

STROKE IN SICKLE CELL DISEASE:MANAGEMENT AND PREVENTION

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THE CAUSES OF DEATH FROM SICKLE CELL ANEMIA

<u>CAUSES</u>	<u>Total death %</u>
1- Infection	44
2- Splenic sequestration	16
3- Sudden unexpected death	14
4- Cerebrovascular event	12
5- Congestive heart failure	7
6- Unknown	7

HAPLOTYPES IN SCA

- 1-BENIN TYPE-Haplotype 19 (Middle
-West Africa)
- 2- ALGERIA (Arabic North Africa)
- 3-CAR(Central african Republic)
- 4- SENEGAL (Atlantic West Africa))

- **In Çukurova Region, most of the SCA patients have haplotype 19 (%80).**

Alouch JR, Kılınc Y, Aksoy M, Yüreğir GT, Bakioğlu I, Kutlar A, Kutlar F, Huisman THJ. Sickle cell anemia among Eti-Türks:hematological, clinical and genetic observations. British J Haematol 64:1, 45-49, 1986

PROGNOSIS IN SICKLE CELL DISEASE

- MORE THAN 50% OF THE CASES LIVE BEYOND 50 YEARS. MOST OF THE DEATHS ARE NOT DUE TO THE RESULT OF CHRONIC ORGAN FAILURE BUT AS A RESULT OF THE ACUTE PAINFULL CRISES, CHEST SYNDROME OR FROM THE STROKE.

PREDISPOSING FACTORS for STROKE IN SICKLE CELL DISEASE

- As an isolated event,
- Pneumoniae,
- Aplastic crisis,
- Viral diseases,
- Painfull crises,
- Priapism,
- Dehydratation.

EPIDEMIOLOGY

- The frequency of significant stroke is 221 times more and total frequency of all stroke attacks is 440 more in SCD patients.
- Significant stroke frequency is;
 - 11% in first 20 years of life
 - 24% at 45 years.
- In childhood, stroke is most frequent in 2-5 years and 6-9 years

STROKE

- **ISCHEMIC**
 - Silent stroke
 - Significant
- **HEMORRHAGIC**
 - Significant stroke

- **SIGNIFICANT**
 - Ischemic
 - Hemorrhagic
- **SILENT**
 - Ischemic stroke

SIGNIFICANT STROKE

- Hemorrhagic strokes are occurred generally in adulthood, but ischemic strokes are more frequently seen in childhood.
- Hemorrhagic stroke is originated from newly developing collateral vessels (Moya moya)
- The death may be the result of hemorrhagic stroke, but is is very rare after ischemic stroke.

SILENT STROKES

- NEUROIMAGING ABNORMALITIES MAY BE SEEN WITHOUT SIGNIFICANT CLINICAL FINDINGS IN CHILDREN WITH SICKLE CELL DISEASE.
- If there are neuroradiological abnormalities without clinical findings, it is recognized as SILENT STROKE.

SILENT STROKES

- The prevalence of silent strokes changes 17-35% in childhood SCD.
- MR equipments with more higher resolution, diffusion and perfusion and recent new techniques in MRI, reported cases are increased.

