Chronic organ failure in adult sickle cell disease

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Sickle cell disease is now a chronic adult illness characterized by progressive multiorgan failure, particularly involving the brain and kidney. The etiology is multifactorial; it includes hemolysis and nitric oxide deficiency. As patients age, most experience neurologic insult. Twenty-five percent of older adults have had a clinical stroke and at least half of the population have had a silent infarct, cortical atrophy, and neurocognitive impairment. Periodic screening with neuroimaging and neurocognitive testing is recommended. Identification and correction of modifiable risk factors such as nocturnal hypoxemia, obstructive sleep apnea, and physical exercise programs should be implemented. Patients with neurocognitive impairment require cognitive remediation and educational accommodations. Chronic renal disease occurs in 25% of older adults and results in 50% of their deaths. Renal failure often develops insidiously. It can be prevented or minimized by early screening and treatment of modifiable risk factors including hypertension and microalbuminuria. There is an increasing number of therapeutic options, including inhibitors of the renin angiotensin system, angiotensin-II receptor blockers, endothelin-1 receptor antagonist, and haptoglobin therapy. Patients with sickle cell disease have increased mortality rates from renal failure compared with nonsickle cell patients, in part from a lack of access to early multidisciplinary care, including timely initiation of dialysis and renal transplantation.

Learning Objectives

- To describe chronic organ damage caused by chronic renal and central nervous system disease (CNS) in adult sickle cell patients
- To learn the modifiable risk factors for chronic renal and CNS disease
- To discuss the current screening recommendations for chronic renal and CNS disease in adult patients
- To review therapies to modify and treat chronic renal and CNS injury

Introduction

Sickle cell disease (SCD) has changed from a fatal pediatric illness to a chronic adult disease characterized by progressive multiorgan failure. The survival rate for pediatric patients continues to improve. Although individual sickle cell centers report median survival of 58 to 67 years for SCD, the overall survival for adults has made little progress and even decreased in regions.[1,2] The etiology for the variation in survival is multifactorial, but clearly influenced by early detection and treatment of multiorgan dysfunction. Decades ago, before the Cooperative Study of Sickle Cell Disease (a landmark natural history study), the median age of death was 14 years. At the completion of the Cooperative Study in 1988, the median age of death was 48 years for women and 42 for men.[3] Recently, the National Center for Health statistics published population-based surveillance data for all causes of death among 12 000 patients with SCD. The overall age of death was 43 years for females and 40 years for males. Lanzkron et al found the pediatric survival increased 3% per year between 1999 and 2005.[4] In contrast, during the same period, adult survival decreased 1% per year.

The poor overall survival in adults is accompanied by deteriorating quality of life and increased morbidity from multiple complications. Although sudden death remains a serious problem in SCD, irreversible chronic organ failure is the primary cause of death and morbidity in most patients. In addition, detected or undetected chronic organ dysfunction is a causal factor in most acute deaths.[5]

In the Powars et al landmark 40-year observational study of 10 056 patients, half the adults had irreversible organ damage.[5] A single organ dysfunction was an independent predictor of mortality and a risk factor for subsequent multiorgan failure. In particular, lung disease, renal failure, and central nervous system (CNS) complications strongly predicted mortality and progressive clinical deterioration. More recently, Telen et al reported that 32% of adults had a history of neurologic disease, which correlated with early mortality.[6] Most clinical mortality reports underestimate the central role of chronic organ dysfunction in death. Manci, in analyzing data from 120 autopsies, found evidence of chronic organ failure in 75% of patients but clinically noted in only 25% of the clinical histories.[7] Other reports have also noted a marked discrepancy in the pathology reports compared with the clinical observations. The purpose of this report is to highlight the importance of CNS and renal disease in adult sickle cell patients.

