Congenital Inclusion Body Hemolytic Anemia Associated with Epilepsy and Disordered Pyridoxine Metabolism

By GABRIEL GRECORATOS, GEORGE J. VENNES AND ROBERT H. MOSER

During the preceding decade there has been great interest in the clinical importance of vitamin B6, especially as it relates to the nervous and hematopoietic systems. The purpose of this communication is to report an unusual case of congenital hemolytic anemia associated with a convulsive disorder in which there was presumptive evidence to suggest a defect in pyridoxine metabolism. The patient was originally reported by Lange and Akeroyd in 1958. This paper will document the concluding events in the evolution of this curious syndrome. Unfortunately, the sudden death of our young patient precluded a therapeutic trial with pyridoxine. Nevertheless, we believe that sufficient data were obtained to justify reporting this case in some detail.

Case Report

K. S., an 18-year-old white female, was first seen in the Hematology Clinic, U. S. Army Tripler General Hospital, in January 1961.

The early history of her disease which was detected at 30 months of age, has been reported in detail. To summarize briefly, she was a chronically ill child with unrelenting hepatosplenomegaly, icterus and refractory hypochromic microcytic anemia. She required frequent transfusions and underwent splenectomy at age 4; there was little change in the clinical course. A diagnosis of "congenital hemolytic anemia with abnormal pigment metabolism and red cell inclusion bodies" was entertained. She had received medication consisting of methylphenethyl hydantoin and trimethadione for a chronic convulsive disorder. A brief period on corticosteroids had been unavailing; she was maintained on phenobarbital, oxytetracycline and chlorpheniramine. For the preceding 5 years, she had enjoyed a period of comparative well-being. Her father was transferred to Hawaii and she came under our observation.

When first seen, the patient weighed 77 pounds; she was remarkably thin and small but appeared alert yet retarded intellectually, with slow responses and childish affect. Skin was coarse with a slate-gray color. Conjunctivae were pale, and sclerae icteric. A mucopurulent postnasal discharge was overlying a pale and edematous nasal mucosa. Palate was high and excessively arched. There was moderate gingival hyperplasia. Hepatic edge was palpable 3 cm. below the right costal margin; it was firm, smooth and nontender. An old left subcostal surgical scar was evident. There was diffuse bilateral adenopathy of the anterior and posterior cervical, supraclavicular, axillary and inguinal areas. Nodes were soft, small, nontender. The remainder of the physical examination was normal.

Laboratory data: Hemogram: Hematocrit 31 per cent; hemoglobin 6.5 Gm./100 ml.; WBC (corrected) 9470/mm.³; neutrophils 61 per cent, eosinophils 2 per cent, basophils 4 per cent, lymphocytes 26 per cent, monocytes 7 per cent; there were 110 nucleated RBC's per 100 WBC's. Erythrocyte sedimentation rate was 1 mm. per hour. Morphologic examination of the erythrocytes revealed remarkable anisocytosis, poikilocytosis and hypochromia; there was moderately severe stippling, polychromasia, microcytosis and macrocytosis. Howell-Jolly bodies were abundant, Cabot rings were rare, and many target cells were present. Most curious were bizarre inclusion bodies of variable size (fig. 1): submitted Oct. 17, 1963; accepted for publication Dec. 30, 1963.
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Fig. 1.—Peripheral blood smears; Wright's stain. (A, B) hypochromic RBC's, marked poikilocytosis, anisocytosis, target cells, coarse, irregular, basophilic stippling, Howell-Jolly bodies. A few of the erythrocytes contain large, fairly visible, refractile inclusion bodies (C) Similar findings; a NRBC is also present in the field. (D) Extreme hypochromia present; target cells, schistocytes.