SILENT STROKES

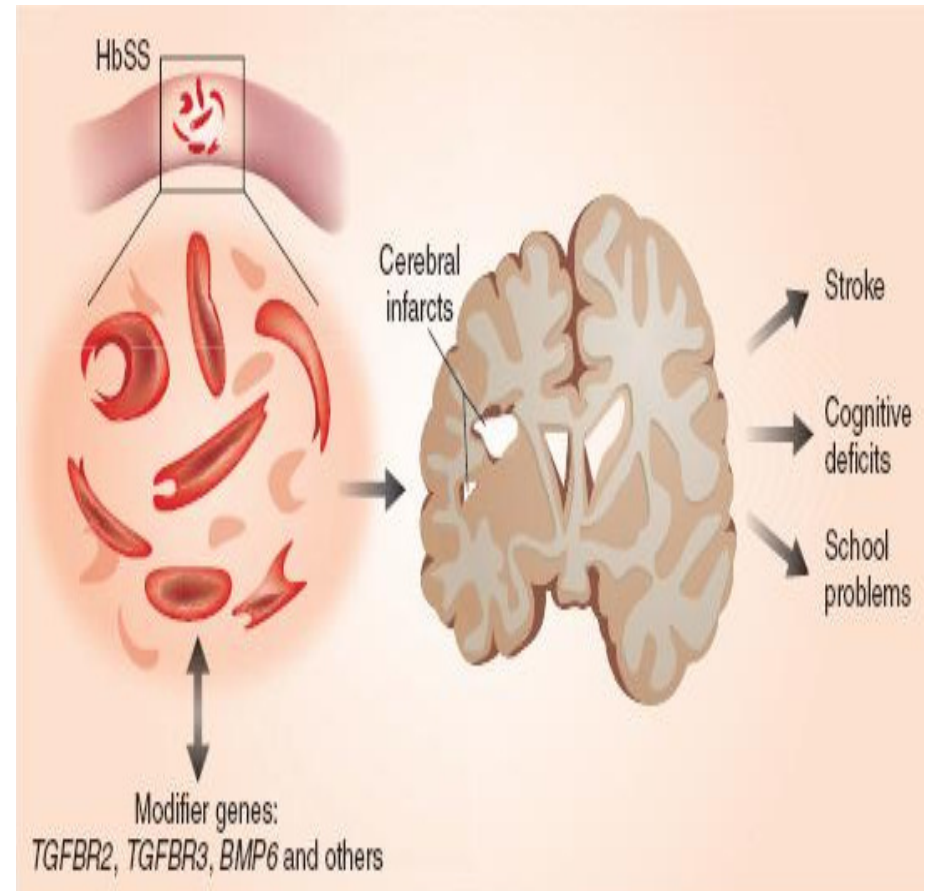
- The children with silent strokes are more prone to new strokes than the children with physiologically normal .
- The silent strokes are located mostly in Frontal lobe(borderzone strokes).
- The cognitive processes are more disordered in the children with silent stroke.

GENETIC PREDISPOSITION

- The phenotypic variations in SCA children is dependent to the functions of regulatory genes.
- In addition to this, the presence of the story with stroke in the past history of the family means genetic factors play some roles in occurrence of stroke.

Genetic predisposition

- Nomininee genes are related with;
- -adhesion of the endothelial cells,
- -inflammation,
- -thrombosis.
 - VCAM1-G1238C
 - IL4R-503P
 - ADRB2-27E ve TNF(-308)G
 - IL4R-503P ve TNF(-308)G
 - LDLR-Nco/variant
 - Some alleles of the angiotensin genes.
 - TGFBR2, TGFBR3and BMP6 related mutations



THE PATHOGENESIS OF STROKE

- Responsible Factors:
 - The relation between sickled red blood cells and vessel endothelium,
 - Revascularization (reperfusion) disorder
 - Procoagulant status
 - Hemolysis

VESSEL ENDOTHELIUM & SICKLED RED BLOOD CELLS

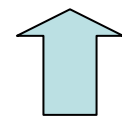
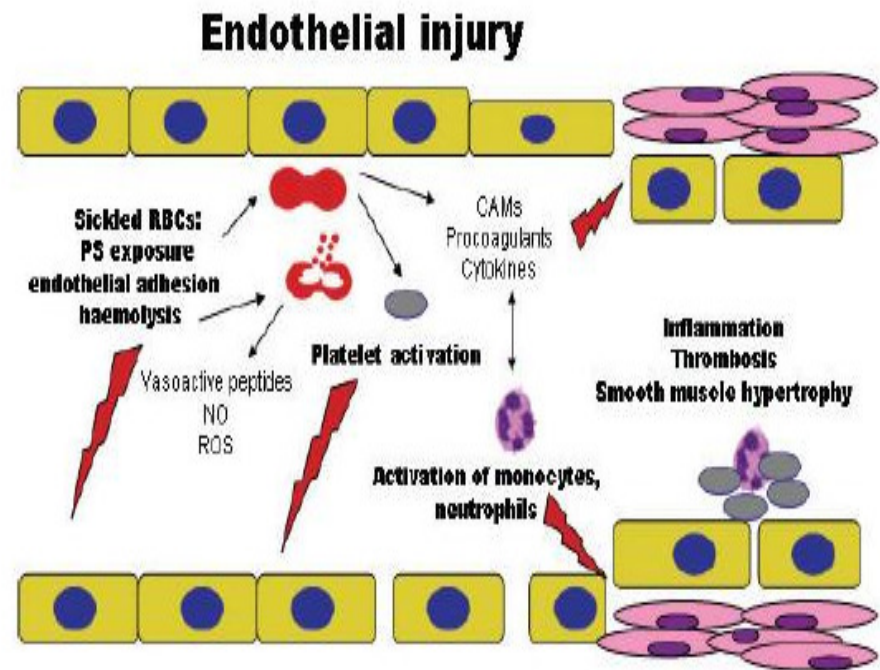
- The sickled RBCs are more dense and less flexible by the polymerization of HbS in microcirculation.
 - Sickled RBCs are more adhesive to vessel endothelium approximately 20 times more than normal.
 - This situation causes prolonged transit time of the sluggish RBCs and vessel occlusion.

