Bulletin of

Staff Meeting

University of Minnesota Hospitals

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Hemolytic Jaundice

INDEX

PATHOLOGY OF TUMORS AND [illegible]

CASE REPORTS

CONGENITAL HEMOLYTIC ICTERUS

CASE #1:

9 years old (brother), admitted March 22, expired March 26, 1934.

Pain

3-1-34 - Complains of pain in right side of head and neck. Slight swelling and tenderness. Marked anorexia.

3-3 to 5-34 - Pain in arms, legs, elbow and knees, and left side of chest. No redness or swelling of joints. Mother's impression is that patient had fever.

3-15-34 - Several vomiting spells prior to change of color in urine.

Past History

Thought to have had nephritis in 1931. Ill for one week. Dark colored urine and questionable hematuria for past 3 years. In 1932, physician thought patient apparently had some trouble with liver. Whooping cough in January 1934.

Physical Examination

Very ill, anemic, irritable child, 9 years of age. Eyes show edema of lids with bluish discoloration of both upper lids. Marked pallor of face and suggestive puffiness. Lips and gums anemic and cyanotic. Shotty nodes palpable in cervical region.

Chest: Short systolic murmur over apex of heart; diminution of breath sounds at right base. Abdomen - very large liver approximately five fingers below right mid-costal margin; large spleen about three fingers below ribs in left upper quadrant; distention of abdomen; kidneys not palpable. External genitalia - normal. Extremities - small scars from previous gun shot wounds; no petechiae. Blood pressure 110/70.

Laboratory: Urine - negative. Second day after admission, urinalysis showed trace of albumin, occasional red and white blood cells. Blood - Hb. 23%, red blood cells 1,200,000, white blood cells 9,000; Pmn's 52%, L 48%. Icteric index 9.2 units. Fragility test began at .5%, complete at .36%.

Hemogram: Eosinophils 0%, basophils 1%, myeloblasts 1%, leucoblasts 2%, promyelocytes 6%, myelocytes 6%, metamyelocytes 3%, segmented cells 73%, lymphocytes 4%, monocytes 4%. Numerous nucleated red cells. Marked hypochromic anemia with anisocytosis and anochromasia. Numerous microcytes measuring 4 to 5 microns in diameter and staining darker than the normocyte. These dark microcytes are characteristic of congenital hemolytic icterus or microcytic anemia. There is marked leucocytosis. White blood count later went up to 70,000. In the subsequent differential count, there was found occasionally stem cells and 12% immature type of cells (leucoblasts, promyelocytes, myelocytes). The majority of the white blood cells were, however, old, mature type of cells. It was noted that most of the polymorphonuclears were crowded with toxic granulations. Occasionally, atypical monocytes and cells resembling the Rieder type of cells were also found.

Hematological Impression: Congenital hemolytic anemia with leukemoid reaction due to an infectious stimulation. (A chronic myelogenous leukemia with superimposed infection must be ruled out).

X-Ray - of abdomen, chest and sinuses: liver greatly enlarged; density in right lung suggesting bronchopneumonia; tremendous thickening of wall of skull. The thickening of wall of skull, enlarged liver and spleen suggest the possibility of an unusual type of anemia.

Progress

Condition critical, transfused with 250 cc. of blood. White blood cells rose to 75,500. Definite evidence of right lobar pneumonia. Blood culture negative in 48 hrs. Schick and tuberculin test - negative. Given three blood transfusions, total 1000 cc. Temperature gradually rose to 106°, dyspnea and cyanosis increased. Expired on fifth day of hospitalization.

Autopsy

Body is that of poorly developed, poorly nourished white boy, 137 cm. long. Slight posterior hypostasis and

slight rigor but no edema, cyanosis no jaundice. There is a very pale waxy appearance of the skin of the entire body. Pupils are equal and regular.

Peritoneal Cavity contains about 400 cc. of dark fluid. Liver edge 6 cm. below costal margin in right mid-clavicular line. Appendix normal. Diaphragm at 5th interspace on right, at 6th rib on left.

Pleural Cavities and Pericardial Sac normal.

Right Lung weighs 400 grams, Left 325. Bronchi contain mucoid material. There is almost complete consolidation of lower lobes of both, giving appearance of confluent bronchopneumonia. On section, pus can be expressed from these lobes.

Heart weighs 200 grams. Coronaries and valves are normal. Root of Aorta shows no atherosclerosis.

