CLINICAL CONFERENCE

Congenital Hypertrophic Pyloric Stenosis with Jaundice

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DR. BARNETT: I think few of us would consider that we know enough new about pyloric stenosis to justify presenting an infant with it to a group of this type. However, the patient to be presented had what appears to be a complication of pyloric stenosis, which we had not encountered previously and one which is of both practical and theoretic interest. The patient will be described and the discussion opened by Dr. Fraad.

DR. LEWIS FRAAD: Infants with congenital hypertrophic stenosis with or without complications continue to fascinate pediatricians, even though the first American cases were reported in 1788.

The patient is a boy, the first-born infant of a 21-year-old mother. The pregnancy and delivery were uneventful. The birth weight was 2.5 kg. Upon discharge from the newborn nursery at 6 days of age, occasional regurgitation of feeding was noted. By the age of 3 weeks the infant had gained only 90 gm. Five days prior to admission to the hospital, vomiting became profuse and projectile. One day before admission the infant's skin appeared yellow to the mother. Upon admission to the hospital at the age of 4 weeks, the infant's weight had decreased to 2,360 gm. He appeared dehydrated and markedly jaundiced. The liver was palpated at the costal margin. An olive-shaped mass measuring approximately 2.5 by 1.5 cm was easily palpated in the mid-epigastric region.

The pertinent laboratory findings in the blood at the time of admission were as follows: Hemoglobin, 19.5 gm/100 ml; CO₂ content, 37.2 meq/l; chlorides, 79 meq/l; sodium, 142 meq/l; potassium, 3.0 meq/l; bilirubin, 18 mg/100 ml of which 13.1 mg was reported to be of the indirect-reacting variety.

Oral feedings were discontinued. With hydration by intravenous fluids, the electrolyte concentrations in the serum returned to normal values but the high value for bilirubin and the jaundice persisted. Identification of the type of bilirubin by paper chromatography revealed that it was all of the indirect variety. Ramstedt pylorotomy and liver biopsy were performed on the third hospital day. The infant had an uneventful postoperative course. The gross and microscopic appearance of liver tissue obtained by biopsy was considered normal. The jaundice faded rapidly after operation. On the fifth postoperative day the bilirubin level in the serum reached 0.44 mg/100 ml.

At the time of discharge on the fourteenth hospital day the baby's weight was 2,600 gm. The patient, now 4 months of age, has continued to thrive without signs of jaundice or of vomiting.

Although pediatricians, surgeons and pathologists have been interested in pyloric stenosis for many years, the etiology of this condition is still unknown. The following list of theories regarding the cause of pyloric stenosis shows at a glance the confusion reigning in the sphere of etiology: 1) Muscle hypertrophy is the primary lesion; 2) muscle hypertrophy is secondary to (a) pyloric (b) gastrointestinal allergy; (c) vitamin deficiency in the pregnant mother, (d) hypertonia of the vagi, (e) myenteric ganglion disorder of the stomach analogous to congenital aganglionic megacolon, (f) adrenal cortical disease, (g) pituitary changes, (h) maternal emotional disturbance. This is a partial list. Obviously with so many competing theories none is acceptable.

The genetic factors in pyloric stenosis are worthy of mention. The disease seems to involve a far higher percentage of monozygous twins than it does fraternal twin pairs. The
risk of pyloric stenosis is 1 in 10 for brothers or for sons of parents, one of whom is known to have had the disease. The risk for daughters or sisters of known cases is about 1 in 50. The risk of pyloric stenosis is four times greater in male children if the mother had the disease than if the father had it. Instances of pyloric stenosis in half siblings of an affected parent have been reported. The genetic patterns are interesting and should be studied further.

In recent years a revived interest in the medical treatment of pyloric stenosis has been manifest. Scopolamine methyl nitrate (Skopyl®) has been used successfully in the medical management of pyloric stenosis, particularly in Sweden and in England. Perhaps we should re-evaluate the medical management of pyloric stenosis. However, even during the past year, reports of large series of babies treated surgically in the United States have been added to the large existing American literature. Again, mortality rates of less than 1% in these large series were reported. Where skillful surgery is not available medical treatment probably is indicated. However, where expert surgery and expert anesthesia are available, where nursing care is at a premium, and where the hospital staphylococcus stalks, we believe that prompt surgical intervention is the treatment of choice at the present time.

Dr. Julian B. Schorr: The diagnosis of hypertrophic pyloric stenosis was apparent when this infant was admitted to the hospital. Our major concern was related to the marked icterus which was also present. The following possible causes of the jaundice were considered:

Prolonged physiologic icterus seemed unlikely because of the history of the appearance of jaundice at 4 weeks of age. However, it should be recalled that prolonged physiologic jaundice may occur in infants with congenital hypothyroidism.

Congenital galactosemia occasionally presents with jaundice, but the jaundice appears shortly after the first milk feedings, and it may well be on the wane by 1 month of age, even when milk products have not been removed from the infant’s diet. In order to eliminate galactosemia as a possible cause for this infant’s jaundice, the urine was tested for the presence of a reducing sugar, using both Benedict’s solution and one of the diagnostic paper strips now available (Testape® or Clinistix®). Neither test was positive. If galactosuria had been present, there would have been a positive test with the Benedict’s solution but a negative test with the paper strips, which contain glucose oxidase and therefore do not react with galactose.

