baldini et al. (31) have reported three cases of AI diagnosed in an acute setting, in TDT patients. Interestingly, none of them had previously shown symptoms and clinical signs of adrenal insufficiency and all had previously normal basal serum cortisol and ACTH values.

In summary, regular surveillance, early diagnosis, treatment and follow-up in a multi-disciplinary specialized setting are recommended (30).

vi) Hypoparathyroidism

Hypoparathyroidism (HPT) is a rare complication with leading symptoms of hypocalcemia, associated with high serum phosphorus levels and absent or inappropriately low levels of parathyroid hormone (PTH). In patients with TDT it is mainly attributed to transfusional iron overload, and suboptimal iron chelation therapy. Management of HPT depends on the severity of hypocalcemia (32).

Conventional treatment of HPT includes oral calcium and vitamin D supplements with the goal of controlling hypocalcemic symptoms, preserving serum calcium in the low-normal range and phosphate in the high normal range. While correction of serum calcium to low-normal range does not fully correct mineral and bone metabolism it may be associated with increased risk of complications such as nephrolithiasis, nephrocalcinosis and soft tissue calcifications. Therefore, it is imperative to find out ways to individualize treatment of patients with HPT to achieve the best prognosis while minimizing complications (33).

B. Complications in SCD

SCD is a systemic condition, with complications that affect almost all organs of the human body and clinical manifestations depend on many factors and not only from the genetic condition. Acute stroke and chronic cerebral ischemia are among the most debilitating consequences of SCD (34).

Cerebral infarction occurs in approximately 10% of patients in the first two decades of life and silent cerebral infarctions occur in approximately 17% of pediatric patients and are linked with both poor cognitive functioning and learning development (35). Emerging evidence suggests that organ damage is likely to overlap in certain organs, particularly the lungs, heart and kidneys. Accordingly a link has been found between elevated tricuspid regurgitant jet velocity (TRJV) and nephropathy in adults with SCD and an association between pulmonary hypertension and markers of renal injury, cutaneous ulceration and priapism in males with SCD (36). For all these reasons, a comprehensive center and multidisciplinary team for ongoing support are key for the optimal care of patients with SCD , especially when multiple types of organ damage are present.

Genotype-phenotype association studies have identified the existence of genetic modifiers that can modulate complications. Although increased survival to adulthood is certainly progress, people with SCD die at a much younger age than race-matched peers and the overall median survival is 58 years.

Adolescents and young adults in the second and third decades of life suffer significant morbidity with higher rates of SCD-related complications and higher health care costs (37). This is in part due to observations showing that these young adult patients receive fewer transfusions and are less likely to be on hydroxyurea and/or chelation therapy when eligible for such treatments as they transition from pediatric to adult care (38).

The most common cause of death is cardiac, respiratory, renal, infectious, neurologic, gastrointestinal, and hepatobiliary disease in descending order, and leukocytosis remains a key predictor of poor outcome along with renal insufficiency recurrent episodes of acute chest syndrome, low Hb F concentration, severe anemia higher rates of hemolysis, and dactylitis before 1 year of age (39).

The first symptoms of SCD may be expected a few months after birth when HbS level rises. While in less severe sickle cell disorders, clinical problems may develop later in life, SCD is a chronic disease characterized by anemia and multi-organ damage, but punctuated by acute painful episodes. These random crises are of variable severity and triggered by different factors such as cold weather, infection, or dehydration. Chronic organ damages, as well as acute, random painful crises, can be life-threatening. They also can have a profound effect on all aspects of life; as a consequence, psychological and social problems are very common in these patients and their families.

Genetic counselling and psychosocial support are pivotal at all stages of development and into adulthood. As mentioned before, SCD is a chronic disease, characterized by hemolytic anemia associated with painful vase-occlusive crises, progressive organic injures due to vascular disease and infections.

The existence of ***hemolysis*** in SCD has been documented by both indirect and direct methods. The existence of bone-marrow erythroid hyperplasia, reticulocytosis, indirect hyperbilirubinemia, and elevations of plasma hemoglobin and serum lactic acid dehydrogenase

(LDH) values show hemolytic disease. Direct studies of erythrocyte survival, including the Ashby differential agglutination technique, as well as isotopic methods, have all shown a markedly decreased RBC survival in the range of 10 to 30 days mean cell life-span. Data obtained using endogenous production of carbon monoxide have shown that the mean rate of heme catabolism is approximately six times normal but varies from 3 to 14 times normal in individual patients. These data document, by a relatively new technique, the consistent presence of a severe hemolytic process in sickle cell anemia.

