Hemoglobin C

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Abstract
Hemoglobin C (HbC) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamic acid for lysine at position 6 of the globin chain. Another amino acid substitution occurs at the same site of β globin causing the sickle cell hemoglobin (HbS). The prevalence of HbC reaches 40-50 % in West Africa (Burkina Faso, Ivory Coast, Ghana). The disease is also found in Togo and Benin (20%), in individuals of African descent in the Caribbean (3.5 %) and in the USA (3 %), in North Africa (1 to 10 % in Morocco and Algeria) and in Southern Europe (Italy, Turkey). Subjects heterozygous for HbC (AC) are asymptomatic and may present with a mild microcytosis with an increased red blood cell resistance to hemolysis. Subjects homozygous for HbC (CC) have usually compensated hemolysis with splenomegaly. There is an increased risk of hypersplenism, biliary lithiasis, folate deficiency and worsening of anemia following Parvovirus B19 infection. The association of HbC with β thalassemia, especially with β+thalassemia (more common than β0thalassemia in the ethnic groups concerned by HbC) results in a clinical picture similar to that of HbCC. Cβ0thalassemia is more severe and can exceptionally mimic beta thalassemia intermedia. Compound heterozygotes SC present with a sickling disorder similar to sickle cell anemia (SCA), although it is generally milder than in the SS form. However, 2 % of SC patients have more severe disease with frequent vasoocclusive crisis (VOC) and acute chest syndrome (ACS). Priapism may occur, mainly in adults. Aseptic necrosis of femoral heads and, in a lesser extent, of shoulders, and proliferative retinopathy with risk of vitreous haemorrhages are common complications of the SC genotype. Splenomegaly persists after 5 years, often in adulthood, leading to recurrent spleen infarcts or sequestration, hypersplenism. Pregnancy is associated with increased risk of VOC, ACS and toxaemia. Sudden hearing loss may occur, mainly after 30 years; recovery is function of early treatment (venesections, exchange transfusion). Corticosteroids may be dangerous (inducing VOC and ACS) and should not be used. Life expectancy is above 65 years. In SC, during childhood, prevention of pneumococcal infection is essential with prophylactic penicillin and pneumococcal vaccine at least until the age of 5 years. Parents should examine their children for splenomegaly and pallor, for early detection of splenic sequestration. Management of pain in VOC is symptomatic. Transfusion is required for acute anemia. Early detection of proliferative sickle cell retinopathy is required from 15 years and prophylactic scatter photocoagulation to avoid complications. Pregnancy requires regular antenatal care by obstetricians in collaboration with sickle cell specialist. Partial exchange transfusions are recommended during 3rd trimester to improve pregnancy outcome. Frequent VOC are treated with venesections to lower haematocrit. Recurrent stuttering priapism is treated with oral or self-injections of alphaagonists (etilefrine

or phenylephrine). Hydroxyurea may be indicated in patients with recurrent VOC and or ACS, or severe sensorineural complications.

Keywords
Hemoglobin C, *β globin gene*, hemoglobin C trait, hemoglobin C disease, hemoglobin C/βthalassemia, sickle cell/hemoglobin C disease

Disease name
Hemoglobin C (HbC)

Included diseases
Hemoglobin C trait, hemoglobin C disease, hemoglobin C/βthalassemia, sickle cell/hemoglobin C disease

Definition
HbC ($\alpha 2\ \beta 2^{6glu\_lys}$) is a variant hemoglobin with a mutation in the β globin gene causing substitution of glutamic acid for lysine at position 6 of the globin chain. Another amino acid substitution occurs at the same site of β globin causing the sickle cell hemoglobin (HbS). HbC may be present in the heterozygous state (genotype A/C or hemoglobin C trait), the homozygous state (CC or hemoglobin C disease) and a variety of compound heterozygous states, such as hemoglobin C/βthalassemia (C/βthal), sickle cell/hemoglobin C disease (SC genotype) which leads to a sickling disorder generally less severe than sickle cell anemia.

Diagnostic criteria and clinical description
HbC is determined by at least one allele carrying the beta 6 glu → lys mutation.