Enlarged

Spleen weighs 500 grams, has a firm rubbery consistency and a granular appearance on cut section.

Liver weighs 1275 grams, appears dark and congested in the gross and on section.

Gall-Bladder normal.

Gastro-Intestinal Tract, Pancreas and Adrenals normal.

Right Kidney weighs 90 grams, Left 125. Kidneys normal externally and on section.

Bladder and Genital Organs normal.

Few enlarged Lymph Nodes along aorta in region of lungs.

Abdominal aorta shows no atherosclerosis.

Organs of Neck normal.

Head not examined.

Diagnoses

1. Congenital hemolytic icterus (clinical).
2. Bilateral bronchopneumonia.
3. Enlargement of spleen and liver.
4. Ascites and anasarca.

Microscopic

"Touch" smears from liver, spleen and lymph nodes show many immature cells indicating myeloid metaplasia.

Spleen - (paraffin section) - marked congestion of pulp. Few areas of myeloid metaplasia.

Kidney - No evidence of nephtiris.

Lung - Pneumonia.

Liver - No leukemia. Few myeloid cells present. These may be blood stream cells.

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CASE #2:

8 Years old (sister).

Pallor

Always has been pale. In good health up to March 20, 1934, when she became suddenly ill at 4 P.M. with vomiting of greenish material.

Gastro-Intestinal Upset

3-21-34 - Became very pale, weak, complained of moderate frontal headache and epistaxis.

3-22-34 - Temperature 104. No history of eating contaminated food. Family had eaten rabbit in January, no ill effects noted. Urine is slightly dark colored since onset. No diarrhea or chills. Slight cough with no expectoration.

Physical Examination

Pale, weak, white female, age 8, with yellowish, dusky tinge to skin. Eyes - sclerae faintly yellow, fundi normal. Nose - slightly congested. Throat - moderate hypertrophy of tonsils; mucous membranes and gums pale. Neck - few enlarged nodes. Chest - clear; soft systolic murmur at apex. Abdomen - liver palpable 3 fingers below right costal margin and slightly tender; spleen is five cm. below left costal margin. Reflexes diminished.

Laboratory

Blood - Hb. 28%, rbc's 1,027,000, wbc's 5,100, Pmn's 51%, L 49%. Numerous hyperchromatic microcytes in blood smear. Icteric index 9.2 units. Van den Bergh diphasic faintly positive. Blood - Wassermann negative. Gastric acidity - total acid 10°; no free Hcl. Following histamine, total acid 42°, free Hcl 11°. Fragility test - lysis began at .56, complete at .40. Normal control began at .48, complete at .40. Reticulocyte count 5%.

Progress

Given 3 transfusions, total 950 cc. blood in 4 days. Improvement marked. Hb. 40%. Reticulocytes 8%. Improved for subsequent 25 days. Jaundice became more apparent.

Jaundice

4-16-34 - Quantitative stool - urobilinogen (C.J.W.) 385.2 mg. per day.

4-23-34 - Icteric index - 26 units. Stool - urobilinogen - 901.1 mg. per day. Reticulocyte count - 18%, Hb. 53%.

5-4-34 - Icteric index - 17.7 units, Hb. 54%. 200 cc. citrated blood given.

Operation

5-7-34 - Splenectomy. Pathological examination: Spleen weighs 560 grams and is dark bluish-purple in color. Cut surface is dark and oozes dark thick blood for a long period of time after cutting. Microscopic - shows intense congestion of splenic pulp. No fibrosis of either pulp or follicles. Sinuses appear unchanged. Picture is consistent with congenital hemolytic icterus. Postoperative course uneventful.

Family History

1. Father (L.K.) complains "of never having been well." Has attacks of kidney trouble 2 to 3 times a year in which he becomes pale (somewhat yellow) and urine becomes dark. Attacks begin with severe weakness and chills. Blood smear examination - marked predominance of hyperchromatic microcytes. Fragility tests - lysis begins at .70 plus and complete at .5+. Control with same solution began at .54 and complete at .46. No palpable spleen.

2. Paternal uncle (E.K.) has complained of stomach trouble for many years. Series of 9 x-rays in 1933 revealed no change but he was placed on an ulcer regime without results. Blood smear reveals numerous hyperchromatic microcytes. Hb. 78% (Sahli). Hemolysis begins .52, complete .40. Control began .48, complete .40. He was informed in 1933 that he had a large spleen, which at present extends about 2 fingers below left costal margin.