The ***vase-occlusive crisis (VOC)*** are highly painful crises and the main characteristic of the disease. They can appear in any location, and their frequency and intensity are variable: 1/3 of the patients do not suffer pain crises while 1% present more than 6 episodes per year. Pain crises represent 50% to 60% of consultations and 60% to 80% of hospitalizations. Infants are protected from these crises during the first months of life due to the high Hb F levels. The first episode of pain is usually dactylitis in the small bones of the hands and feet, and about 50% of the children present this manifestation at the age of 2-years-old (40).

Cerebral vascular accidents (CVAs) are the main cause of morbidity, and leads to ischemic and hemorrhagic attacks. It is 300 times more frequent than in the normal population, and the peaks of maximum incidence are between 2 and 8 years and over 50 years. 10% of children between 2 and 10-years-old have clinical infarcts and 17% have silent infarcts associated with occlusion of the internal carotid and middle cerebral arteries. Alterations in the blood flow of the internal carotid and middle brain arteries can be detected by transcranial eco Doppler (TCED) and the risk of stroke is between 0.5% and 1%. However, if the blood speed in the middle cerebral artery is higher than 200 cm/sec, the risk increases to 10 to 13%. Cerebral infarction can be prevented with periodic transfusions every 3-4 weeks to maintain HbS <30%. Once a patient has presented a heart attack the risk of recurrence is 50% (41).

Finaly, ***frequent infections*** are the most common cause of child mortality because they are at high risk for encapsulated germ infections: pneumococcus, Haemophilus, and meningococcus. This elevated risk of infections is the consequence of functional asplenia (partial loss of splenic function) and the presence of plasma complement (C) and/or opsonisation disorders. 80% of patients with HbSS and HbSβ^0 have functional asplenia before 1 year of life, and a complete loss of spleen function (autosplenectomy) at 5 years. The risk of fatal invasive pneumococcal disease is very high during the first 5 years of life as well as the increased risk of staph aureus infections, viridians streptococcus, *E. Coli* and *Salmonella* (42). In some rare cases the infection by parvovirus B-19 blocks the erythropoiesis and therefore the production of red blood cells (RBCs) in the bone marrow. This leads to a severe non-regenerative anemia with very low values of hemoglobin concentration and reticulocytes called ***aplastic crisis (AC)***.

In addition to these general clinical manifestations of SCD, severe complications affecting many different organ systems damage like the chest, spleen, kidney, liver and bone may complicate the patient's follow up

1. Acute chest syndrome (ACS)

Acute chest syndrome (ACS) is a frequent, and sometimes fatal, SCD complication, characterized by fever, respiratory distress, pain, hypoxemia, and pulmonary infiltrates, easily identified on chest X-ray. ACS can be considered a VOC of the pulmonary vasculature and recurrent episodes of ACS are a significant risk factor for sickle chronic lung disease and death. Infection embolism and pulmonary infarction contribute to the initial pulmonary damage. The highest incidence occurs in the first decade, between 1 and 7 years. Moreover, more than 30% of patients suffer at least 1 episode, and it the second important cause of children's death (43). It may develop as a single event, or during a painful VOC. The clinical course is usually self-limited when small areas of the lung tissue are involved, but without proper care, ACS can rapidly progress and result in death. Chest pain when breathing is the most common presenting complaint in adults. Fever, cough, tachypnea (abnormally rapid breathing), hypoxemia (an unusually low concentration of oxygen in the blood), or abdominal pain are common presentations for infants and children (43). It is always best to rule out infection in these cases and obtain appropriate blood cultures and serologic studies. There may or may not be radiographic evidence (X-ray) of pulmonary infiltrates at the initial time of symptoms. Rib infarction, stomach ulcer, or gallbladder problems can also result in chest pain and should be checked as well.

2. Splenic sequestration

Splenic sequestration is a feared complication of SCD that primarily affects young children. Splenic sequestration (blood trapped in the spleen) refers to a sudden condition of pooling of large amounts of blood in the spleen leading to a sudden pallor, weakness tachycardia, abdominal pain with splenomegaly and a rapid drop of hemoglobin concentration to as low as 10-30g/l) that results in hypovolemic shock . Without a quick treatment with blood volume expanders and blood transfusion to reverse the hypovolemic shock, the child's death occurs within hours. The spleen is at particular risk for complications from sickle cell anemia due to its role as a filter of the blood. Splenic sequetration severity is variable and is a cause of death in 10 to 30% of pediatric patients. Their recurrence is estimated at 50% after the first episode and can occur in 30% of children before 6 years. Those who survive a first episode are at high risk of having a recurrent event (44). For this reason, it is of vital importance to educate the patient's family to aid in the prevention of these episodes.

