Problems in Management of Subarachnoid Hemorrhage in Sickle Cell Anemia

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The purpose of this paper is to report problems of diagnosis and management in a case of subarachnoid hemorrhage from intracranial aneurysm in a patient with known sickle cell anemia. In addition, the results of an in vitro experiment dealing with one of these problems, the effect of contrast media on the sickling phenomenon, are presented.

Sickle cell anemia is an hereditary and familial form of chronic hemolytic anemia peculiar to negroes, and occurring in 0.3 to 1.3 per cent of various groups of negroes examined. The incidence of the sickle cell trait varies somewhat among negroes in different parts of the United States (from 8.5 to 13.4 per cent). Though not sex linked the abnormality is somewhat more common in females.

Clinically this form of anemia is characterized by rheumatoid manifestations, leg ulcers, and acute attacks of pain. It is distinguished morphologically by the presence of peculiar sickle-shaped and oat-shaped red corpuscles, as well as signs of excessive blood destruction and active blood formation.

Neurological manifestations consisting of drowsiness, headache, nuchal rigidity, stupor or coma, hemiplegia, aphasia, convulsions, irritability, nystagmus, pupillary changes, blindness, cranial nerve palsies and paresthesias of the extremities are frequent. The lesions in the central nervous system are most often due to thromboses precipitated by the sickling phenomenon, but subarachnoid hemorrhage may also occur. Depending upon the type of central nervous system lesion resulting from the sickling phenomenon, the cerebrospinal fluid may be normal or under increased pressure, with xanthochromia, sickled erythrocytes, and elevated protein.

Seventeen different inherited variants of normal hemoglobin have been recognized. The most common one, hemoglobin S, is present in sickle cell anemia. The basis of the sickle cell phenomenon is the very low solubility of hemoglobin S in the deoxygenated form. It has been shown that the low arterial oxygen saturation in sickle cell anemia is due to two factors: (1) an increased alveolar arterial oxygen tension gradient; (2) an abnormal oxyhemoglobin dissociation curve. The high viscosity of blood with low oxygen saturation has been demonstrated to be an important factor in the production of the thromboses commonly seen in this disease. Thrombotic processes in the lower leg which result in chronic skin ulcers may be explained by the concurrence of sickling and low temperature causing excessively high blood viscosity. Lowering of the blood pH has also been shown to contribute to the formation of sickle cells.

Case Report

The patient was a 36-year-old negro school teacher and housewife, admitted on December 27, 1962, 24 hours after a subarachnoid hemorrhage verified by lumbar puncture at another hospital.

Past Medical History. Sickle cell anemia was first diagnosed in 1949, and the patient had been hospitalized on numerous occasions since that time for evaluation and blood transfusion. She had experienced repeated episodes of venous thrombosis of the arms and severe chronic pyelonephritis. Previous surgery included cholecystectomy and appendectomy. She had been married for 6 years and had had no children.

Examination. The blood pressure was 130/75; pulse, 76; temperature, 100.4°. Positive physical findings included scleral icterus, slight nuchal rigidity, and a Grade II harsh systolic murmur over the precordium. She was right handed.

A positive sickle cell preparation was obtained...
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using the sodium bisulfite technique. The reticulocyte count was 40.8 per cent; hematocrit, 22 per cent; hemoglobin, 7.4 gm.; and the white cell count was 16,000/mm. with a normal differential. The platelet count was adequate. Serum electrolytes were normal and the blood urea nitrogen was 8 mg. per cent. The cerebrospinal fluid was xanthochromic and the cell count was 1,725 white blood cells and 125,000 red blood cells/mm. The cerebrospinal fluid sugar was 104 mg. per cent, and the spinal fluid protein was 80 mg. per cent.

Course. The morning after admission, the patient became semicomatose and was found to have a left hemiplegia and left hemianopia. Reflexes were normal and sensation was intact. A carotid arteriogram demonstrated a right middle cerebral artery aneurysm. An emergency right frontal craniotomy was performed and the aneurysm was clipped. The postoperative course was uneventful and at the time of discharge on January 9, 1963, the patient was neurologically intact with the exception of a resolving left hemiparesis and left homonymous hemianopia.

Follow up has continued over a period of 2 years; during this time the patient has remained neurologically intact and has continued to teach school without difficulty.

Comment

A review of the literature revealed an almost identical case10 reported in 1942 in which subarachnoid hemorrhage was assumed to be due to sickle cell anemia with hemolytic crisis. At autopsy, four days following the onset of symptoms, a ruptured left middle cerebral artery aneurysm was found.