3. Brother of father (C.K.) has no history of congenital hemolytic icterus. Blood smear had no microcytes. A sister of the father at age of 21 became acutely ill and expired in 4 days. Relatives were informed that the spleen had enlarged and burst.

4. Sister of patient (V.K.), age 4, shows no microcytes and is in apparent good health. Spleen not palpable.

II. ABSTRACT

HEMOLYTIC JAUNDICE

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Historical

Disease suffers under burden of many names (congenital hemolytic anemia, chronic hemolytic jaundice, familial hemolytic jaundice, constitutional jaundice and acholuric janudice.) Most applicable is chronic hemolytic jaundice as disease may be congenital, acquired or familial. First observed by Murchison in 1885, hemolytic jaundice was established as a clinical entity by Hayem in 1898. Widal's emphasis on the exacerbations or "crises of deglobulization" led to designation of the acquired form as the Hayem-Widal type. Two years later Minkowski recorded its familial occurrence; and afterward Chauffard-Minkowski type. This name also includes the isolated congenital cases. An excellent review of the subject up to 1922 has been written by Tileston. Apparently, the first case for which a splenectomy was done was in 1903 by Banti.

Familial Evidence

Weber presents a geneologic table containing 5 generations. The first of a family died at 76, there was history of jaundice. Of 15 children, one was affected. 10 children of this latter showed 3 cases. The 4th generation from an affected female contained 2 cases out of 6 offspring, only 4 of which survived infancy. Two children from an unaffected member of the latter generation are well. There were chronic leg ulcers in 3 of 7 cases. Wise also reports 5 cases of congenital hemolytic icterus in one family for which splenectomy was done. Recently he has added another to the same family history.

Types

Two types of the disease have been described, the congenital and acquired, distinguished chiefly by the difference in age of onset and the severity of the course. However, Giffin seriously questions whether many of the cases of the acquired type reported in the literature should, in the absence of characteristic changes in the blood, be rightfully included as cases of congenital hemolytic jaundice. Regardless of the age at which the predominant features of the disease become manifest, he believes that all of the cases reported in Pemberton's 118 splenectomies were probably fundamentally congenital in origin.

Wise mentions the fact that in the literature the mild cases are called congenital and the severe, acquired. Doubt has been cast upon the existence of true acquired cases and it may be that this class is not correct and all cases should be recognized as congenital.

The acquired hemolytic jaundice has been subdivided into the cryptogenic variety (undiscovered etiology), and the secondary form which has been found to accompany, or at least is coincident

with a variety of conditions including syphilis, tuberculosis, malaria, miscellaneous bacterial infections, pregnancy, liver cirrhosis and carcinoma. Hemolytic jaundice which develops after the 25th year is thought to be acquired. Many cases occurring in late childhood or in early adult life considered acquired, have been found on investigation of other members of the family to be congenital. The course is more severe, at times acute and often fatal. Anemia is more marked, red blood cells fall below 2,000,000, crises more frequent and severe, and the regenerative capacity of the bone marrow is often unable to meet the increased blood demand in the orderly manner characteristic of the hereditary form. Reticulocytes are sometimes greater, megaloblasts and megalocytes are seen in the blood smear. Fragility not regularly increased. Splenomegaly and painful hepatomegaly are present during crises. Auto-agglutination is found in the acquired, apparently never in the congenital.

Pathology

Spleen is large in both types, 800 to 1000 grams. Capsule is thick and occasionally adhesions are found about the poles. Infarcts are common. Section is dark in color, rarely with visible pigmentation and on microscopic examination the only change is the marked congestion. Congestion is the same as chronic passive congestion, in which the sinuses are engorged. In hemolytic jaundice, this is more noticeable in the pulp.

There is not the very marked fibrosis seen in the Banti spleen, nor is there marked sclerosis of Malpighian follicles. Phagocytes of red cells sometimes seen and the sinus endothelium is pronounced. The liver, bone marrow and lymph glands show considerable phagocytic activity and pigment deposition. Bone marrow is red and hyperplastic with numerous normablasts and myelocytes.