some were positive for iron with Prussian blue counterstain (fig. 2). Reticulocyte count was 21 per cent, and platelets numbered 1.2 million/mm³. Except for the presence of hemoglobin, urinalysis was normal. There was no porphobilinogen; uroporphyrins could not be detected; 81.8 µg. of coproporphyrin was found in one 24-hour urine specimen. Total serum bilirubin was 2.0 mg./100 ml. with 0.2 mg./100 ml. conjugated (direct). Saline osmotic RBC fragility revealed hemolysis beginning at .50 per cent and complete at .28 per cent; control values began at .46 per cent and were complete at .36 per cent. Coombs' antiglobulin tests, direct and indirect, were negative. Hemoglobin electrophoresis on paper and starch block revealed normal hemoglobin "A"; fetal hemoglobin was 0.4 per cent. Cephalin flocculation was 1+ and thymol turbidity .8 units; serum glutamic oxalacetic transaminase was 58 units. Serum iron was 25.2 µg./100 ml.; total iron binding capacity was 259 µg./100 ml. Total serum proteins were 7.9 Gm./100 ml.; serum protein electrophoresis revealed albumin 66.4 per cent, alpha-1 globulin 1.5 per cent, alpha-2 globulin 4.4 per cent, beta globulin 9.4 per cent and gamma globulin 18.3 per cent of the total protein content. Serum copper was 120 µg./100 ml. X-ray of the chest revealed normal heart and lungs. An electroencephalogram was abnormal with diffuse and focal abnormalities indicative of a convulsive disorder, as well as multifocal areas of spike formation.
Fig. 2.—Peripheral blood smears. Wright's stain, counterstained with Prussian blue for iron. (A, B) Numerous iron-positive granules present in almost all the erythrocytes (siderocytes). The iron-positive bodies are distinct from the larger inclusion bodies which do not stain with Prussian blue but appear as slightly refractile inclusions (B, lower right hand corner).

Special studies: Free erythrocyte protoporphyrin content was 66 μg./100 ml. RBC—a normal value. However, free erythrocyte coproporphyrin content was 55 μg./100 ml. RBC—50 times greater than normal. Investigation of urinary content of intermediary products of tryptophan metabolism following a 5 Gm. loading dose of L-tryptophan revealed increased excretion of anthranilic glucuronide, orthoaminohippuric acid, acetylkynurenin, and hydroxykynurenin. Excretion of pyridone and xanthurenic acid was sub-
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Table 1.—Urinary Excretion of L-Tryptophan Metabolites* (μmoles of Metabolite Excreted/24 Hours)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Patient K. S.</th>
<th>Normal Control Subjects (Avg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After 5 Gm. L-tryptophan</td>
</tr>
<tr>
<td>Pyridone</td>
<td>30</td>
<td>117</td>
</tr>
<tr>
<td>N(^1) methylbutynicotinamide</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>Kynurenic acid</td>
<td>14</td>
<td>238</td>
</tr>
<tr>
<td>Xanthurenic acid</td>
<td>5</td>
<td>77</td>
</tr>
<tr>
<td>Indican</td>
<td>111</td>
<td>194</td>
</tr>
<tr>
<td>Anthranilic glucuronide</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>o-Aminohippuric acid</td>
<td>28</td>
<td>162</td>
</tr>
<tr>
<td>Acetylkynurenin</td>
<td>17</td>
<td>206</td>
</tr>
<tr>
<td>Kynurenine</td>
<td>9</td>
<td>523</td>
</tr>
<tr>
<td>Hydroxykynurenine</td>
<td>11</td>
<td>400</td>
</tr>
<tr>
<td>4-Pyridoxic acid</td>
<td>2.48</td>
<td>2.15</td>
</tr>
</tbody>
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*Performed through the courtesy of Drs. J. M. Price and R. R. Brown, University of Wisconsin. Normal values supplied by them.

normal; excretion of kynurenic acid and kynurenine was probably within normal limits (table 1).