Brain

Stroke

The majority of adult sickle cell patients suffer from CNS injury that progresses with age.[8-12] Clinical stroke, the most recognized complication, is 1 manifestation of global neurologic insult.[13] The prevalence of clinically overt stroke reaches 24% of patients by 45 years of age, with an adult peak at 29 years for both ischemic and hemorrhagic strokes. The incidence of first stroke is 500 to 1280

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per 100 000 person years in sickle cell anemia (SCA) compared with 12 per 100 000 person years in African Americans younger than 35 years of age.[11] Hemorrhagic stroke in SCD is 30 times greater compared with non-SCD patients. Recently, an analysis of the administrative patient data from California confirmed the extremely high rate of stroke in SCD adults, with 56% being ischemic stroke, 24% intracerebral, and 20% subarachnoid hemorrhage.[14] The high rate of annual subarachnoid hemorrhage in SCD is related to the high prevalence of intracranial aneurysms, which are distinct from the moyamoya vasculopathy. The prevalence of aneurysms in sickle cell adults is not exactly known, but recent data indicate that approximately 10% of unselected young adults without overt neurologic problems (median age, 30 years) undergoing magnetic resonance imaging (MRI) screening for silent infarction had saccular aneurysms on incidental screening.[9]

Silent cerebral infarction

Silent cerebral infarction is well studied in children with SCD and is associated with neurocognitive impairment and increased risk of CNS complications. The cumulative risk for silent cerebral infarction increases with age; by 18 years, 39% of patients have lesions. Recent data suggest that cumulative risk continues with age. Kassim, using standardized definitions and technology, reported a prevalence of silent infarction in 53% of adults with SCA with a mean age of 30 years.[9] In a group of neurologically asymptomatic SCA adults without multiorgan dysfunction, Vichinsky et al found that 15% of the population with a median age of 32 had silent cerebral infarctions larger than 5 mm.[12] Of interest, many of these patients had normal screening MRI scans as part of childhood collaborative studies, suggesting that a normal MRI scan in childhood does not preclude new lesions occurring with age.

Atrophy

Increasing studies indicate that adult patients with SCD have progressive global gray and white matter volumetric loss involving critical brain regions independent of clinical or silent infarction.[10,12] Compared with controls, adults with SCA have volume loss in the frontal, temporal, and parietal lobes; basal ganglia; and thalamus. Volume loss is consistent throughout each of the subregions including the caudate, pallidum, putamen, and thalamus. Perfusion studies indicate that many of these areas of atrophy have decreased perfusion, particularly in small and terminal branches of arterial blood vessels.[15] Recent studies confirm that corpus callosum atrophy and damage often accompanies these other findings. Quantitative diffusion-tensor imaging in adults indicate fiber tract density damage and evidence of axonal injury in the corpus callosum compared with controls.[16]

Neurocognitive function

Comprehensive assessment of neurocognitive function in neurologically intact adults with SCA indicates clinically significant impaired neurocognitive performance compared with controls.[10,12,17,18] Important differences in neurocognitive performance on the Wechsler Adult Language Scale-III verbal IQ, picture IQ, and full-scale IQ indexes, as well as on tests of memory, language, learning, attention, retrieval, and overall executive functioning are observed. Additional differences in neurocognitive testing between patients and controls were noted on processing speed, working memory, global cognitive function (full-scale IQ), and the majority of measures of executive function (Delis-Kaplan Executive Function System), and selective attention. These neurocognitive abnormalities are independent of lacunar infarcts but are amplified by lesions. In general, silent infarction causes a steep decline in cognitive function over time and is a risk factor for early dementia. Because this study excluded complications and risk factors associated with neurocognitive decline, the results likely underestimate the level of cognitive difficulties experienced in the general adult population with SCA. Overall, one could expect these patients to have challenges in skills of daily life such as planning, employment, financial management, medication adherence, utilization of community resources, and social functioning.[19]