Pathogenesis

Consists of abnormal or exaggerated blood destruction. The great increase in urobilin excretion indicating red blood cell destruction points to a hemolytic activity which may not under normal conditions be brought into action. The decreased resistance of the red blood cells and splenomegaly must also be explained. Widal, Vaguez, Aschenheim, Benjamin and Sluka hold that the primary factor is in the blood, a dystrophy of red cells manifested by decreased resistance, whereby cells in the circulation are destroyed in excessive amounts by the normal hemolytic processes of the body. The splenic enlargement is thus brought about largely by the great number of red blood cells destroyed and filtered out in the spleen. The second theory concerns the views of Chauffard, Banti and Eppinger that the primary lesion is abnormally increased hemolysis, directly or indirectly related to splenic activity - hypersplenism. We may safely assume that it is closely connected with decreased resistance of red cells to the normal process of cell destruction.

Symptomatology

Jaundice may be present at birth, occurs rarely after 25 years of age, is usually mild yellow in color. There is malaise, headache, slight fever, general constitutional debility and usually no incapacitation except during crisis.

M. Barron cites the following points for differential diagnosis:

1. Jaundice, usually more "icteric than sick" (Chauffard).

2. Splenomegaly and occasionally an enlarged liver during crisis. Gall-bladder disease and gall-stones in approximately 68%. (Mayo).

3. Anemia variable in intensity, usually secondary in type with microcytosis.

4. The fragility of erythrocytes is increased, normal .42 to .30%; in congenital hemolytic jaundice .60, .7 to .55, .40%.

5. Blood serum - indirect bilirubin excessive up to 85 parts per million. Normal is 3 to 5.

Icteric index may rise to 100. The renal threshold to indirect bilirubin is thought to be very high.

6. Acholuric.

7. Van den Bergh - direct immediate negative, direct delayed positive(?). Indirect positive marked.

8. The absence of jaundice symptoms, such as itching and bradycardia.

9. Reticulocyte count usually from 5 to 35%. Several cases have been reported to be extremely high, up to 95% (Baty, Reynolds).

10. No bilirubinuria, there is excessive urobilinogen and urobilin in the urine and feces.

11. Chronic leg ulcers have occurred.

12. Unexplained optic atrophy was found in one case by Wise.

13. The cholesterol has been found to be normal before and after splenectomy.- The N.P.N. is normal, uric acid normal.

14. Recurrent crises with splenomegaly, anemia and at times a tender enlarged liver followed by remissions are characteristic of the disease.

Roentgenological Picture

The German and American investigators have attempted to classify the constitutional anemias in children which are thought to have a congenital or familial basis. It has been shown that congenital hemolytic anemia, Sickle cell anemia and the erythroblastic anemias of children have a characteristic x-ray picture of the skeleton. This is thought to be due to a hyperactivity of the bone marrow by response to a degenerative process in the blood. Paul Junius (Bonn) demonstrates very marked bony changes which occur in varied degrees in this class of anemias.

There is apparently a thinning of the cortex of the long bones, particularly the humerus and the tibia and fibula, due to the widening of the spongiosa and marrow portion of the bone. This extends throughout the entire length of the bone. The metacarpals at times show rarefaction of bony structure. There is sometimes a widening of the diameter of the bones. In the skull, the changes are variable. In early cases, there is very slight thickening of the skull bones and increased porosity. In advanced cases, the bone is markedly thickened, the external table becomes very thin and the diploe markings are increased and appear to break through the external table. These changes are thought to be very characteristic for this class of anemias, for there are apparently no other diseases in the living animal in which there is so marked a degree of marrow hyperplasia at the expense of the cortical portion of the bone.

Treatment

Patients with congenital hemolytic jaundice are usually not troubled by its presence. Duration of life is not shortened, nor are their activities interfered with, except during crises or because of a large abdominal tumor. Removal of the spleen, however, removes both of these types of disability and is followed by the disappearance of jaundice. This type of splenomegaly is usually not complicated by adhesions and the operation may be performed without undue difficulty. The use of adrenalin preoperatively in reducing the size of the spleen has been tried with variable success.

Pemberton, in a series of 118 cases at the Mayo Clinic, cites the hospital mortality as 3.4%. The operative data which were suggestive of affectation of the liver in 55 cases showed a mortality of 5.4%, compared with 1.6% in which the liver was presumed to be normal.

Elliot in 1917 had an operative mortality of 16% in 65 cases.

Splenectomy has been done at practically all ages. Bell performed splenectomy in a child of 15 months. Taylor, in

children 9, 11 and 13 months, performed splenectomy after which the jaundice began to fade rapidly.