VESSEL ENDOTHELIUM & SICKLED RED BLOOD CELLS

- Sickled RBCs;
 - Stimulates transcription factors (NF- κ B),
 - Causes to secrete endothelin-1 and as a result inhibits the relaxation of vessels.
 - Causes to increase the expression molecules (VCAM, ICAM) at vessel endothelium.
- The interaction between WBCs and endothelium is either by means of linkage proteins (trombospondin) or direct binding (P-selektin, VCAM) .

VESSEL ENDOTHELIUM & SICKLED CELLS

- Although it is not probable that the single important mechanism could be responsible for the adhesion.

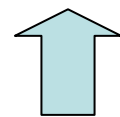


Reperfusion Damage

- The repetitive vessel occlusions and reperfusion occurs in SCA.
- It could be possible that reperfusion damage plays an important role for vessel injury in SCA.

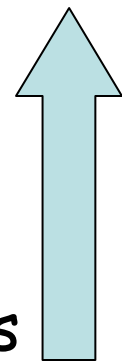
Reperfusion Damage

- The reperfusion activation by NF- κ B and increased leucocyte adhesion causes excessive inflammatory response.
- Free oxygen radicals synthesized during reperfusion interacts with endothelial NO and stimulates the occurrence peroxy nitrite. Peroxy nitrite has toxic effect and increases the tonus of the vessel.



Prokoagulant Status

- Tissue factor expression is increased by the interaction of the endothelium and monocytes and macrophages.
- The marker parameters of the invivo coagulation and thrombolysis during vaso-active crises are:
 - Trombin-antithrombin complex,
 - Active prothrombin particles
 - D-dimers
 - The level of the plasmin-antiplasmin complexes
 - Protein C and Protein S
 - .