In adult patients with SCD, there are several clinical, environmental, genetic, and laboratory risk factors for neurocognitive decline and brain injury that increase with age. The clinician should be aware of these, correct those that are modifiable, and screen all high-risk patients for consideration of therapeutic interventions. Optimal screening and management of smoking, hypertension, cardiac disease, arrhythmias, diabetes, thrombophilia, hyperlipidemia, and obesity are important. Comorbid chronic renal and lung disease requires early multidisciplinary intervention. History of intermittent hypoxia or acute fall in hemoglobin should raise concern of neurocognitive injury or stroke risk. Any mechanism that may result in transient or chronic decrease in cerebral vascular reserve is likely a catalyst for CNS injury, including cognitive impairment. This can occur with transient episodes of oxygen desaturation, acute worsening anemia, or CNS vascular flow abnormalities. Obstructive sleep apnea and nocturnal hypoxemia are common treatable causes of neurocognitive injury in the general population, including patients with SCD. The rate of nocturnal hypoxemia increases following a stroke and worsens cognitive function. Screening and intervention with continuous positive airway pressure or oxygen therapy should be considered.

Neuroimaging findings including stroke, silent infarction, and volume loss predict neurocognitive dysfunction and likely accelerate neurocognitive decline over time. These are risk factors for early dementia. Global cognitive impairment and executive function loss are associated with white matter damage and infarctions that are often associated with cerebrovascular disease. Gray matter loss (including atrophy of hippocampal areas) accelerates memory loss, including verbal and visual recall. Gray matter damage occurs in cerebrovascular disease, but can occur independently from chronic pain, inflammation, and intermittent hypoxia.[10] Nontraumatic subdural hematoma secondary to sickling may be detected. Neuroimaging evaluation should include magnetic resonance angiography because intracranial and extracranial cerebral vascular disease, including stenosis, aneurysms, and moyamoya, is common. In addition to anatomical imaging, cerebral metabolic and flow studies are predictors for limited cerebral oxygen reserve.[20,21] Increased cerebral blood flow detected from perfusion studies and transcranial Doppler are risk factors for neurologic injury in both adults and children. Unfortunately, transcranial Doppler studies in adults have not yet been validated. Cerebral oxygenation and oxygen extraction can be detected by multiple techniques. Increased oxygen extraction determined by MRI perfusion studies may become an important screening test for high risk adults.

There are several laboratory risk factors for cerebral infarction, intracranial hemorrhage, and neurologic decline that largely overlap. Genetic studies have uncovered several candidate genes that increase stroke risk; however, these laboratory findings have not yet been used in clinical care. Low steady-state hemoglobin with hemolysis is central to neurologic injury. Anemia significantly correlates to lower oxygenation and poorer neurocognitive performance in SCD and in the aging general population. Anemia accelerates age-related neurocognitive decline. Hemoglobin is likely a surrogate marker for

reduced oxygen delivery to the brain, and the accompanying chronic nitric oxide deficiency stimulates the development of vasculopathy. Initially, anemia-induced neurocognitive impairment and cerebral oxygen desaturation may be reversible. Both transfusion and administration of hydroxyurea may improve cerebral blood flow, oxygenation, and neurocognitive function. In the general population, oxygen administration in anemic and healthy individuals improves cognitive performance. These observations suggest some of the cognitive difficulties in SCD may be due to reversible hypoxic dysfunction.

There are no standard screening recommendations to detect neurocognitive or neurologic injury in the neurologically asymptomatic adult. Several diseases are accompanied by neurocognitive problems and early screening interventions are increasingly being recommended. It seems reasonable to undergo neurocognitive testing and MRI scans as patients transition to adult care. Early detection of neurologic dysfunction will allow recommendations before difficulties emerge and enable the anticipation of the functional decline in time that occurs in CNS injury. There are multiple challenges to screening neurologically asymptomatic adults. These challenges include insurance coverage, consensus agreement on the optimal test to use for screening adults, and evidence-based treatment of those adults with abnormalities. However, encouraging data suggest that hydroxyurea therapy results in meaningful improvement in cognitive function.[22] In addition, cognitive remediation, educational accommodations in college, and aid in organizational and time management skills will benefit young adults as they age. Evolving neuroimaging studies and abbreviated neurocognitive screening measures for adults are undergoing study, and changes in recommendations may occur.

