RESUMEN.- OBJETIVO: La drepanocitosis es una de las enfermedades hereditarias más frecuentes. Las tendencias migratorias y el mestizaje han elevado la incidencia de esta enfermedad en Europa. Se ha publicado mucho sobre esta enfermedad, pero existen en la literatura pocas revisiones que traten en conjunto sus manifestaciones sobre el sistema genitourinario.

MÉTODOS: Se ha llevado a cabo una revisión exhaustiva, usando como instrumento principal la base de datos online PubMed, sobre los avances en la fisiopatología y manifestaciones uro-nefro-andrológicas de esta enfermedad.

RESULTADOS: Entre estas manifestaciones se encuentran la nefropatía de células falciformes, enuresis, nocturia, hematuria, priapismo, carcinoma medular renal e infartos y necrosis en diversos órganos del aparato genitourinario.

CONCLUSIONES: Las particularidades de este síndrome y el espectro multisistémico que abarca, hacen necesario el conocimiento de esta enfermedad y de sus manifestaciones genitourinarias.
INTRODUCTION

Sickle cell disease (SCD) is a hemoglobinopathy of mendelian inheritance that is inherited in an autosomal codominant manner. It is especially prevalent in regions where Plasmodium falciparum malaria is endemic (1-4) and regions populated by people with ancestors originating from sub-Saharan Africa. The disease is also seen in India, Saudi Arabia, and Mediterranean countries, including Italy, Greece, and Turkey (1, 5). SCD is one of the most common hereditary diseases in the world (6), and much has been published on it. Nevertheless, few reviews in the literature have addressed its manifestations in the genitourinary system (5, 7-9).

Each year approximately 300,000 children with different hemoglobinopathies are born worldwide, and of these, more than 80% are African with SCD (1, 10). The estimated worldwide prevalence of heterozygotes is 5% (11). In some areas of sub-Saharan Africa, the incidence of homozygotes can reach 2% (1). The disease affects about 1 in every 600 African Americans and one in 12 African Americans are heterozygous for the disease (4, 5). In the United States about 60,000 people are living with SCD, and in the United Kingdom the number of sufferers totals about 10,000 (10). In 2006, in Spain, the records of the Spanish Society of Pediatric Hematology showed that the prevalence of SCD had tripled in the preceding 4 years. Most likely these figures underestimate the situation. Catalonia is the Spanish community with the highest flow of African immigrants with the greatest genetic impact of this disease (Table I) (12, 13).

MATERIALS AND METHODS

We conducted a comprehensive review of current literature that encompassed the most recent works addressing the pathophysiology and the urological, nephrological, and andrological manifestations of SCD. The main instrument used for this purpose was the PubMed online database.

RESULTS

Pathophysiology

SCD was first described in 1910 by James Herrick, of Chicago, in a 20-year-old male from the island of Grenada (14). In the 1970s, life expectancy for this disease was approximately 14 years, and by the late 1980s it reached about 20 years. Today it is almost 50 years (15,16).

In this condition a point mutation occurs in the gene encoding the beta chain of hemoglobin (chromosome 11), which causes the amino acid valine to replace glutamic acid in the sixth position. This change make the molecule of hemoglobin less soluble and precipitates the formation of polymers under certain conditions (acidosis, hypoxia, and dehydration); furthermore, the electrophoretic mobility of the hemoglobin molecule is altered (2). The term hemoglobin S (HbS) is used to describe hemoglobin affected by this single amino acid substitution, where the letter ‘S’ represents “sickle” in reference to the form adopted by the red blood cells (sickle cells) when observed in the microscope (Figure 1) (17).
The sickle cells, deformed and rigid, adhere to the vascular endothelium and obstruct small postcapillary venules, leading to occlusion and infarction. After some time, the change in the shape of the erythrocyte is irreversible because of damage to the cell membrane, shortening its half-life and causing hemolysis (18, 19).

When hemolysis occurs, lactate dehydrogenase, potassium, hemoglobin, oxygen free radicals, and arginase are released into peripheral blood. This phenomenon leads to self-activation and deterioration of endothelial function that in turn promotes a procoagulant state and recruitment of leukocytes. This helps to spread the chronic vascular inflammatory component of the syndrome and to cause heterocellular aggregate formation between activated leukocytes and sickle cells, contributing to the vaso-occlusive phenomenon (18, 19).

