Sickle cell trait in orthopaedic surgery: A real issue or just a bogeyman

Background: Sickle cell disease is a hereditary blood disease characterized by the production of abnormal haemoglobin, HbS. HbS precipitates in the red cells under specific circumstances. The sickle cell trait (SCT), long considered an asymptomatic, condition, is instead associated with several complications. SC carriers are under physical stress more predisposed to develop certain morbidities such as pulmonary embolism, deep vein thrombosis, rhabdomyolysis and heat-associated collapse. An intense physical stress associated with the HbS carrier condition can lead to sudden death. Major surgeries, and especially orthopedic surgery, are physically stressful events. A targeted screening of high-risk patients could be useful for several advantages.

Introduction

Sickle cell disease

The sickle cell disease (SCD) is a hereditary blood disease characterized by the production of an abnormal haemoglobin, the sickle hemoglobin (HbS), due to a mutation in the β1-globine gene, in the short arm of the chromosome 11. HbS precipitates in the red cells under specific circumstances, forming polymers that distort the cells into the characteristic sickle shape: this process is known as sickling. Vaso-occlusion and hemolytic anemia are the major features of the sickle hemoglobinopathies. In sickle cell disease affected individual are either homozygous for the sickle hemoglobin (HbS) or compound heterozygous for the HbS and another beta globin mutation (HbC, HbS-β thalassemia). Several factors influence the susceptibility of red cells to sickle: the HbS and HbF concentrations, the HbS haplotype, and another beta globin mutation (HbC, HbS-β thalassemia). Other factors such as dehydration, infection, acidosis and hypothermia may increase red blood cell sickling [2]. Four main haplotypes, representing four different mutations have been identified (the Asian or Arabo-Indian haplotype, the Benin haplotype, the Senegal haplotype and the Bantu or CAR haplotype). The haplotype influences the sickle cell disease severity: the Bantu haplotype is associated with the most severe disease and the Senegal haplotype, with the least severe disease [2]. Bone involvement is the commonest clinical manifestation of sickle-cell disease both in the acute setting such as painful vaso-occlusive crises, and as a source of chronic, progressive disability such as avascular necrosis Figure 1 [3].

Sickle cell trait

The sickle cell trait (SCT), long considered an asymptomatic, benign condition, is instead associated with several complications [4]. The sickle-cell trait (SCT) occurs when a mutated Sβ1-globine and a normal βA-globin gene are inherited (HbAS). HbS carriers are approximately 300 million people worldwide [2], with the highest concentration in Africa, Middle East, India and the Mediterranean region. Recently its incidence has increased in Europe and North America because of the high rate of migration from areas in which the disease is prevalent [5]. Traditionally, sickle-cell trait has been viewed as a non-disease, partially protective against falciparum malaria [6], without any of the complications and symptoms characteristic of the sickle cell disease. Due to the almost completely asymptomatic nature of the condition sickle cell trait is generally a laboratory diagnosis. Hemoglobin
levels, red cell morphology, red cell indices, and
the reticulocyte count are entirely normal in
patients with sickle cell trait [7], and irreversibly
sickled cells (ISCs) are not normally present
in the peripheral blood smear. The diagnosis
of sickle cell trait is made by demonstrating
the presence of significant quantities of HbS.
Hemoglobin determination by high-pressure
liquid chromatography (HPLC) is the method
most commonly used to diagnose HbAS [8].
Although sickle-cell trait is a benign condition
in a majority of affected individuals, occasionally,
it can be associated with significant morbidity
and mortality. Increased red blood cell sickling
and polymerization can occur in sickle cell trait
under several conditions: severe tissue hypoxia,
acidosis, increased viscosity, dehydration, and
hypothermia. Several observational studies and
small case series [9-17] describe the morbidity of
sickle cell trait, and a recent review [2] grouped
the complications of sickle cells trait on the
basis of the strength and specificity of observed
associations. The complications are grouped as:
“definite”, “probable”, “possible” and “unproven
or unlikely”. The group of definite associations
includes: renal medullary cancer, hematuria both
microscopic and macroscopic, renal papillary
carcinoma, hyponatremia, splenic infarction,
exercise-related sudden death, exercise-related
rhabdomyolysis. Groups of probable and possible
comasorbidity include: venous thromboembolic
events (deep vein thrombosis or pulmonary
embolism), fetal loss, acute chest syndrome,
and proliferative retinopathy. Between the
unproven co-morbidity there are anemia, stroke,
higher prevalence of diabetic retinopathy and
albuminuria, leg ulcers, avascular necrosis of
the femoral head, and liver necrosis. The assignment
of complication into these groups was not based
on a systematic review of the literature and thus
the importance of some of the condition may
have been overrated and others may have been
underrated [18]. SC carriers are under physical
stress more predisposed to develop certain
morbidities such as pulmonary embolism, deep
vein thrombosis, rhabdomyolysis and heat
associated collapse. Several screening performed
on athletes and soldiers also report a much more
serious complication: an intense physical stress
associated with the HbS carrier condition can
lead to sudden death [19-22]. Major surgeries,
and especially orthopedic surgery, are physically
stressful events Figure 2. As far as the treatment
of hemoglobinopathies is of a medical nature,
the surgeon should be aware of the possible
complications arising from being HbS carrier.