Hemolytic disorders may present with jaundice at any age. Although the specific pathogenesis of the hemolytic process may not always be apparent, the presence of jaundice accompanied by anemia, abnormal appearing erythrocytes in the peripheral blood smear and an elevated reticulocyte count suggests hemolysis. The serum concentration of bilirubin of 18 mg/100 ml, present in this infant, is higher than the level encountered in hemolytic processes beyond the immediate newborn period. In addition, the complete blood examination revealed nothing to suggest the presence of a hematologic disorder.

Sepsis, or such specific infections as syphilis, leptospirosis or toxoplasmosis, may be accompanied by jaundice. In these instances, however, other signs and symptoms of the underlying disease are usually apparent.

Obstructive jaundice due to a congenital anomaly of the extrahepatic biliary tract usually appears before the infant is 2 weeks old, and the serum bilirubin rises slowly so that it rarely reaches levels of 18 mg/100 ml by 1 month of age.

Neonatal hepatitis is frequently implicated as the cause of jaundice appearing in a 1-month-old infant, and the diagnosis of this disorder is frequently difficult. Again in this disorder, high concentrations of bilirubin in the serum are rare except in patients who obviously are severely ill.

The congenital defect in bilirubin metabolism present in the Crigler-Najjar syndrome of familial nonhemolytic jaundice results in high levels of indirect-reacting bilirubin, but the onset of jaundice is during the first few days of life and signs and symptoms of kernicterus are frequent.

In regard to jaundice as a complication of pyloric stenosis, the only report we were able to find of such an association was in a paper by Martin and Siebenthal. These authors reported two infants with pyloric stenosis and jaundice. One infant developed symptoms of pyloric obstruction at 6 weeks of age, having had persistent clinical icterus since the second day of life. The other infant developed jaundice at the age of 4 weeks, several days after the
onset of symptoms of pyloric obstruction. Laboratory studies in one patient were limited to a blood count and urine analysis, both being normal. In the other infant, the cephalin flocculation test was normal and the concentration of bilirubin in the serum at the time of admission was 17.3 mg/100 ml, almost all of which was of the indirect-reacting fraction. Both of these infants were treated surgically, and in each case the pylorus was described as being angulated posteriorly and laterally around the gastrohepatic ligament in such a way as to cause compression of the common bile duct.

When this paper was abstracted in the 1956-1957 Yearbook of Pediatrics, Gellis commented that he had also seen "jaundice accompanying pyloric stenosis but without obstruction to the ducts," and that the icterus had promptly cleared after treatment of the pyloric tumor.

The infant we are presenting showed no evidence of a disorder other than pyloric stenosis that could be related to the jaundice. At operation a typical tumor was found and incised. No abnormal displacement of the pylorus was noted, and I believe there is some question as to whether a pyloric tumor can be displaced in such a way as to compress the common bile duct. Within 4 to 5 days after the operation, the jaundice disappeared and the infant has remained well.

In summary, we have presented an infant with jaundice complicating pyloric stenosis. The jaundice reflected a marked increase in indirect-reacting bilirubin in the serum. However, the rapidity of the post-operative decrease in bilirubin in the serum was very much like what would be expected following relief of a biliary tract obstruction.

Why an infant should develop an indirect-reacting hyperbilirubinemia in the presence of pyloric stenosis is perplexing. Martin and Siebenthal suggested mechanical obstruction of the common bile duct by the tumor. Another possibility is that there was an autonomic nervous system imbalance leading to persistent spasm of the common bile duct, and therefore to a functional obstruction. In either case, in an infant of 1 month of age we would expect to see a direct-reacting hyperbilirubinemia, rather than an elevation of the indirect-reacting fraction.

In the hope that he might find an answer to this perplexing problem in the laboratory, we asked Dr. Arias of the Department of Medicine to see this infant. He will tell us the results of his studies and his interpretation of their significance in terms of the present concept of bilirubin metabolism.

Dr. Arias: This patient was observed to have nonhemolytic acholic jaundice in association with hypertrophic pyloric stenosis. On repeated examination there was no bilirubin in the urine; the serum bilirubin was virtually all unconjugated; there was no evidence of hemolysis and the entire picture abated within 5 days after pyloromyotomy. It is not possible to explain fully the sequence of events that can lead to such a situation, but I should like to discuss this case in the light of current knowledge of bile pigment metabolism.