Previously it was thought that only homozygotes had symptoms, but today it is known that heterozygotes (with the sickle cell trait) may also develop symptoms when subjected to high altitudes or strenuous exercises (18, 19).

Pathophysiology of Renal Manifestations

In SCD, under physiological conditions, oxygen pressure in the renal medulla is equal to or less than 20 mmHg (20). From childhood, the hyperosmolarity, low oxygen concentrations, and acidosis in the renal medulla cause the polymerization of hemoglobin, which starts at tensions below 45 mmHg. Erythrocytes “dehydrated” by these conditions have a high concentration of HbS, which precipitates. Initially, blood viscosity increases locally, the venous capillaries are filled with sickle cells, and interstitial edema occurs. Sickle cell obstruction of the vasa recta causes microthrombosis, infarction, and collateral vessel formation. This leads to a reduction in the number of functioning vasa recta and loss of normal architecture of the renal medulla, which interferes with the countercurrent mechanism necessary for urine concentration and water-electrolyte balance (11, 20-22).

In late childhood and adolescence, the permeability of capillaries increases and erythrocytes enter the collecting system with a complete loss of the vasa recta. Blood flow in the renal cortex and the glomerular filtration rate (GFR) increase owing to the secretion of prostaglandins, which causes vasodilatation in the renal medulla. This increased flow in the renal cortex leads to glomerular hypertrophy (glomerulomegaly) (11, 20-22).

In adulthood, when glomerular damage is established, the GFR begins to decline during the third and fourth decades until end-stage renal disease (ESRD) is reached (11, 20-22). The continuous transfusions required by these patients can cause renal tubular siderosis (11, 21).

Clinical Presentation of Genitourinary Manifestations

Sickle cell nephropathy

The prevalence of proteinuria has been estimated to be between 20% and 25% in patients with SCD, and that of deterioration in renal function to be between 5% and 30%. Acidosis and tubular dysfunction (incomplete distal tubular acidosis) may also occur (5,7-9). In a study relating to hemodialysis centers, Derebail et al. found that compared with the general African-American population, HbAS (sickle cell trait) was twice as common among African Americans with ESRD (15% versus 7%); nevertheless, in the United States SCD accounts for less than 1% of new cases of ESRD (23).

The incidence of renal failure in patients with SCD varies between 5% and 18%. The mean age at diagnosis is 23 years and the survival time after diagnosis of ESRD is 4 years despite treatment with dialysis. Median survival is approximately 29 and 51 years with and without renal failure, respectively. The best predictors of renal failure are hyperfiltration, proteinuria, hypertension, severe anemia, and hematuria (22, 24). Notably, the incidence of hypertension is lower in SCD; however, since blood pressure values considered normal in the general population may be pathological in these patients, they are referred to as having “relative hypertension” (5,7-9). The most frequent glomerular lesions are glomerular hypertrophy and focal segmental glomerulosclerosis, but other forms of glomerulopathy may also occur (22, 24).

![FIGURE 1. Morphology of the sickle erythrocyte (sickle cell) and a normal erythrocyte.](image-url)
Acute renal failure is usually related to prerenal factors such as volume depletion but it may also result from concomitant infection (sepsis) or rhabdomyolysis due to heavy physical activity, acidosis, hypoxia, or anesthesia. Less frequently, renal vein thrombosis or intravascular hemolysis is responsible, and it can arise from obstructive causes (clots or, less often, papillary necrosis). The prognosis in these patients is usually good (22, 24).

Curiously, patients with SCD do not experience more complications than the general population when they undergo dialysis or kidney transplantation, although it has been reported that infections, mainly septicemia, are responsible for 23.3% of deaths after renal transplantation in patients with SCD (25).

The proper preparation of patients with normal blood transfusions and treatment with hydroxyurea to elevate fetal hemoglobin levels can reduce the frequency of sickle crises. For these reasons, chronic hemodialysis and renal transplantation represent reasonable options for patients with ESRD, and the same protocols must be followed as in patients without SCD (22, 25).