The operation must be done between attacks and not in a crisis. It has been estimated that in a crisis one-half of the blood cells may be destroyed. Most operators give transfusions before operation; others warn of the danger of increasing jaundice and producing anuria by transfusions. In the presence of adhesions, the following has been suggested: Ligation of the vein near the celiac axis detachment of the colonic insertion of the greater omentum and ligation in the middle third of the vessel, or ligation 6 or 10 cm. from the spleen. Necrosis of the spleen has been said to follow this procedure.

Results of Splenectomy

1. The reticulocyte count usually diminishes.

2. The hemoglobin increases rapidly.

3. The bilirubinemia decreases.

4. The fragility of the red blood cells is apparently unchanged. A few writers report a return to normal.

5. The diameter of the red blood cells has been shown to increase in some cases, although they usually remain unchanged.

6. There is an eosinophilia following splenectomy.

7. The blood volume has been shown to increase 40%.

8. The excretion of urobilin and urobilinogen diminishes to within normal limits, occasionally it persists.

Late results in Pemberton's series at the Mayo Clinic show 86% of the patients recovering from operation to be alive and 85% in good health.

Summary

1. Congenital hemolytic jaundice first observed by Murchison in 1855, and established as a clinical entity by Hayem in 1898. The acquired hemolytic icterus is called the Hayem-Widal type, and the familial form is known as the Chauffard-Minkowski type.

2. The two types of the disease described are distinguished chiefly by the difference in age in onset and the severity of the course of the disease. The majority of the writers are inclined to doubt the existence of the acquired form in the absence of familial history.

3. The acquired type is thought to be more acute with more severe crises and higher reticulocyte count. The fragility is not regularly increased and the auto-agglutination phenomenon is present.

4. The pathology is similar in both. Spleens are large, capsule thick, infarcts common, and there is considerable congestion of the pulp. There is a moderate fibrosis and some sclerosis of Malpighian follicles, but much less than the Banti spleen. Bone marrow is red and hyperplastic.

5. There are two theories in regard to pathogenesis. One group believes that the primary factor is in the blood, a dystrophy of red cells manifested by decreased resistance. The splenic enlargement is brought about by the great number of red blood cells destroyed and filtered out in the spleen. The other group believe that the lesion is abnormally increased hemolysis, directly or indirectly related to splenic activity.

6. Jaundice, splenomegaly, hepatomegaly, hyperchromatic microcytic anemia, increased fragility, excessive urobilinogen in feces and urine, high reticulocyte count and crises are the outstanding features.

7. Thinning of the cortex of the long bones and skull with an increased thickening and rarefaction of the medulla have been noticed in cases of congenital hemolytic icterus.

8. Ultimate prognosis as to life is fair, except during crisis or with increased size of the spleen, there is very little incapacitation.

9. Splenectomy is the procedure of choice. The mortality (operative) is 3.4% in Pemberton's cases. If associated liver enlargement is present, mortality is 5.4% compared to 1.6% in those cases in which the liver was presumed to be normal.

10. Operation should be done between attacks and not in a crisis. Transfusions and adrenalin have been given preoperatively to reduce the size of the spleen.

11. When severe adhesions or hemorrhage occurs, ligation of the splenic vein is attempted. Some question this procedure.

12. Following splenectomy, there is a disappearance of the jaundice, a decrease in the reticulocyte count, a rise in the hemoglobin, a possible increase in the diameter of the red blood cells, an increase in blood volume. The fragility remains about the same. Late results show 83% of patients to be in good health.

Case Reports and Abstract

by Pediatric Fellow -

S. Anderson.

III. ANNOUNCEMENTS

1. SURGERY SEMINAR

Dr. William T. Peyton will speak at the Surgery Seminar on Thursday, May 17, at 4:30 in the Todd Amphitheater. Subject: "Mixed Tumors." Anyone interested is cordially welcome.

2. PHYSIOLOGICAL-PHARMACOLOGICAL SEMINAR

Physiological-Pharmacological Seminar will meet Friday, May 18, at 12:30 in room 116 M.H. H. N. Wright: The Treatment of Carbon Monoxide Poisoning.

3. SEMINAR IN PATHOLOGY

12:30 P.M., Monday, May 21, 1934, 104 Anatomy. Variations in the histology of the thyroid gland - Dr. Louis E. Nolan.