Clinical course: The patient was followed at monthly intervals in the Hematology Clinic for approximately 6 months. She remained in a special school and was able to function rather well within limits imposed by her illness. She was chronically icteric; evidence of hemolysis was always present but remained compensated at a low level. Hematocrit values ranged from 29 to 32 per cent and hemoglobin from 6 to 7 Gm./100 ml. She did relatively well other than for one episode of tonsillitis in February, 1961. At that time her hematocrit was 27 per cent and hemoglobin 4.8 Gm./100 ml. The patient was treated with penicillin; because of an acceleration of the hemolytic process, she was given 350 ml. of her father's blood. Upon completion of the transfusion, she experienced a sudden elevation of temperature to 104\(\frac{1}{2}\) F.; this was followed by a convulsive seizure. Subsequently, she returned to her previous "compensated state" with a hematocrit of 36 per cent. We were advised that similar febrile and icteric reactions had been observed in the past following transfusions of paternal blood.

On July 6, 1961, the patient was readmitted to the hospital for a tryptophan loading study and collection of blood for free erythrocyte coproporphyrin and protoporphyrin determinations. There had been no change in the clinical state. Admission hematocrit was 30 per cent and hemoglobin 7.8 Gm./100 ml. Following these studies, it was decided to transfuse the patient to replace the blood which had been withdrawn. The donor was the patient's father; serologic compatibility was again demonstrated. This represented the 119th recorded transfusion for the child. Following the blood, the patient became febrile to 104 F.; this was followed by two convulsive episodes. There was evidence of increasing hemolysis with gradual decline of hematocrit values from an immediate post-transfusion level of 36 per cent to 27 per cent within 72 hours. Concomitantly there was an increase in reticulocyte count to 35 per cent; jaundice became extreme. Total bilirubin was 78.8 mg./100 ml.; conjugated bilirubin, 60 mg./100 ml. Plasma hemoglobin immediately following transfusion was 21 mg./100 ml.

Radioactive rose bengal test demonstrated almost complete lack of dye pickup by the liver, indicating marked hepatocellular damage.

Seventy-two hours after transfusion, the patient regurgitated gross blood. Her pulse became feeble with a rate of 116; blood pressure remained normal. Prothrombin time was 53 seconds with control of 14 seconds (activity of less than 11 per cent). The patient was disoriented and obtunded. It was considered that she could not tolerate radiologic and esophagoscopic examinations. Treatment was supportive with vitamin K\(_1\), hydrocortisone 300 mg. daily, oxytetracycline 2 Gm. daily given via hypertonic glucose in-
fusions; parenteral multivitamins, nasogastric suction and high colonic purges completed the regimen. Bleeding continued slowly but steadily and hepatic decompensation proceeded to coma. Her hematocrit was maintained at approximately 30 per cent with washed red cell transfusions from her father and other compatible donors. She expired on July 17, 1961.

Necropsy Findings

Autopsy was performed 20 hours after death with the body having been maintained at refrigerator temperature; weight was 76 pounds, with deep jaundice and lacking the development of an 18-year-old female. Cause of death was hemorrhage from esophageal varices.

The liver weighed 1500 Gm. and extended 3 cm. below the right costal margin in the midclavicular line. Capsule surface was smooth, glistening and dark brown with a firm, rubbery consistency. A prominent lobular pattern was demonstrated on section with lobules outlined by dark brown pigment. There was no gross interlobular fibrosis or fatty metamorphosis. The extra-hepatic biliary system and the portal venous system were patent.

Hepatic architecture appeared well preserved; however, minimal portal fibrosis without septal formation was evident. Fibrosis could be demonstrated in the centrolobular zone surrounding the central vein. This was accompanied by extensive acute liver cell degeneration, principally in the central portion of the lobule. There was no inflammatory infiltration in the areas of degeneration and very few lymphocytes and plasma cells in portal areas (fig. 3).

Three distinct types of pigment were demonstrated with Comori’s iron stain, PAS and Stein’s stain for bile. Iron pigment was identified within the intact liver cells of the periportal zone of the lobule and within Kupffer’s cells in the areas of degenerating hepatic cells (fig. 4). Bile pigment was discovered in the central portions of the lobule, staining as a soft flocculent material with hematoxylin and eosin and Stein’s bile stain. Widely separated bile plugs were demonstrated. The third pigment failed to take up Comori’s iron stain and accepted Stein’s bile stain and PAS poorly. This material, which was granular with particles of relatively uniform size, was located principally in the centrolobular area within intact hepatic cells. It could not be identified in the portal triads or in Kupffer’s cells where hepatic degeneration was most prominent.