The diagnosis of subarachnoid hemorrhage in the present case was made on the basis of the history and confirmed by spinal puncture. Establishing the correct etiology of the hemorrhage presented a diagnostic problem, since bleeding secondary to the sickling phenomenon or to rupture of an intracranial aneurysm were equally good possibilities. Differentiation between these two disease processes required cerebral arteriography, but this was not done initially because of the unknown effect of contrast media on the sickling phenomenon. Evidence of a second hemorrhage, and deterioration of the patient's neurological status, justified the possible additional risk of carotid arteriography, which demonstrated an aneurysm of the right middle cerebral artery (Fig. 1). The patient received a total of 16 cc. of Hypaque 50 per cent in 2 separate injections of 8 cc. each. Injections were made into the right common carotid artery. The arteriogram was well tolerated and there was no evidence of clinical change to suggest further sickling.

In view of the evidence of a second subarachnoid hemorrhage within 36 hours, it was decided to clip the aneurysm through an immediate direct approach by right frontal craniotomy.

Problems of Management. Preparation for operation posed such problems as selection of the proper anesthetic agent, the use of urea, and the use of hypothermia. Because of the increased sickling which occurs with hypoxia and with lowering of the blood pH due to build-up of CO2, adequate oxygenation during anesthesia was vital. A gaseous mixture of nitrous oxide and oxygen was used with careful maintenance of the oxygen volume at 30 per cent. Controlled hyperventilation was also used. Prior to clipping the aneurysm, the systolic blood pressure was dropped briefly to 70 mm. Hg with Arfonad.

Urea was not used to facilitate operative exposure because its effect on the sickling phenomenon was not known. Because of the hypertonicity of urea it was thought that additional sickling might occur with its use. A rapid review of the literature prior to operation yielded no information which fully answered this question. Recent investigative work has shown11 that urea does not produce sickling when mixed with sickle cell blood in vitro, probably because urea crosses the red cell membrane freely and exerts no noticeable osmotic effects.

Use of hypothermia to reduce the oxygen requirement of brain tissue during clipping of the aneurysm was considered. It also received consideration because of its effect in shifting the oxygen dissociation curve of hemoglobin and thereby reducing the percentage of sickle forms. However, because of evidence12 indicating a marked net increase in the viscosity of the blood with lowered body temperature, hypothermia was not used.
The additional problem concerning the effect of Hypaque on the sickling phenomenon remained unanswered. Even though no apparent complication arose during arteriography in this case, further investigation of this question was considered necessary. A recent study by Perillie and Epstein demonstrated that sickling does occur in vitro when blood is mixed with hypertonic saline, sucrose, and mannitol. This is true of blood from patients with S-S, S-C and some A-S hemoglobinopathies. The percentage of sickle forms appeared to vary with osmolality of the hypertonic solution and the amount of S hemoglobin present. The possibility that Hypaque and other hypertonic contrast media might also cause sickling was entertained. The following in vitro experiment was done to answer this question.

Experimental Technique

Venous blood was taken in oxalated tubes from a series of negro patients with known hemoglobinopathies (Table 1). This series included 5 patients, with proven sickle cell anemia (S-S) 1 with sickle-cell hemoglobin C disease (S-C) and 2 with sickle-cell trait (A-S). The type of hemoglobinopathy in each case had been determined by hemoglobin electrophoresis.

All tests were done at room conditions for temperature and oxygen. Blood from each patient was drawn into a standard erythrocyte counting pipette and diluted 200 times with normal saline. The mixture was shaken vigorously. A drop of the suspension was placed in a hemocytometer and examined under high power for sickle cells. In Cases A and C (Table 1) approximately 3 per cent of

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<tr>
<td>A</td>
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TABLE 1

Type of hemoglobinopathy in experimental bloods used
progressive dilutions of Hypaque, and in most cases with concentrations of 5 per cent Hypaque, only 2–3 per cent of the cells were the erythrocytes were observed to be sickled. In the remaining cases some elongated red cells were observed (Fig. 2a), but no true sickle cells. The experiment was then repeated using Hypaque 50 per cent as the test solution rather than saline. Marked sickling was observed in the case of each sickle cell anemia (S-S hemoglobin) blood sample (Fig. 2b). The percentage of sickle cell forms in each case varied from 30 to 40 per cent. Identical preparations were then made using Hypaque in various dilutions with saline. The percentage of sickle cells decreased with sickled (Fig. 3). Fig 2c shows sickling produced with 20 per cent Hypaque in Case C (Table 1). When S-C hemoglobin blood was mixed with Hypaque 50 per cent, approximately 20 per cent of the erythrocytes assumed the sickle shape. No sickling was observed in either of the A-S hemoglobin bloods tested.