As mentioned before, 80% of patients with HbSS and HbSβ^0 have functional asplenia before 1 year of age, and complete auto-splenectomy at 5 years, but the patients with HbSC and HbSβ^+ are at risk of splenic sequestration throughout their life. The precise trigger for spleen sequestration is often unknown but it can occur with or shortly after a VOC or infection. Minor sequestration events are common in young children with SCD. Some cases can happen with viral illnesses. Mild episodes can cause an enlarged spleen and blood changes such as worsened anemia or decrease of hemoglobin from the patient's baseline concentration or thrombocytopenia.

Due to overall less sickle-related infarction, the spleens of patients with HbSC or HbS-β+ thalassemia may remain enlarged (persistent splenomegaly) or retain the ability to enlarge into adulthood. Therefore, they are also at risk for sequestration. Because sequestration tends to recur and because of the sudden onset of this life-threatening condition, splenectomy (removal of the spleen) should be considered if the child has had more than one episode.

3. Sickle cell nephropathy (SCN)

SCD has a substantial impact on renal structure and function causing acute and/or chronic kidney injury leading to a variety of renal syndromes that include hematuria, proteinuria, hyposthenuria, renal papillary necrosis, renal tubular disorders, and sickle cell glomerulopathy. Moreover, impaired renal function contributes substantially to the decreased life expectancy of patients with SCD. 30% of adult patients develop chronic renal failure, a contributory factor in many deaths (44).

Acute kidney injury (AKI) in SCD may be the consequence of repeated cycles of hypoxia and ischemia in the renal medulla, associated with VOC, and may have contributions from dehydration, ingestion of non-steroidal anti-inflammatory drugs (NSAIDs), or infection. As patients with SCD have hyperfiltration and low baseline creatinine levels, it is important to look at trends in creatinine rather than absolute value. AKI develops in approximately 75% of VOC episodes that are complicated by acute multi-organ failure and hemodialysis is needed in 18% of these episodes (45).

In patients with SCD who present with oliguria and/or a rapidly rising of creatinine, AKI should be considered, a global fall or renal function (GFR), and should be referred for emergency management. Measures to mitigate renal damage should be instigated immediately, including clinical assessment to include daily weight, fluid balance and palpable bladder, stopping NSAIDs, withholding angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), reviewing drug lists for potential nephrotoxins, and hydrating patients well.

4. Sickle-Cell Hepatopathy (SCH)

Sickle-cell hepatopathy (SCH) is a term given to various pattern of liver injury seen in patients with SCD and their clinical spectrum of disease ranges from ischemic injury due to sickling of red blood cells in hepatic sinusoids, pigment gall stones, and acute/chronic sequestration syndromes. It occurs predominantly in patients with homozygous SCD, and to a lesser extent in patients with sickle cell trait, Hb SC disease and Hb S-β thalassemia (46).

SCH is an uncommon complication characterized by extreme hyperbilirubinemia and either mild or severe hepatic dysfunction. Children and adults can present with either form; however, adults have a higher frequency of the severe form. Exchange transfusion may be the only effective management for initial episodes of severe sickle cell hepatopathy. A form of liver

dysfunction in SCD is acute hepatic sequestration a complication of VOC occurring in approximately 10% of patients (47). Hepatic involvement in SCD is not uncommon since liver disease may result from viral hepatitis and iron overload due to multiple transfusions of blood products or due to disease activity causing varying changes in vasculature.
The hepatic disease may primarily be caused by the sickling process, but more commonly arises as a consequence of the multiple transfusions that these patients require in their lifetime (multi-transfusion hepatopathy). The main hepatic complications of multiple transfusions include acute and chronic infection with hepatitis B and C and iron overload. Clinical manifestations of SCD in the liver are predominantly due to vascular occlusion with acute ischemia, sequestration, and cholestasis, although chronic cholestatic syndromes have also been described. A further potential consequence of the chronic hemolysis is the development of pigment stones, with consequent cholecystitis and acute and chronic biliary obstruction from choledocholithiasis (Table 1).

Table 1. *Hepatobiliary Complications of Sickle Cell Disease (From: Banerjee S, et al. Hepathology. 2001; 33:1021-8).*

A. Clinical syndromes
a. Acute sickle hepatic crisis
b. Hepatic sequestration/reverse sequestration
c. Sickle cell intrahepatic cholestasis
d. Acute sickle cell intrahepatic cholestasis
e. Benign hyperbilirubinemia
f. Chronic intrahepatic cholestasis
g. Miscellaneous
h. Budd-Chiari syndrome
i. Hepatic infarction
j. Hepatic infarction
k. Hepatic biloma
l. Zinc deficiency with hyperammonemia
B. Complications of chronic hemolysis and multiple transfusions
a. Cholelithiasis and choledocholithiasis (pigment stones)
b. Hepatic iron overload
c. Viral hepatitis B and C (rare in current practice)