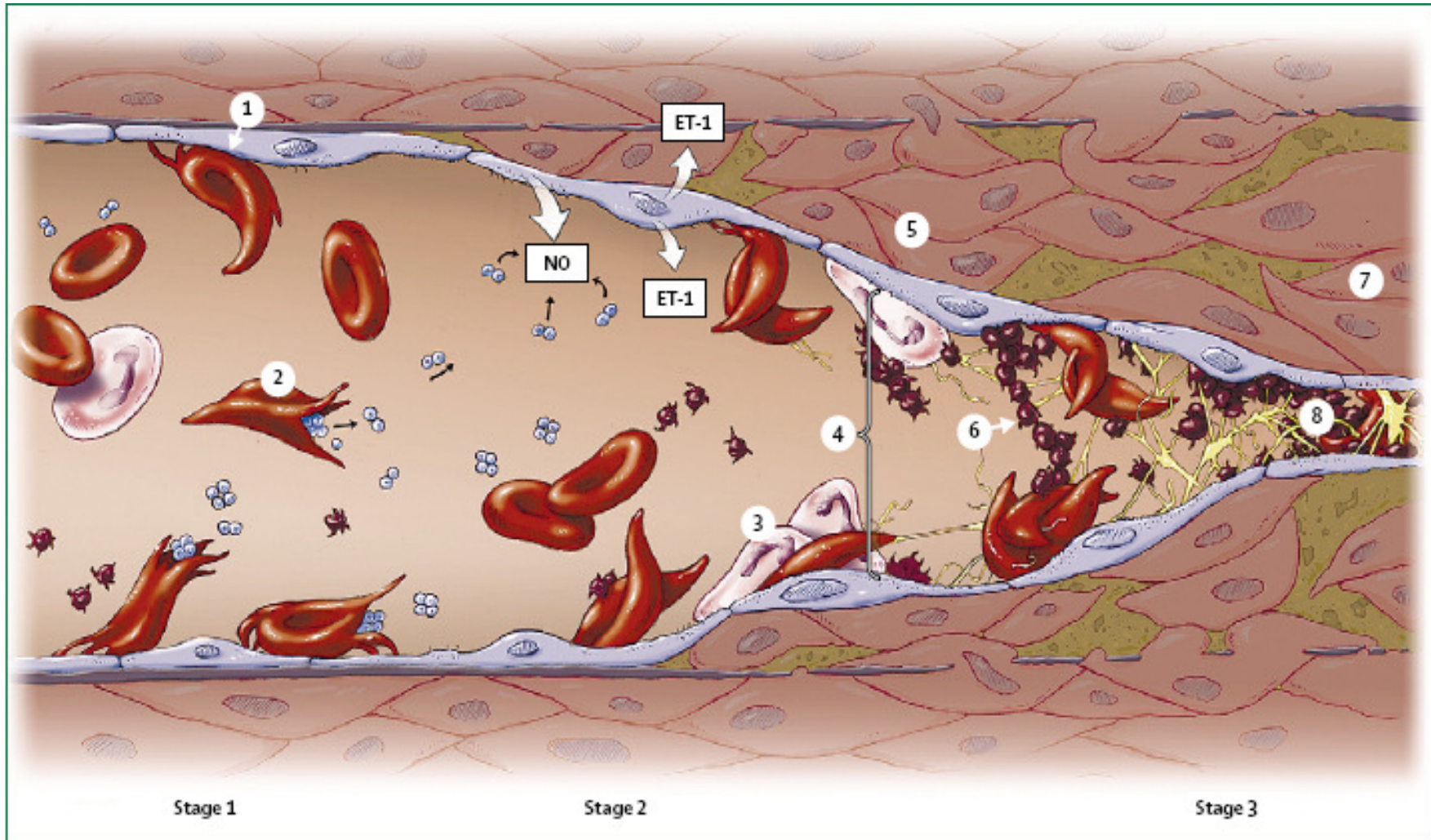
Hemolysis

- The presence of free Hb in vessels causes NO to convert nitrate and metHb and inactivates NO.
- The amount of NO is decreased during acute or chronic hemolysis.
- This situation causes to vasoconstriction, activation of platelets, activation of the endothelium and coagulation.

The most frequent laboratory findings in hemolysis in SCD

- Reticulocytosis(polichromasia)
- Indirect bilirubinemia
- Increased urinary and fecal urobilinogen
- Decreased serum HAPTOGLOBIN
- Decreased serum HEMOPEKSIN
- Increased serum methHEMALBUMIN
- Increased LACTIC DEHYDROGENASE(LDH)
- Increased ASPARTAT TRANSAMINAZ(AST-SGOT).

Patogeneze



Lesion in STROKE

- The stenosis or obstruction of the Intracranial artery (Generally A. Carotis),
- Mostly Proximal Middle Cerebral or Anterior Cerebral Arteries are involved.

THE PATHOLOGY OF THE STROKE

- The endothelium of the vessels are injured chronically by the sickled cells. The intimal bulging and narrowing of the lumen of the vessel wall superposes by means of the proliferation of the fibroblasts and smooth muscle. The lumen is narrowed by the vascular lesion or totally obliterated by sickled RBCs and finally causes to acute infarksiyona yol açar.

The Determination of the Risk of STROKE

- The important indicator for the stroke is the presence of increased velocity of blood more than 200m/sec at MCA or dCA by TCD.
- It is shown that the increased bulbar conjunctival flow rate determined by CAIM (*computer assisted intravital microscopy*) shows paralellism to the velocity rate at MCA by TCD .
- This situation supports the idea of small vessel disorder is an indicator of large vessel disease.