The kidneys were of uniform size and had a combined weight of 325 Gm. The capsules stripped easily, revealing a smooth, bile-tinged cortical surface. There was marked widening of the cortex with a distinct corticomedullary junction. The medulla was prominently bile-stained and streaked with dark brown pigment. There was no gross hemorrhage or necrosis. Renal pelves and calyces were not dilated.

Pigmented casts, staining well with Comori’s iron and Stein’s bile stain, were present in most of the convoluted and collecting tubules. Iron-positive material was also visible in the epithelial cells of proximal tubules. No degenerative changes were seen within tubules or glomerular tufts.

A third granular pigment was present within the tubular lumen and epithelial cells. This was histochemically similar to that present in the liver although granules were slightly darker and disposed in a radial, laminated, crystalline pattern. In certain areas they closely resembled leucine crystals. Morphologically they were distinct from the bile casts and did not take Comori’s stain for iron. The pigmented areas were faintly positive with Stein’s bile stain (figs. 5, 6, 7).

The leptomeninges revealed moderate bile staining over the pons. However, microscopic examination of the underlying tissue and remainder of the central nervous system did not reveal bile staining, iron deposition or hemorrhage.

The lungs grossly and microscopically revealed moderate pulmonary edema and congestion. No bile staining or hemosiderin deposition was noted within alveolar septa. There were hemosiderin-laden macrophages within alveolar sacs, characteristic of pulmonary congestion and edema.
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Fig. 3.—Photomicrograph of liver showing hepatic necrosis and hemosiderin deposition (H & E x150).

Erythrocytic hyperplasia was demonstrable within the bone marrow; other cell series were unremarkable.

There were no gross or microscopic abnormalities in the remaining organs.

METHODS

The routine hematologic methods used were those described by Wintrobe and Cartwright. Serum iron and iron binding capacity determinations were done by the technic of Peters et al. Hemoglobin electrophoresis by the paper method was performed as described in the Spinco Technical Bulletin and starch block hemoglobin electrophoresis was done according to the method of Pearson and McFarland. Studies on the excretion of the tryptophan metabolism intermediary products were performed by Drs. Price and Brown of the University of Wisconsin; methods for these determinations have been adequately described elsewhere. Free erythrocyte protoporphyrin and coproporphyrin determinations were performed by Dr. Haut, Department of Medicine, University of Utah, according to procedures described previously. Urinary coproporphyrins were performed by the technic presented in the Navy Manual of Biochemistry. Serum copper determinations were performed by the method of Rice.

DISCUSSION

Originally this case was considered to represent a unique variety of congenital hemolytic anemia. Peculiar erythrocyte inclusion bodies and abnormal pigment metabolism were hallmarks. Etiology was unknown. Lange and Akerovd had speculated upon an intrinsic erythrocyte defect, probably associated with aberration of hemoglobin synthesis and production of bilifuscin. Increased nucleic acid content of inclusion bodies and decrease of whole
Fig. 4.—Photomicrograph of liver showing extensive hemosiderin deposition (Gomori's Iron x150).

blood glutathione content were other facets of this unusual metabolic defect.

Several facts emerged during our study which differed from observations recorded during the original investigation. We were unable to demonstrate the ring of fine iron-positive granules which had been described surrounding large inclusion bodies within erythrocytes. However, we discovered moderate-sized erythrocytic inclusion bodies which were iron-positive. These cells appeared to be siderocytes. The serum iron had risen from 179 μg./100 ml. recorded in 1958, to 252 μg./100 ml. at the time of our investigation in 1961. This elevation was attended by a rise in saturation of transferrin to 97 per cent. These changes occurred over a period of 3 years and probably were related to the unrelenting hemolytic process. During this period, therapeutic iron compounds were not administered and transfusions were few.