SC clinical implication in major orthopedic
surgery

An increased complication rate of orthopedic
surgery in SCD compared with the general
orthopedic population has been reported in
the literature [23]. We have not been able
to find studies showing a higher incidence
of complication in major orthopedic surgery
in patients with SCT nevertheless adequate
knowledge of the condition and precautions to
avoid factors predisposing to red cell sickling
could contribute to the reduction in morbidity
and mortality theoretically associated with
surgery stress not only in SCD but also in HbS
carriers.

Importance of screening and research

The absence of a screening program of this almost
always asymptomatic condition, so widespread in
the world and more and more also in not typically
affected countries, can lead to an underestimation
of its frequency in patients undergoing surgery
for diseases not clearly linked to the SC trait.
Sickle cell trait in orthopaedic surgery: A real issue or just a bogeyman

Commentary

the diagnosis with standard electrophoresis; high-performance liquid chromatography (HPLC) can provide discrimination and relative quantification of hemoglobin, allowing for differentiation of SCT from SCD syndromes [29]. In clinical setting HPLC is the method most commonly used to diagnose HbAS [8] and has also been adopted for hemoglobinopathy screening by many reference laboratories owing to its ability to precisely quantify hemoglobin components [29]. Public education about SCT and SCD, accurate SCT testing, transparency of screening protocols and high-quality research initiatives are also mandatory to avoid some critical issue emerged in the past related to stigmatization and concern for social or occupational implications [29].

Conclusion

The SCT condition is not exempt from specific complications. Some of these complications occur as a result of physical stress and adverse environmental conditions. The literature does not report any special precautions for surgical patients with SC trait, but shows an increased complication rate in orthopedic surgery in sickle cell disease. Carrier status is widespread in the world, but for its frequent asymptomatic nature is often unknown by the patient. The patient’s unawareness of their state of HbS carrier and the lack of screening programs can lead to an underestimation of surgical complications actually associated with the SCT. Waiting for more significant studies on possible surgical complications of SCT, we recommend to perform targeted screening on patients from high-risk populations for this mutation. A more

Figure 2. Radiographic image of bilateral hip replacement with total hip arthroprosthesis for avascular necrosis of the femoral head in SCT.

An appropriate screening technique is mandatory to ensure accuracy and reliability of subsequent studies. The sickle solubility test detects the presence or absence of sickle hemoglobin, but cannot differentiate individuals with SCD and SCT and can be falsely negative in infants with high hemoglobin F or in individuals with very low percentage HbS (<10%); comigration of certain rare hemoglobin variants with HbS may obscure the diagnosis with standard electrophoresis; high-performance liquid chromatography (HPLC) can provide discrimination and relative quantification of hemoglobin, allowing for differentiation of SCT from SCD syndromes [29]. In clinical setting HPLC is the method most commonly used to diagnose HbAS [8] and has also been adopted for hemoglobinopathy screening by many reference laboratories owing to its ability to precisely quantify hemoglobin components [29]. Public education about SCT and SCD, accurate SCT testing, transparency of screening protocols and high-quality research initiatives are also mandatory to avoid some critical issue emerged in the past related to stigmatization and concern for social or occupational implications [29].

Conclusion

The SCT condition is not exempt from specific complications. Some of these complications occur as a result of physical stress and adverse environmental conditions. The literature does not report any special precautions for surgical patients with SC trait, but shows an increased complication rate in orthopedic surgery in sickle cell disease. Carrier status is widespread in the world, but for its frequent asymptomatic nature is often unknown by the patient. The patient’s unawareness of their state of HbS carrier and the lack of screening programs can lead to an underestimation of surgical complications actually associated with the SCT. Waiting for more significant studies on possible surgical complications of SCT, we recommend to perform targeted screening on patients from high-risk populations for this mutation. A more
complete clinical picture could lead to a greater awareness of risks and to a reduction of associated complications. The analysis of a greater number of data through adequately-powered studies in the future may lead to an evidence based management.

References