Risk factors in SCD

- Clinical risk factors
 - Past history of stroke in family members,
 - Suffering from silent stroke,
 - The experience of acute chest syndrome associated with hypoxia.
 - Night hypoxia with or without apnea,
 - Acute hemolytic attack by the decrease of Hb levels more than 2g/dl of normal,
 - Systolic hypertension
 - Cognitive disorders

Risk Factors in SCD

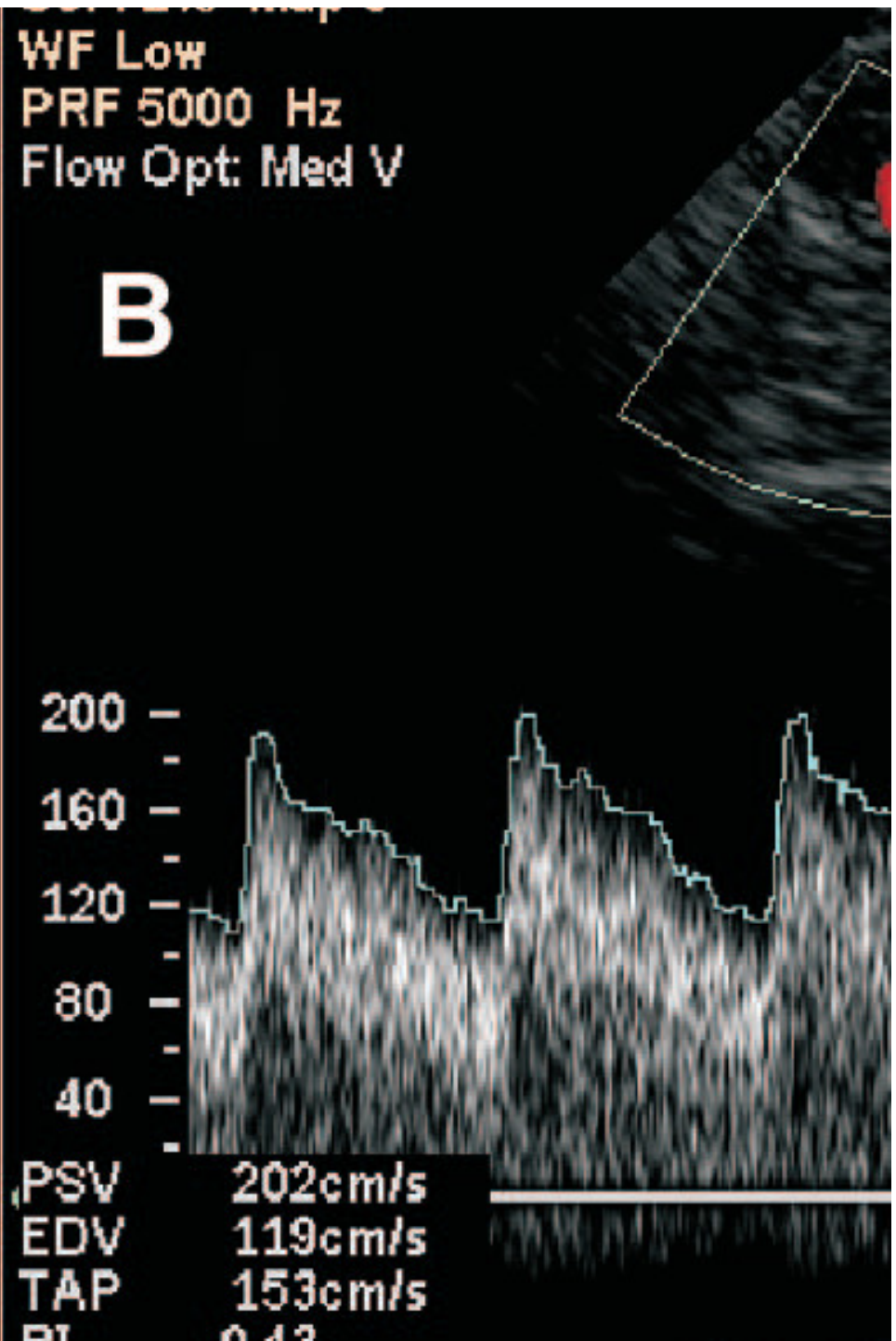
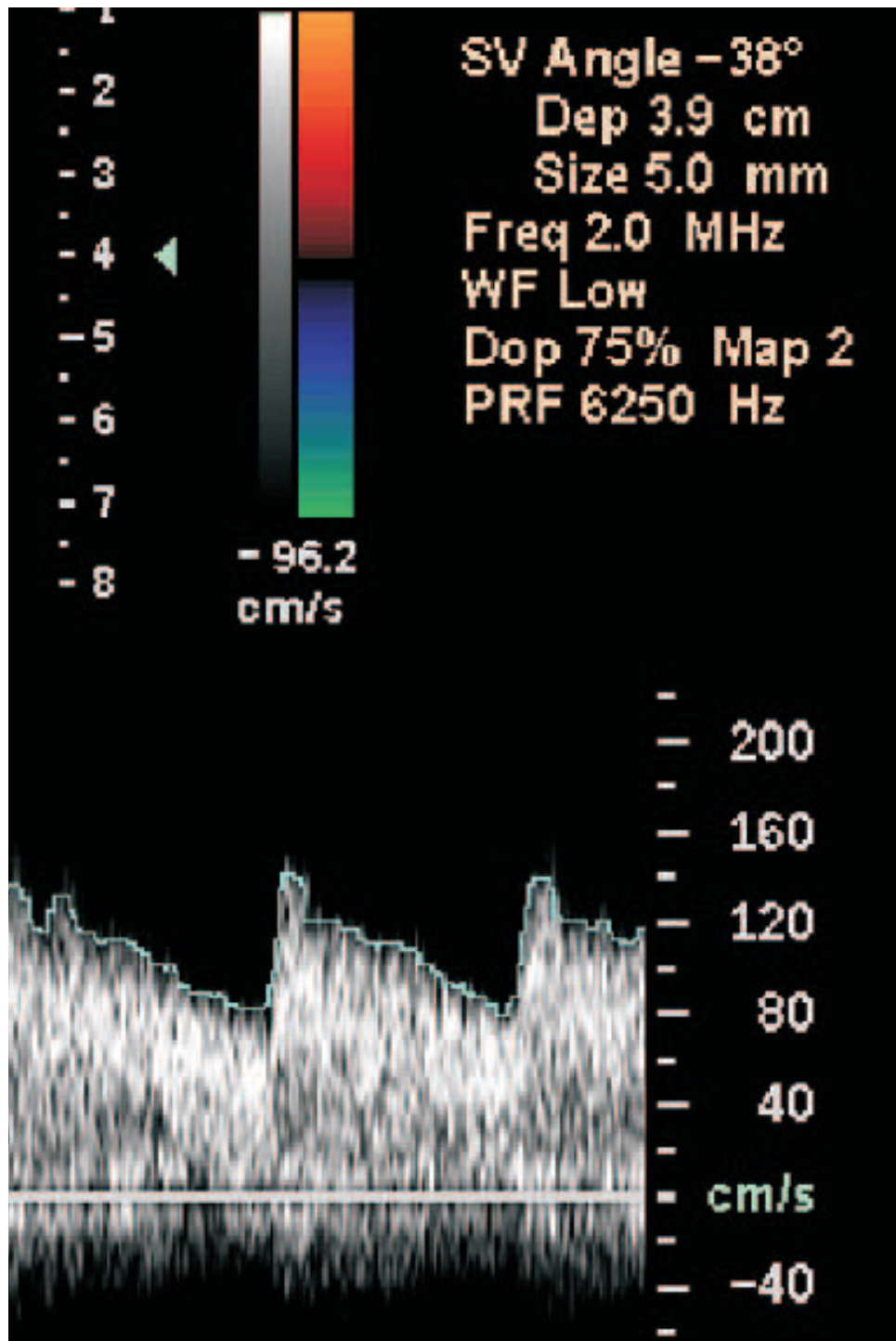
- Laboratory risk factors:
 - Hb levels less than 7.5g/dL associated with high reticulocyte count,
 - WBC counts $> 15 \times 10^9$
 - Platelet counts $> 450 \times 10^9$
 - Hb F levels less than 13% at 2 years,
 - Absence of association of α -thalasemi trait situation,
 - DPBI*0401 HLA sub type
 - HLA-A*0102, HLA-A*2612