The sequestration syndromes are usually episodic and self-limiting requiring conservative management such as antibiotics and intravenous fluids or packed red cell transfusions. However, rarely these episodes may present with coagulopathy and encephalopathy like acute liver failure, which are life-threatening, requiring exchange transfusions or even liver transplantation. Unfortunately there is paucity of the literature regarding the end point of exchange transfusion in this scenario and liver transplantation may also be beneficial in end-stage liver disease. Hydroxyurea, the antitumor agent, which is popularly used to prevent life-threatening complications such as ACS or stroke in these patients, has been used only sparingly in hepatic sequestrations.

5. Avascular necrosis (AVN)

Avascular necrosis (AVN) is a complication of SCD characterized by death of bone tissue that is believed to be caused by a temporary or permanent disruption in blood supply to the bone in the hip or shoulder joint. AVN can affect a single joint or more than one joint at the same time and femoral head AVN, has long been recognised as a frequent complication of SCD (48). AVN most commonly affects the femoral or humeral heads. Studies of patients with SCD with varying hemoglobinopathies and age ranges (0 to ≥ 45 years) report femoral and/or humeral head AVN can occur in up to 50% of patients with SCD by he age of 35 years and it is associated with vaseocclusion (VO) within the vasculature in and around the bone. This VO leads to tissue hypoxia, inflammation, and subsequent bone necrosis and its prevalence ranges from 3% to 27%, based on imaging and clinical diagnoses. Current prevalence is, probably, a little higher since it has been reported that 41% of patients had silent AVN of at least one hip when evaluated by radiography and magnetic resonance imaging. Compared with other complications of SCD, AVN is the second most prevalent chronic complication in both HbSS and HbSC individuals. The presence of AVN has been associated with a higher number of hospitalized sickle cell pain crises, irreversible organ damage, and mortality. AVN typically is asymptomatic until late-stage disease, and once symptomatic, there is rapid progression to collapse, especially in AVN secondary to SCD as compared with other aetiologies. Surgical intervention is one of the few treatment options available for AVN.

In summary, all these disorders are complex, and their prevalence is highly variable. For this reason, it is unlikely that all the services necessary for the best diagnosis, follow-up, and treatment of SCD patients can be offered by only one health care provider (HCP), and a multi-disciplinary team of health and social services with local centers networking together with are the most convenient to offer a full range of services, including specialist access and supervision when required. In reality, however, such healthcare organization HCP is rarely available, even in developed countries, and in the majority of care has to be delivered close to the patient's home by a local team or clinicians, with expertise in SCD and available for an in-person consultation or by telephone/internet communication. Regardless, it is of utmost importance that patients are educated on infection prevention, pain management, and early detection of complications starting with general measures that are beneficial to maintain health and avoid acute disease events. These measures include avoiding overexertion, excessive temperatures, hypoxia, and maintain an adequate water intake. It is always convenient to prevent megaloblastic erythropoiesis with the folic acid intake

Conclusions

Sickle cell disease/anemia and thalassemia are hemoglobinopathies which are the most common monogenic diseases in the world: up to 7% of the global population are carriers of an allele for an inherited hemoglobin disorder and 400,000 affected children are born each year (2). The global number of neonates affected by the abnormal hemoglobin of sickle cell anemia is estimated at 5.5 million at the heterozygous state and 300,000 at the homozygous state with fulminant disease with homozygous hemoglobin S (HbS) (49).

More than five decades ago, thalassemia major was fatal in the first decade of life. Recent advances in chelation therapy with new oral iron chelators and in imaging methods for assessing organs' iron content resulted in striking improvements in outcomes for younger patients with TDT, but few older patients have benefited from these improvements since the first years of life. Therefore, it is well known that the older generation of adult patients have higher morbidities and co-morbidities such as heart disease (heart failure and arrhythmias), chronic hepatitis (which may evolve into cirrhosis and rarely, in hepatocellular carcinoma), endocrine disorders (hypogonadism, hypothyroidism, diabetes, hypoparathyroidism), and osteoporosis that limit their quality of their life (50).

Currently available guidelines deal with three main areas of SCD management: prevention of infections, stroke, and management of acute and chronic complications; treatment of the various complications (VOC, pain, infections, worsening of anemia, acute chest syndrome, vasculopathy); and specific treatment of severe disease with disease-modifying therapies (transfusion and hydroxyurea) (51).

Much of the morbidity and mortality from these complications can be reduced with regular surveillance, early treatment, and follow-up in a specialized multidisciplinary centers devoted to the care of hemoglobinopathies (51, 52).

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