The treatment of stroke in adults with SCD is largely expert consensus-based and summarized in recent excellent reviews.[8,11,13,23,24] Exchange transfusion rather than simple transfusion is the preferred initial treatment. Preliminary data suggest chronic automated exchange transfusions may be more efficacious than standard transfusions. Thrombolytic therapy could be considered in adults, but its risks and benefits are unknown.[25] Because SCD patients may have an increased rate of intracranial hemorrhage, thrombolytic therapy use in ischemic stroke should be determined by a multidisciplinary team on a case-by-case basis. Evidence-based guidelines for hemorrhagic stroke in SCD are lacking. Transfusions are often initially used because of the high rate of concomitant ischemic stroke. Standard American Heart Association guidelines for hemorrhagic stroke are followed for sickle cell patients. Vascular imaging is important to detect associated aneurysms that may require surgical planning. Long-term management of ischemic stroke in adults has not been prospectively studied, but indefinite transfusions, usually with antiplatelet therapy, are standard. Many pediatric patients have been transitioned off transfusion to hydroxyurea as adults, but a high recurrence rate has been reported.[26] Combination hydroxyurea and transfusions may be beneficial in recurrent episodes.[27] Encephaloduroarteriosynangiosis is increasingly used in patients with moyamoya to improve cerebral oxygenation and decrease recurrent infarction and intracerebral hemorrhage.[28] The management of silent infarctions is not standardized. Transfusion therapy may be beneficial and, at a minimum, hydroxyurea therapy is indicated. Most adult patients have hemosiderosis, and early chelation therapy is indicated in chronic as well as intermittently transfused patients.

The management of neurocognitive impairment requires aggressive treatment of comorbid factors in SCD and the general population, such as nocturnal hypoxemia.[29] Physical exercise improves memory in infrared spectroscopy measurements in older adults as well as those poststroke.[30] In addition, it appears that, in transgenic sickle cell mice and patients, moderate exercise training decreases inflammation and may even improve sickle cell biology.[31,32] However, exercise is not often included in the health maintenance programs for sickle cell patients with and without stroke because of theoretical concerns that metabolic changes imposed by exercise may initiate sickling and clinical events.[32]

Rapid advances in gene therapy and stem cell transplantation may soon be available to neurocognitively injured adult sickle cell patients. Preliminary results indicate gene therapy, nonmyeloablative, haploidentical stem cell transplantation, and *BCL11A* gene editing therapy are promising options. Ongoing trials will determine their safety and efficacy in this adult population.[33-35]

Chronic renal disease

Chronic renal disease is a major cause of morbidity and mortality in aging sickle cell patients. At least 25% of older sickle cell adults have chronic kidney disease, which accounts for half the deaths in this older population.[36] In the SCD surveillance project in California, pulmonary and renal failure were the leading complications in hospitalized patients older than 50 years of age.[14] The 5-year survival following the diagnosis of renal failure is variable but is approximately 55% and is remarkably shorter than for nonsickle cell patients.[37,38] A multidisciplinary approach addressing early prevention, early identification, access to treatment, and new therapies are needed.