The Manifestations of Stroke

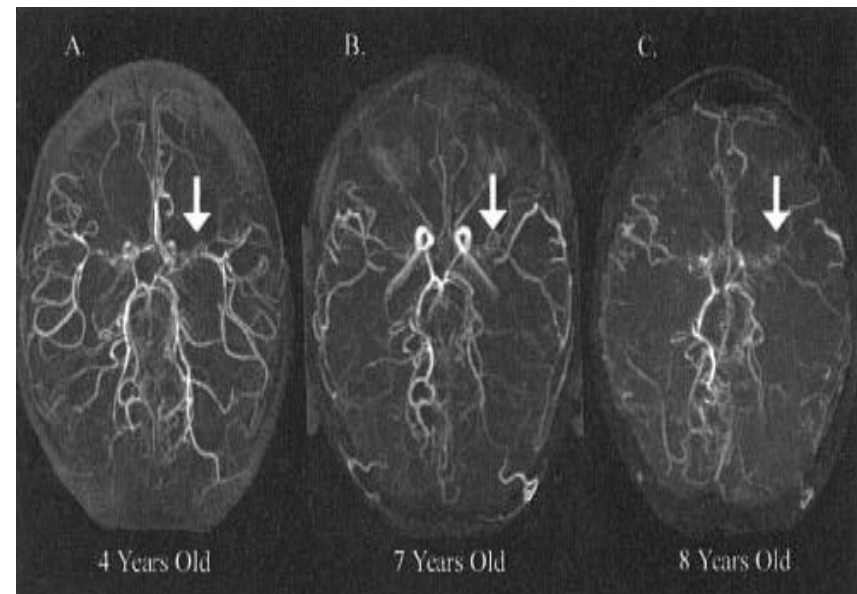
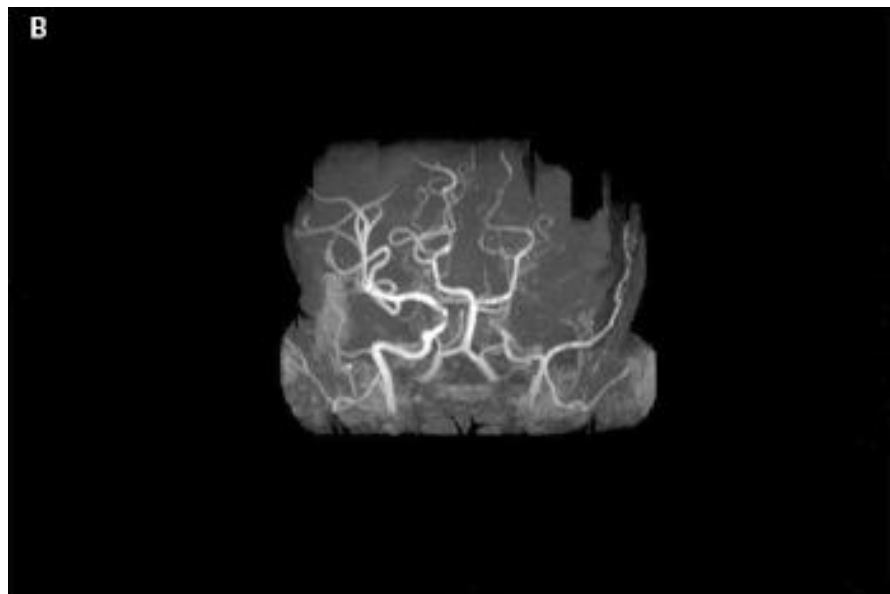
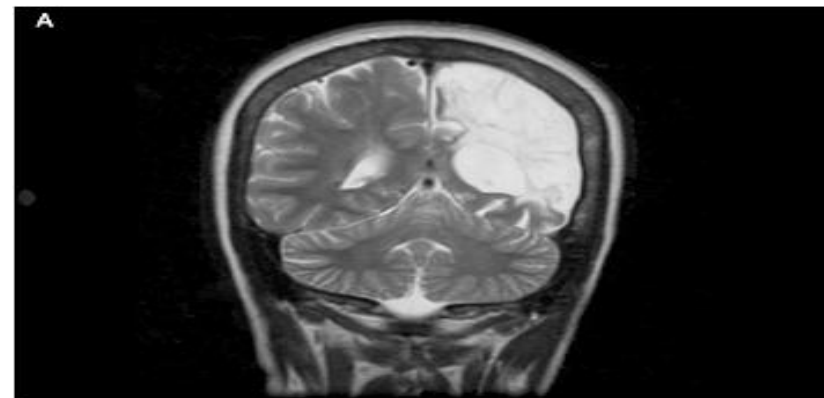
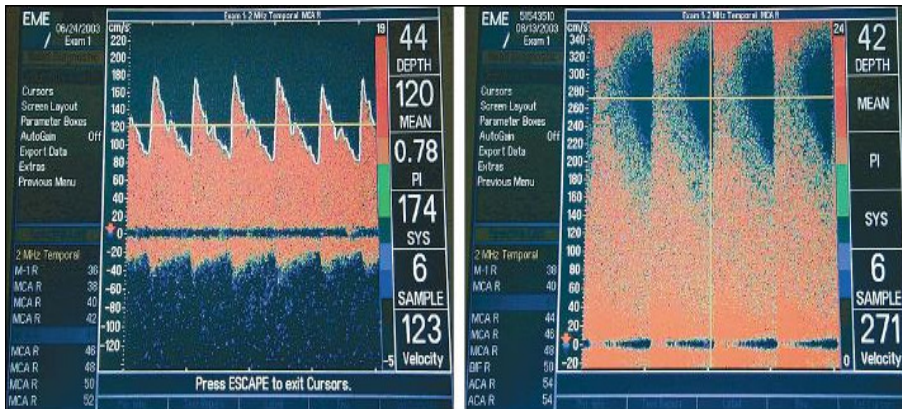
- HEMIPARESIS,
- SPEECH DIFFICULTIES,
- FOCAL SEIZURES,
- GAIT DISTURBANCES