Hemoglobin C trait
Hemoglobin C trait is defined by the heterozygous condition associated with one normal adult hemoglobin (HbA) β gene and one variant HbC β gene.

Clinical features
This condition is totally asymptomatic and by itself unrelated to a sickle genetic condition.

Laboratory features
The hemoglobin level is usually normal but mild microcytosis is common. The mean cell hemoglobin concentration (MCHC) is usually higher than normal around the top of the normal range. Early light scattering appears with some impedance-type automated blood cell counters, as there is increased red blood cell resistance to hemolysis. Blood film shows some target cells.
Hemoglobin acetate electrophoresis at alkaline pH, isoelectric focusing or HPLC show that HbA represents more than 50% of hemoglobin and HbC slightly less. Coexistence with α thalassemia reduces HbC level (HbC<36 % with α+ heterozygous thalassemia, (-α/αα), HbC<30 % with homozygous α+ thalassemia, (-α/-α)).

Electrophoresis
On cellulose acetate electrophoresis at alkaline pH, HbC has the same mobility as the common hemoglobin variants E, A2, O Arab. Precise identification of HbC requires thus citrate agar electrophoresis (HbC can be separated from HbE and HbA2, which have the same mobility than HbA, and from HbO Arab, which has the same mobility than HbS). There is an almost specific profile of HbC on high performance liquid HPLC.

Chromatography
Combined cellulose acetate electrophoresis at alkaline pH, on citrate agar and/or HPLC allows to differenciate HbC from HbE, HbO Arab, HbC Harlem.

Hemoglobin C disease
HbC disease is defined by the coexistence of two βC alleles (homozygous state CC).

Electrophoretic profile
95% of total hemoglobin is HbC with the remainder being adult haemoglobin HbA2 (less than 4%) formed by the pairing of alpha and delta chains ($\alpha 2\ \delta 2$), and fetal Hb (HbF); there is no normal HbA.

Clinical and laboratory features
Individuals with HbC disease have usually compensated hemolysis or mild to moderate anemia. The spleen may be enlarged. Because of chronic hemolysis, there is an increased risk of cholelithiasis, folate deficiency and worsening of anemia with Parvovirus B19 infection (very rarely requiring transfusion). Some rare patients may have proliferative retinopathy as a consequence of microcirculation abnormalities. Blood film shows numerous target cells, occasional cells may contain straight -edged six sided HbC crystals.

Hemoglobin C βthalassemia
HbC may be co inherited with either β0 or β+thalassemia. β+thalassemia is more common

than β0thalassemia in the ethnic groups concerned by HbC. This compound heterozygous state is observed particularly in persons of African ancestry and is also reported in North Africa, Italy (Sicily) and Turkey.

Clinical features

Compound heterozygotes for HbC and βthalassemia have moderate to severe anemia with splenomegaly and sometimes hypersplenism, similar to homozygous HbC if the βthalassemia allele is β+. The clinical picture is more severe if the β thalassemia allele is β0.
Coinheritance of HbC and hemoglobin Lepore, δβthalassemia, or HbE leads to a clinically mild disease comparable to Cβthalassemia.
Association of HbC and HbO Arab leads to similar phenotype of HbC disease.

Laboratory features

The hemoglobin concentration varies from 8 to 10g/dl in HbC β0thalassemia, 10g/dl to normal values in HbCβ+thalassemia. Mean corpuscular volume (MCV) is markedly reduced; reticulocyte count is elevated. The blood film shows hypochromia, microcytosis, target cells and irregularly contracted cells; HbC crystals may be present.

Electrophoretic profile shows that the major hemoglobin is HbC with HbF between 2 to 10%. HbA is absent in the Cβ0thalassemia genotype, up to 30% in Cβ+thalassemia.