The experiment was repeated using Conray 60 per cent and Conray “400”. A higher percentage (50 per cent) of sickle cells occurred with maximum concentration of

Fig. 2. a. Erythrocytes from patient C in Table 1 suspended in normal saline, ×250. b. Erythrocytes from same patient suspended in Hypaque 50 per cent, ×250. c. Erythrocytes from same patient suspended in Hypaque 20 per cent, ×125.
these solutions than with Hypaque 50 per cent.

The osmolality of blood is 283 ± 11 mOsm/L. Using freezing point depression determinations the osmolality of Hypaque was found to be 1,440 mOsm/L for a 50 per cent solution and 434 mOsm/L for a 5 per cent solution. By calculation a 3.5 per cent solution of Hypaque was found to be isotonic. This finding is in agreement with the sickling curve shown in Fig. 3.

The effect of Urevert (lyophilized urea and Travert) on each of the sickle cell bloods was determined using the same technique which has been described. No sickling was observed; this is in agreement with studies previously reported. Hypaque is a buffered solution with a pH between 6.5 and 7.5. The Hypaque used in this experiment proved to have a pH of 6.8. Because of the possibility of increased sickling in an acid solution, the study was repeated with Hypaque dilutions using a .05 molar phosphate buffer solution rather than saline. The resulting Hypaque solution had a pH of approximately 7.4. No change in the percentage of sickled forms was evident with the more basic test solution.

In each phase of the experiment accurate cell counts were technically difficult to obtain because of the layering of cells in the viscid contrast media. Fig. 3 therefore represents only an approximate number of sickle forms at each dilution of Hypaque.

Discussion

Experience with the present case suggests that subarachnoid hemorrhage occurring in patients with sickle cell anemia should be investigated by angiography. In vitro data show that the sickling phenomenon does occur when hemoglobin S-S and hemoglobin S-C blood is mixed with contrast materials. This sickling is a function of osmolality of the solution and occurs whenever the osmolality exceeds that of the blood, the latter corresponding to a 3.5 per cent solution of Hypaque.

It must be assumed that sickling may also occur in vivo after injection of the contrast media tested if the relative concentration is great enough. With slow intravenous injection, as for intravenous urography, it is doubtful that the concentration of dye is sufficiently high to result in sickling. With rapid intra-arterial injection of these agents, sickling may very well occur.

The quantity of Hypaque 50 per cent in the common carotid artery during carotid arteriography has been shown to reach 55 per cent by volume in whole blood. Additional study by the same investigators revealed that the amount of Hypaque in the blood passing through the jugular bulb during common carotid arteriography ranged from 6 to 11 per cent by volume.

Present data suggest that the volume of contrast material for individual injection should be minimized to an amount consistent with adequate visualization of the aneurysm. In addition, dilution of the Hypaque should lower the percentage of sickle cells formed.

The sickling phenomenon which occurs with hypertonic solutions in vitro may be elicited even in the presence of high oxygen tensions. Increased sickling during carotid arteriography would therefore not be prevented by simultaneous inhalation of oxygen by the patient.

Data from this study and from the literature suggest that the use of hypertonic urea solutions is permissible since urea crosses the red cell membrane and does not cause dehydration and consequent sickling.
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Because of the abnormal oxygen dissociation curve and increased alveolar arterial oxygen tension gradient, anesthetic management must provide adequately high levels of oxygenation. In addition, attention must be paid to adequate ventilation and thus insure against CO₂ retention and subsequent sickling due to acidosis.

The use of hypothermia as an adjunct to surgery appears to be contraindicated on two grounds: acidosis leading to increased sickling, and increase of an already abnormally high blood viscosity leading to greater risk of thrombosis.

Summary

1. A case of subarachnoid hemorrhage, secondary to an aneurysm, in a patient with sickle cell anemia is reported.

2. Problems of diagnosis and treatment of intracranial aneurysm in a patient with sickle cell anemia are reviewed.

3. Results of an in vitro study show that significant sickling does occur when sickle cell (S-S hemoglobin) blood is mixed with contrast materials.

4. Presently available evidence suggests that, in sickle cell anemia, the volume and concentration of contrast material should be minimized, that urea may be safely used, but that the use of hypothermia may be contraindicated.

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References