Enuresis, nocturia, and nephrogenic diabetes insipidus

In the general pediatric population, the prevalence of enuresis at 5 years is 15% while nocturia is present in 40% between 6 and 11 years. The prevalence of enuresis in children with SCD ranges from 20% to 69%, while that of nocturia can reach 68% (26). Enuresis can also affect adults with the disease. In addition, there is some female predominance (27), the cause of which is not entirely clear.

Multiple factors can contribute to enuresis and nocturia, including decreased ability to concentrate urine (hyposthenuria) owing to failure of the countercurrent mechanism of the renal medulla. A decrease in the bladder functional capacity has also been reported (26, 28).

The fact that patients respond to treatment with desmopressin (DDAVP) in the same way as normal children leads us to believe that hyposthenuria is not the only mechanism. It is noteworthy that the presence of nephrogenic diabetes insipidus associated with polyuria (no response to DDAVP) has also been described. Nocturnal urinary osmolality in patients with SCD and enuresis is similar to that in non-enuretic children, so there may be a multifactorial etiology (5).

Hematuria

Hematuria is the most common complication in heterozygous patients (6). Although it may be seen at any age, it is more common in the third and fourth decades of life and it can also occur in older patients (5, 20). It is usually painless and self-limited (5, 8, 20). Interestingly, the left kidney is affected in 80% of cases, and this has been attributed to the greater length of the left renal vein and to the nutcracker phenomenon, which increases the relative hypoxia in the renal medulla (5, 6, 20, 22, 24).

Patients attending the emergency room on account of hematuria may have flank or abdominal pain, vomiting, and fever associated with infection or diffuse papillary necrosis (6, 20). They may also have severe anemia (8). Although hematuria is common in patients with SCD, other causes of hematuria should be excluded (6, 8, 20).

Urinalysis may show sickling of the red blood cells (8). The finding of erythrocytes, leukocytes, and sloughed papillae suggests renal papillary necrosis. Because these patients may come from areas where the prevalence of genitourinary tuberculosis is high, it is appropriate to look for acid-fast bacilli in urine (20) and it may be necessary to order blood cross-matching. When hematuria is present in a patient with undiagnosed but suspected SCD, a hemoglobinogram and a coagulation profile including D-dimer must be obtained to rule out intravascular coagulopathy (8, 20).

Given the fact that the hematuria is generally self-limited, treatment is conservative. Only bed rest, oral hydration, and control of the hematocrit are needed in most cases. If it is necessary to transfuse or the hematuria persists for more than a week, the patient should be hydrated with hypotonic fluids and bicarbonate and loop diuretics should be administered in an attempt to counteract the acidosis and dehydration causing the sickling phenomenon in the renal medulla (6, 8, 20). When these measures fail, intravenous DDAVP has been shown to reduce bleeding by increasing concentrations of factor VIII and von Willebrand factor, although there are few studies confirming its long-term usefulness (6, 11). Epsilon-aminocaproic acid (EACA) has been used because of its antifibrinolytic properties, but it has several adverse effects, including obstruction of the glomerular arteries, the renal pelvis, or the ureter by blood clots (6).

As a last resort, segmental embolization may be an option. The neodymium:YAG laser and holmium:YAG laser can be useful (6, 8). It must be
taken into account that in these patients, hematuria is recurrent and may appear later in the contralateral kidney, so partial or total nephrectomy should be a last resort (6, 8).

**Renal papillary necrosis**

The renal medulla and papilla are particularly vulnerable to ischemic necrosis owing to their hypertonic environment and the peculiar arrangement of their blood perfusion. Even in the healthy adult, there is a state of hypoxia owing to the low blood flow of the vasa recta. Thus, all conditions that reduce blood flow may cause ischemic necrosis of the medulla (29).

Renal papillary necrosis (RPN) may appear in 15%–50% of patients with SCD or sickle cell trait. RPN usually takes the form of subacute ischemic events and is most frequently diagnosed in an asymptomatic patient or during the evaluation of hematuria (8, 20).