STROKE TANISI

- BİLGİSAYARLI TOMOGRAFİK TARAMA(lezyonun ilk 6 saatinde infarkt için + sonuç vermeyebilir).
- MANYETİK REZONAN GÖRÜNTÜLEME (Stroklı hastaların %90'ında 2-4 saatte anormalleşir).
- MANYETİK REZONAN ARTERİYOGRAFİ (intrakranyal ve servikal damarlar hakkında bilgi edinilir).



NEUROIMAGING IN SCD



TREATMENT of STROKE

- EXCHANGE OF RBCs (limits the amount of sickled RBCs in regions of vdisordered perfusion; prevents the complications during arteriography by hypertonic solutions.
- REGULAR TRANSFUSION PROGRAMME,
- HYDREA THERAPY,
- STEM CELL TRANSPLANTATION.

HYDREA THERAPY IN SCD

- HYDREA(Hydroxyurea) increases fetal hemoglobin synthesis but limits the synthesis ability of bone marrow.
- Because of the decrease especially of the granulopoiesis, the granulocyte and platelet counts must be performed in 2 weeks intervals.
- The effect of HYDREA will appear after months, so the patients must be followed carefully.

HYDREA tek başına anemi semptomlarını
düzelterek sık transfüzyon gereksinimini
azaltabilir.

- HYDREA+Rh EPO ve demir desteğiyle bazı hastalarda HbF düzeylerini belirgin arttırabilir. HbF içeren eritrositlerin yapımını arttırarak , eritrosit içi HbS oranını, dolayısıyla hemoglobin polimerizasyonunu azaltır.

THE HYDREA THERAPY

- DECREASES PAINFULL CRISES,
- DECREASES THE FRQUENCY OF ACUTE CHEST
- DECREASES TRANSFUSION REQUIREMENT,
- DECREASE MORTALITY,
- HEMOLYSIS

THE ADVERSE EFFECTS OF HYDREA THERAPY

- Transient decreases and fluctuations of count blood cells,
- The risks of prolonged hydrea therapy,
- Miscellaneous teratogenic effect of Hydrae.

THE PREVENRION OF SICKLE CELL DISEASE

- To motivate the pairs to prenatal diagnosis if both are trait,
- To educate the people in productive ages and screening programmes,
- To educate the population,
- Screening before marriages,
- To educate teenagers in schools.