Within the past 5 years the nature of the bilirubin pigments giving the "direct" and "indirect" reaction with diazotized sulphanilic acid has been clarified. Previously it was considered that the indirect reaction was given by bilirubin bound to the protein, globin, and that the direct reaction was given by the protein-free sodium salt of bilirubin; the liver was considered the site of removal of bilirubin from globin. In 1953, Cole and Lathe isolated preparations of bilirubin which, although free of protein, yielded either direct or indirect reactions with diazotized sulphamic acid. In 1956, Billing and Lathe, Schmid, and Talafant demonstrated that direct-reacting bilirubin is primarily bilirubin glucuronide, while the indirect-reacting form is bilirubin itself. Both pigments are bound in serum to albumin, and the conjugated bilirubin is excreted in the bile and urine. Isselbacher has recently shown that a small amount of direct-reacting bilirubin is present as bilirubin sulfate. Biosynthesis of bilirubin glucuronide has been achieved in vitro by incubation of free bilirubin and uridinephosphate-glucuronic acid with microsomes prepared from homogenates of human and animal liver. The microsomal fractions contain an enzyme, glucuronyl transferase, which is capable of transferring glucuronic acid from uridinephosphate-glucuronic acid to a wide variety of receptors, including bilirubin. Exogenous glucuronic acid does not appear to participate directly in glucuronyl synthesis according to the currently accepted concepts of glucuronyl formation.

On the basis of these observations, an in-vitro system has been developed which serves
as an assay of glucuronyl transferase activity. A marked deficiency in glucuronyl transferase activity has been demonstrated in patients with the following types of nonhemolytic acholic jaundice: 1) Familial nonhemolytic acholic jaundice with kernicterus (Krigler-Najjar syndrome)\(^{16}\); 2) constitutional hepatic dysfunction (Gilbert’s disease)\(^{12}\); 3) physiologic jaundice of the premature and newborn\(^{13}\); and 4) nonhemolytic acholic jaundice of the mutant strain of Wistar rats first described by the Canadian geneticist, Gunn.\(^{17}\) Presumably this deficiency accounts for an inability to convert the free bilirubin to the glucuronide and results in retention of unconjugated bilirubin in the serum and tissues.

The patient under discussion had virtually all unconjugated bilirubin in the serum. The liver biopsy was histologically normal. A marked decrease in glucuronyl transferase activity was observed when a homogenate of the patient’s liver was assayed with suitable controls. Following surgery there was a dramatic decrease in the concentration of bilirubin in the serum; bilirubinuria appeared for the first time and the stools were greenish-brown and contained abundant amounts of bilirubin. By the fifth day the patient was no longer icteric.

It is tempting to speculate that the pyloric tumor was related to the jaundice, perhaps by producing biliary obstruction. However, it is obvious that the biochemical alterations were not those of biliary obstruction. The child was too old for a prolonged physiologic jaundice of the newborn and the amelioration of the jaundice indicates that the patient does not have Gilbert’s disease.

In an attempt to produce a similar situation experimentally, the common bile duct was ligated in a series of rats which were 2, 3 and 4 weeks old. The animals were killed at varied time intervals after the ligation and homogenates of their livers were assayed for glucuronyl transferase activity. There was a progressive decrease in glucuronyl transferase activity. In view of these observations, it is attractive to speculate that there may be a substance excreted in the bile which will compete with bilirubin for available substrate. Such an inhibitor has been demonstrated by Lathe and Walker to exist in the serum of pregnant women. Conceivably this would offer an explanation as to why the patient was not able to form bilirubin glucuronide and had a marked decrease in the liver of glucuronyl transferase activity while the common bile duct was obstructed. Suffice it to say, these observations tend to raise more questions than they appear to answer. Further studies are being carried out in an attempt to learn more about the relationship between obstruction of the common bile duct and jaundice in the newborn.

**DR. BARNETT:** Before asking for comments or questions concerning this interesting problem, I might say that having seen this infant and the report by Martin and Siebenthal, we are now beginning to hear of similar patients who have been seen at other medical centers. I wonder if anyone here has observed infants with jaundice accompanying pyloric stenosis?

**VISITING PHYSICIAN:** I have seen one similar patient, a female infant who required two operations, the first having been an incomplete pyloromyotomy. The jaundice in her case disappeared following the second operation.

**DR. BARNETT:** Did she remain jaundiced following the first operation?

**VISITING PHYSICIAN:** The jaundice disappeared following the second operation, but she began to excrete bilirubin in the urine as soon as we corrected the dehydration. I assumed that this resulted from an element of bile inspissation rather than from an enzymatic defect.

**VISITING PHYSICIAN:** I wonder if hydration does not play quite an important role in this sort of thing. In a child who is severely jaundiced, adequate hydration with glucose solution, rather than with electrolyte solutions, seems to increase the rapidity with which jaundice clears.

**DR. BARNETT:** Yes, and also in infants with hemolytic disease.

**VISITING PHYSICIAN:** Dr. Barnett, this description of jaundice with pyloric stenosis has only recently appeared in the literature. We have recognized pyloric stenosis since about 1788 when it was described by Beardsley. The description was forgotten for about 100 years, and then was rediscovered so that its recognition became common after the turn of the century. During these past 50 years, pediatricians have become quite keen about diagnosing pyloric stenosis. Certainly so outstanding a thing as jaundice could not have been overlooked until the last 2 or 3 years.

**DR. BARNETT:** You have never seen jaundice in an infant with pyloric stenosis?

**VISITING PHYSICIAN:** I have never noticed it.
REFERENCES

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