In turning to the literature to find precedent for this case, several pertinent papers were reviewed. Schmid et al.29 reported a father and son who had familial hemolytic anemia quite similar to that of our patient. Erythrocyte inclusion bodies and deranged pigment metabolism with excretion of bilifuscin characterized these cases also.

Scott, Haut et al.30 in 1960 reported the fourth case of “congenital hemolytic disease associated with erythrocyte inclusion bodies and abnormal pigment metabolism.” Their case also manifested an abnormal hemoglobin which migrated between the A1 and A2 fractions on starch block electrophoresis.
Fig. 5.—Photomicrograph of kidney showing leucine crystals, hemosiderin deposition and bile casts. The latter appear as flocculent material within the tubules (H & E x150).

The report by Frick et al.31 describing hemoglobin Zürich is interesting because the severe hemolytic episodes followed sulfonamide ingestion. One unusual feature of the Zürich anomaly is the appearance of Heinz bodies in the erythrocytes during the hemolytic episode which disappear soon afterward. A similar phenomenon was reported by de Leeuw et al.32 following ingestion of sulfonamides and other drugs. Hemoglobin electrophoresis was not done in these cases. In our patient and those of Schmid et al.29 and Scott et al.30 the red cell inclusions were independent of drug ingestion, hemolysis was unrelenting, and the abnormal pigment found in the urine was unique.

When we first saw this child, the severe hypochromia which persisted despite high serum iron and total iron-binding capacity values was remarkable. We considered a refractory hypochromic anemia with an associated hemolytic component. Lack of a hereditary history and the existence of significant hemolysis placed this girl in a category different from the hereditary sex-linked anemias of males described by Rundles and Falls.33

The hypochromia, microcytosis, poikilocytosis and anisocytosis of our patient directed our attention to a possible defect in heme synthesis. Reports of PRA and seizures responding to vitamin B₆ also stimulated interest in evaluating pyridoxine metabolism.

The patient lacked many critical aspects of classic pyridoxine-responsive anemia. Perhaps the most remarkable difference was severe and persistent
hemolysis since early childhood. The first recorded reticulocyte count was 21 per cent during a period of “compensated” hemolysis; it remained in this range. A profusion of nucleated erythrocytes characterized all peripheral blood smears. Constant and remarkable elevation of unconjugated bilirubin was the third factor indicating brisk hemolysis compensated at a low hemoglobin level. Such a hemolytic component is not characteristic of PRA. Nor has pigment similar to that present in the urine of our patient been reported in PRA.

The abnormalities in glutathione content and glutathione instability in the erythrocytes of our patient seem worthy of comment. She had received many drugs in early childhood including sulfadiazine and hexylresorcinol. It was a fleeting temptation to relate the hemolysis to administration of one or both of these drugs. This was not tenable for several reasons: (1) sulfadiazine and hexylresorcinol are not among the drugs known to precipitate hemolysis in patients with primaquine-sensitive erythrocytes. (2) There were prolonged intervals when no drugs were given yet hemolysis persisted. To invoke other drugs taken during her prolonged course in the etiology of the heme synthetic defect would necessitate ignoring the early onset which antedated any sustained ingestion of drugs. (3) Although the glutathione level of erythrocytes was low and glutathione instability was demonstrated, glucose-6-phosphate dehydrogenase activity was elevated rather than depressed;
this was a fundamental variance from primaquine-sensitive hemolytic anemia.32,35

Abnormalities of tryptophan metabolism have been described in PRA. In this case, urinary excretion of 4-pyridoxic acid was in the low normal range; low levels of xanthatenic acid and high levels of ortho-aminohippuric acid and anthranilinic glucuronide afforded reasonable evidence that our patient was not deficient in pyridoxine (at least in liver and kidney tissue). However, the increased excretion of acetylkynurenin and hydroxykynurenin suggested a metabolic defect in tryptophan synthesis. Comparing the results obtained in our patient with those of the case reported by Harris et al.,4 it was obvious that the patterns of excretion were similar, with the exception that Harris' patient excreted greater amounts of pyridone and xanthurenic acid.