Sickle cell/hemoglobin C

Clinical features

The coinheritance of βS and βC genes leads to a sickling disorder similar to sickle cell anemia (SCA) but generally less severe than in the SS form. Chronic moderate hemolytic anemia is common but hemoglobin level may be normal; in this last situation, only reticulocytes are increased. Frequency of painful vasoocclusive crisis (VOC) and acute chest syndrome (ACS) is reduced in comparison with sickle cell anemia (SS disease) with more than 50% of patients experiencing no VOC. However, 2% of SC patients have more severe disease with frequent VOC. Pregnancy is associated with increased risk of VOC, acute chest syndrome (ACS) and toxemia, urinary tract infection. Priapism is not rare, occurring mainly in adults. Aseptic necrosis of femoral heads and, in a lesser extent, of shoulders, retinal disease (proliferative retinopathy with risk of vitreous haemorrhages) are common complications of the SC genotype. Splenomegaly persists after 5 years age, often in adulthood, leading to recurrent spleen infarcts or sequestration, hypersplenism.
Sudden hearing loss may occur, mainly after 30 years; recovery is function of early treatment: venesections to lower hematocrit and in case of failure, exchange transfusion. Corticosteroids may be dangerous (inducing VOC and ACS) and should not be used. Ischemic cerebral vascular accidents (CVA), with an onset mainly in adulthood, are essentially triggered by arterial hypertension. After 35 years, obesity is more common in SC form than in SS form and worsens chronic pains (osteonecrosis, spondylopathies).
Life expectancy was evaluated in multicentric study to be above 65 years. The coexistence of HbS Antilles and HbC leads to a more severe phenotype than HbSC that is comparable to homozygous SCA.

Laboratory features

The hemoglobin concentration is higher than in SCA, generally above 10g/dl, reaching sometimes 14-15g/dL in male adults. MCV is lower than in SCA, MCHC is more often elevated.
Sickle cells in blood film are uncommon, target cells numerous. HbS and HbC are present in similar proportions; HbF percentage is slightly elevated, affected by the β S gene carrying haplotype, averaging 3.2% with the Senegal haplotype, 1.5% with the Benin haplotype and 1.4% with the Bantu haplotype. Sickle cell solubility test is positive.

HbC and paludism

HbC like Hb S confers protection from malaria. Protection was found to be higher in CC homozygotes compared to AC heterozygotes, where infection is not prevented but the risk of developing severe malaria and severe anemia is reduced. Protection is stronger in heterozygotes SC for sickle cell disease.

Epidemiology

HbC is thought to have originated as a founder effect in West Africa, west of the Niger river. The prevalence of HbC is a high as 40 % in northern Ghana, up to 50 % on the North Ivory Coast, up to 40 % in Burkina Faso (where 2 % of whole population has SC disease), around 20 % in Togo and Benin, <1% in Central Africa, and inexistent in East Africa.
HbC is found in individuals of African descent in the Caribbean (3.5% prevalence), in the USA (3 % prevalence). There is also a significant incidence of HbC in North Africa (1 to 10% in Morocco and Algeria) and Southern Europe (Italy, Turkey).

Genetic Counselling

Identification of heterozygotes AC is of importance in counselling, due to the risk of

sickle cell HbC (SC) disease in the offspring if the other parent is heterozygote AS. However, SC is an indication for prenatal diagnosis, only if there is a familial history of severe SC disease and/or defective environment.

Management of sickle hemoglobin C

In SC, during childhood, prevention of pneumococcal infection is essential, like in SCA, with prophylactic penicillin given twice a day orally and pneumococcal vaccine until the age of 5 at least. Parents should be instructed to examine their children for splenomegaly and pallor, for early detection of splenic sequestration. Management of pain in VOC is symptomatic, mainly with paracetamol at home and morphine in cases of severe pain in hospital. Transfusion is required for acute anemia (spleen sequestration, erythroblastopenia caused by Parvovirus B19). Early detection of proliferative sickle cell retinopathy is required from 15 years and prophylactic scatter photocoagulation to avoid progression to vitreous haemorrhages and/or retinal detachment of uncertain prognosis. Pregnancy requires regular antenatal care by obstetricians experienced in the management of sickle cell disease, in collaboration with sickle cell specialist. Partial exchange transfusions are recommended during 3rd trimester to improve pregnancy outcome. Frequent VOC (or recurrent stuttering priapisms) are treated with association of oral etilefrine and venesections to lower haematocrit. Acute priapism should be treated promptly by direct aspiration of the corpora followed by injection of alpha agonist (etilefrine or phenylephrine). Hydroxyurea may be indicated in patients with recurrent VOC and or ACS, or severe sensorineural complications.

References

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