In heterozygotes, RPN is more common between 30 and 40 years of age, but it is not unusual to see older patients as an initial presentation (8, 20). There seems to be no sex predominance in the onset of RPN. The clinical presentation is very variable: RPN may appear as macroscopic hematuria with or without renal colic or as acute urinary retention secondary to obstruction of detached papillae (8, 20). It may also present as a urinary tract infection or sepsis. After the onset of hematuria, patients may be asymptomatic until having a new episode years later (20).

Urinalysis may show detached papillae (20). Traditionally, excretory urography was the key to diagnosis, and today this is true of renal and bladder ultrasound and computed tomography (CT). Contrast CT in the excretory phase can be equally as useful as intravenous urography (29). An attempt should be made to use non-ionic contrast because it is less likely to cause sickle cell crisis than ionic contrast (8, 20).

Treatment of RPN in patients with SCD does not differ from that in patients with other causes of papillary necrosis. Aggressive antibiotic therapy is essential for infection and early intervention is required for urinary tract obstruction due to detached papillae. Manual bladder washing may be required, and a three-way bladder catheter may be used for continuous bladder irrigation in patients whose initial presentation was urinary retention. Other factors predisposing to the development of RPN, such as the use of anti-inflammatory drugs, should be avoided. The prognosis of RPN in heterozygotes is generally good (8, 20).

**Urinary tract infections**

Cumming et al. found in their study that the prevalence of asymptomatic bacteriuria in patients with SCD is approximately 10.9% (30). In heterozygotes there is likely to be a higher risk of asymptomatic bacteriuria, but not pyelonephritis. The organisms isolated in the urine cultures are the common pathogens of urinary tract infection (31).

An increased incidence of pyelonephritis has been identified during pregnancy in patients with SCD (20). Villers et al. found that pregnant women with SCD have an increased risk of pyelonephritis [OR 1.3 (CI 1.0-1.8, p=0.05)] and a higher risk of asymptomatic bacteriuria [OR 6.8 (CI 3.1-14.9, p=0.01)] (32).

**Priapism**

Priapism has been described as a complication of SCD since 1934 (33). The incidence in the normal population is approximately 1 in 100,000. In individuals with SCD, the possibility of developing an episode of priapism over life is between 29% and 49%. SCD is the most common cause of priapism in the pediatric population (34, 35). It accounts for approximately 67% of cases of priapism in children under 18 and about 20% of cases in the adult population, making it the single most common cause (33, 34).

Priapism is a true urological emergency. Low-flow priapism is more common in patients with SCD and it is supposed to be due to entrapment of sickle cells in the corpus cavernosum. This “trapped” and deoxygenated blood causes acidosis, which in turn worsens the sickling phenomenon (33). It has been proposed that hemolysis and vascular endothelial dysfunction also play an important role in the pathophysiology of this complication (19).

Most episodes occur during sleep, typically around 4 a.m., perhaps owing to the relative dehydration and acidosis that occur during the night. The loss of normal erectile function seems to be related to the duration of the episode of priapism (more than 4 h) and the age at which the first episode occurred (33).

Hydration, opioid analgesia, supplemental oxygen, and blood alkalization have been the
mainstays of treatment for sickle cell crises in general. One may also try to reverse priapism by intracavernous injection of alpha-adrenergic agonists such as phenylephrine, terbutaline, or epinephrine. These maneuvers should not, however, delay decompression of the corpora cavernosa to avoid irreversible ischemic damage and fibrosis. The surgical management of priapism includes cavernosaphenous and cavernospongiosum shunts or even the urgent placement of a penile prosthesis. These maneuvers should only be considered when all other measures have failed (33, 34, 36).

With regard to the prevention of new episodes, Rachid-Filho et al. have proposed the use of alpha-1-reductase inhibitors (finasteride). In their work, in a sample of 35 patients without controls, a mean reduction in the number of priapism episodes in a month was achieved, from 22.7 per patient at baseline to 2.1 at 120 days of treatment with finasteride (35). Abern and Levine proposed the use of ketoconazole and prednisone for the prevention of recurrent priapism. In a sample of eight patients, of whom two suffered from SCD, they concluded that this combination was well tolerated and that, under monitoring of serum testosterone, they were able to reduce the recurrence of priapism, preserving sexual function (37). Finally, Burnett and Bivalacqua have successfully used phosphodiesterase type 5 inhibitors to prevent episodes of priapism in SCD (34).