As sickle cell patients age, they experience repeated multifactorial renal injuries, often undiagnosed, that lead to the insidious presentation of renal failure.[36,38-42] An acute kidney injury often accompanies serious sickle cell events that may not be reflected in creatinine levels.[40,43,44] Red cell hemolysis with nitric oxide deficiency and endothelial dysfunction results in chronic renal ischemia and is a major cause of renal pathophysiology in SCD.[41,45-47] The downstream effect of the ischemia leads to inflammation, elevation of tyrosine kinase-1 and other promotors of angiogenesis, activation of hypoxia-inducible factor 1α and endothelin-1, as well as oxidative stress.[38,41,48,49] Therefore, patients with renal disease often have other characteristics of the hemolysis phenotype, including pulmonary hypertension, CNS injury, and severe anemia. In several multicenter trials, albuminuria is associated with hemolysis, low hemoglobin, elevated blood pressure, and pulmonary hypertension.[39,45,50]

Screening and early diagnosis of renal disease should be part of the ongoing, periodic care of all sickle cell patients and is essential to improving outcome. Relative hypertension and elevated pulse pressure are high-risk factors for renal disease.[50] Periodic screening for microalbuminuria, hematuria, and estimated glomerular filtration rate are standard. Early detection of renal disease by using surrogate markers of renal disease (including serum cystatin C, urine *N*-acetyl-β-D-glucosaminidase, urinary β2-microglobin, and hemoglobinuria) may be beneficial but are not yet validated.[36,38,47,51] Deteriorating trends in laboratory screening tests, rather than just absolute amounts, should prompt nephrology involvement.

Therapies

There are multiple therapeutic interventions that may decrease chronic renal disease.[36,42,52] Early initiation of hydroxyurea therapy is renal protective, as is chronic transfusion therapy.[36,53,54] The early treatment of proteinuria with inhibitors of the renin angiotensin system may prevent progressive disease. Recently, an angiotensin-II

receptor-1 blocker may be more beneficial than an angiotensin-converting enzyme inhibitor.[52] Because endothelin-1 is a cause of progression of renal disease, research data suggest that endothelin A receptor antagonism therapy was beneficial in hemoglobin S transgenic mice.[42,48] Because hemolysis with free hemoglobin is central to renal injury, decreasing this by haptoglobin infusions is a novel approach. Clinical studies in nonsickle cell patients suggest this may be beneficial.[55,56]

Sickle cell patients often have a delay in initiation of early therapy for advanced renal disease, which results in increased mortality. Improved multidisciplinary care with planning of vascular access, transfusion therapy, initiation of dialysis, and listing on a renal transplantation registry are major priorities and improve survival.[38,57] Recent studies indicate a trend toward improved survival for kidney transplantation. Although survival at 6 years is lower for SCD compared with non-SCD, it has increased to 70%. When matched for multiple covariates, SCD survival is comparable to African Americans with diabetes as a cause of renal failure.[58] Adjustment of narcotic analgesia dosing based on renal clearance needs to be considered.

Sickle cell patients with renal failure usually have erythropoietin resistance. Chronic transfusion therapy is often necessary. Hydroxyurea with erythropoietin is often initially used. Hemosiderosis is a serious problem in renal failure; iron chelators should be routinely used in patients on dialysis who have hemosiderosis.[57] Morbidity and mortality from comorbid complications including thrombosis, cardiac failure, stroke, and infection are more frequent in chronic renal failure patients and can be minimized with patient education and early intervention.[59]

In summary, chronic organ dysfunction is a major cause of sickle cell morbidity and death in adult patients. More aggressive monitoring and improved treatments are necessary. The etiology of organ failure in the adult population overlaps with many of the risk factors seen in pediatrics. Pediatric and adult patients share some common phenotypes and biomarkers,[60,61] such as stroke and renal disease. There may be differences in the biology- and age-dependent potential therapy. In adults, clinical problems such as pulmonary hypertension, cardiac dysfunction, and cardioembolism may be more important than in pediatrics. Biomarkers of intima-media thickness, nitric oxide dysfunction, natriuretic peptide, and genetic variance of free hemoglobin processing such as ApoL1 and HMOX1 may play a more important role in the older population.[62,63] More research in chronic organ failure in adults is critical. Longitudinal studies correlating age, phenotype, genotype, biologic markers, and response to therapy are essential to better understand age-specific therapy.

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