Normal values for free erythrocyte protoporphyrin in our patient indicated yet another point of difference from classic PRA, in which such values are decreased.25 However, her free erythrocyte coproporphyrin was higher than any level that could be related to even a brisk reticulocyte response; this suggested a block in the synthesis of protoporphyrin from coproporphyrin. Watson98 has shown that high erythrocyte coproporphyrin values correlate well with the rate of hemoglobin synthesis or attempted hemoglobin synthesis.
The life-long convulsive disorder in our patient prompted speculation on the role of disordered pyridoxine metabolism. The importance of pyridoxal-5-phosphate in the oxidative metabolism of the central nervous system has been well-documented.\textsuperscript{1,2} The occurrence of sporadic epileptiform convulsions in infants on a pyridoxine-deficient diet has been reported. Seizures occurring in chronic alcoholics have been associated with increased xanthurenic acid excretion. This fact, coupled with correction of the convulsive disorder after administration of pyridoxine suggested that convulsions in chronic alcoholics may be related to pyridoxine deficiency.\textsuperscript{2,3}

In the past few years, a new syndrome involving a convulsive disorder in infants and children has been described.\textsuperscript{37-42} These patients responded to administration of large amounts of pyridoxine even though dietary intake was adequate. It has been suggested that this disorder is due to increased physiologic requirements for vitamin B\textsubscript{6}.

Our case lacks critical documentation to permit inclusion among the pyridoxine-responsive anemias; we did not complete our plan to challenge the anemia and convulsive disorder with a therapeutic trial of pyridoxine. Her early and unexpected demise precluded projected plans for study.

The necropsy findings failed to shed additional light on the problem. Extrahepatic obstruction was excluded by careful delineation of a patent biliary system. Esophageal varices suggested existence of long-term portal hypertension, yet hepatic fibrosis was minimal. Etiology of the acute hepatic cell necrosis was equally obscure. The distinct possibility exists that the final hemolytic transfusion reaction produced sufficient tissue anoxia to tip the balance and precipitate hepatic cell necrosis in a patient whose hepatic compensation was already marginal. The young girl died in progressive hepatic coma with persisting hemolysis.

**Summary**

An 18-year-old girl with severe congenital hemolytic anemia due to an intracorpuscular erythrocytic defect is presented. In addition to persistent and severe jaundice, the child's erythrocytes always demonstrated severe hypochromia, poikilocytosis, anisocytosis, and a remarkable proportion were nucleated. Large numbers of iron-positive inclusion bodies were a constant feature of her erythrocytes, as well. The tryptophan loading test was abnormal, suggesting disordered pyridoxine metabolism. The free erythrocyte coproporphyrin values were elevated, indicating a defect in heme synthesis. The patient had a life-long history of a convulsive disorder. It is suggested that the entire symptom complex was the expression of a defect in tryptophan metabolism related to pyridoxine. However, therapeutic challenge with pyridoxine was not performed; the patient cannot be included among the pyridoxine-responsive anemias.

**Summario in Interlingua**

Es presentate le caso de un puera de 18 annos de etate con un forma sever de congenite anemia hemolytic causate per un defecto erythrocytic intra-
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A parte su persistente e sever jalousia, le erythrocytos del juvenile filia semper demonstrava sever hypochromia, poikilocytosis, e anisocytosis, e un remarkable proportion del erythrocytos eseva nucleate. Grande numeros de corpores de inclusion positive pro ferro eseva un constante caracteristica del erythrocytos. Le test de cargation a tryptophano eseva anormal, lo que suggere un disordine in le metabolismo de pyridoxina. Le valores del libere coproporphyrina erythrocytic eseva elevate, lo que indica un defecto in le synthese de hem. Le patiente habeva un historia de disordines convulsive deposit le comenciamento de su vita. Es opinate que le integre complexo de symptomas eseva le expression de un defecto in le metabolismo de tryptophano relationate con pyridoxina. Tamen, un provocation therapeutic con pyridoxina non esseva executate. Le patiente non pote esser includite in le categoria de anemias responsive a pyridoxina.

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