Sexuality and development

Zago et al. performed an observational study in a population of 125 patients with SCD in Brazil. They detected a delay in the development of secondary sexual characteristics in both sexes. However, comparison of adults and young patients demonstrated that despite delay of puberty, normal sexual maturation is achieved later in life in these patients (38). It is known, however, that basal testosterone levels are lower in patients with SCD. The cause is unknown. Hormonal studies indicate that the reduction is more likely due to primary testicular failure than to hypothalamic-pituitary-testicular axis failure (39-41). Seminal studies showed that ejaculate volume, sperm motility, sperm density, and normal sperm morphology were significantly reduced compared with controls (42).

Infarction and necrosis in the genitourinary tract

In addition to cases of papillary necrosis and renal infarction that are discovered after hematuria, isolated cases of hematuria secondary to bladder necrosis have been reported (43). Cases of testicular infarction, often repeated, have also been reported; usually such infarction goes unnoticed and it can cause hypogonadism and infertility and occur both in homozygotes and in heterozygotes (44).

Renal medullary cancer

Renal medullary cancer (RMC) is a very rare tumor that appears at a relatively young age, is very aggressive, and is almost exclusively related to the sickle cell trait. Prognosis is very poor despite surgical treatment and chemotherapy (5, 8, 45, 46). RMC represents about 2% of all primary renal tumors from 10 to 20 years of age (47). Its etiology is unknown, although recent genetic analysis seems to yield similarities between this tumor and the renal pelvis urothelium (8, 48).

RMC was first identified in connection with this disease in 1995 by Davis et al. (45), who described a sample of 33 patients collected over 22 years. All of the patients were black and they ranged in age from 11 to 39 years. Thirty-two were heterozygous for SCD and one for HbS and HbC (HbSC). No homozygote was reported (HbSS). At ages below 24 years, men were more commonly affected, with a ratio of 3:1, while above 24 years the frequency between the sexes was equal. At diagnosis, the tumor had an average diameter of 7 cm (45).

The most common symptoms at diagnosis are flank or abdominal pain, macroscopic hematuria with or without clots, and systemic symptoms related to metastatic disease. The tumor is located on the right side in 75% of cases (8, 47). The diagnosis of RMC must be considered in any young patient with sickle cell trait and hematuria.

Survival after surgery varies from 1 to 5 months (49). At the time of diagnosis it is not uncommon to find metastases in the lung, liver, mediastinum, or retroperitoneum and lymphatic, venous, or renal cortex invasion (45, 46). Selby et al. described the case of a young black man aged 21 years, a heterozygote for SCD, who was diagnosed with RMC on the basis of CT and had no evidence of metastasis. Radical nephrectomy was performed and the diagnosis subsequently confirmed by pathology. After 2 years of monitoring, the patient was free of tumor, suggesting the importance of early diagnosis. This is the longest survival described so far (50).

Yang et al. conducted a genetic study of the tumor, and found an overexpression of RNA for Topo II alpha. Recently the findings that the major gene
overexpressed in Wilms’ tumor is the Topo II alpha and that this tumor is sensitive to chemotherapy with inhibitors of Topo II alpha (actinomycin D, doxorubicin, and etoposide) suggest that these inhibitors may be effective as first-line treatments for RMC. The macrophage stimulating receptor 1 (c-met-related tyrosine kinase) is also overexpressed, suggesting a possible utility of inhibitors of tyrosine kinase (sorafenib, pazopanib, and sunitinib) in this disease. We have also found overexpression of genes related to angiogenesis, and antiangiogenic agents might be useful for the treatment of RMC (48).

**CONCLUSIONS**

SCD affects many organs and systems at an early age, significantly decreasing both the life expectancy and the quality of life of these patients. Furthermore, its incidence is increasing in Europe owing to miscegenation and immigration trends. The characteristics of this important disease and the multisystemic spectrum that it covers make knowledge of its genitourinary manifestations necessary.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)


