

Evaluation of an Infant with Cholestasis and Congenital Hypopituitarism

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Abstract

We are reporting an infant with persistent abnormal liver function, neonatal jaundice, and intermittent hypoglycemia. Evaluation confirmed congenital hypopituitarism, in the absence of congenital anomalies and midline defect. His jaundice and abnormal liver function improved after treatment with Levothyroxine and hydrocortisone.

Key words: Infant, Jaundice, Hypoglycemia, Hypothyroidism.

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1- INTRODUCTION

The liver is the center for carbohydrate, protein, and fat metabolism. Its role is also to detoxify chemicals in the system. The complexity of the liver machinery and the receptors of the hepatocyte canaliculus help with bilirubin excretion and the formation of bile acids and micelles. The liver can also work independently of insulin to store glucose. The liver function, though, is connected to other organ systems. The liver sets its metabolism based on the foods eaten by short chain fatty acids that circulate into the blood and work in the liver (1). In addition its function is altered based on the health of the endocrine system and hormonal stimulation. It is well known that pan-hypopituitarism can cause metabolic, growth, and bilirubin dysfunction.

2- CASE REPORT

The patient was a 3.758 kg Caucasian male infant was born full term to a 19-year-old gravida 1 para 0 mother. Regular prenatal care was reported. Maternal history was significant for depression treated with fluoxetine and positive Group B streptococcus, treated with ampicillin during labor. Rupture of membranes occurred 12 hours prior to delivery and baby was delivered by cesarean section (C-section) because of failure to progress and was complicated by a nuchal cord and heart rate decelerations. Resuscitation in delivery room included tactile stimulation and blow-by oxygen. Apgar's were 7 and 9 at one minute and five minutes.

Blood sugar on the first day of life was 11 mg/dl. Intravenous (IV) bolus of dextrose 10% (IV D10 bolus) was given at 2ml/kg. The metered blood glucose level normalized to the 60's and then to 80's. His blood glucose dropped to 34 mg/dl when IV fluid was stopped on day 5. Three hours later it dropped to 16mg/dL. IV with 10% dextrose was restarted. Blood tests included TSH 2.7 IU/mL, T4 13.1

ug/dL on day 1 of life. Total bilirubin was 12.5 mg/dL on day 3. The morning cortisol on day 4 was 0.9 mcg/dL (normal: 4.3-22.4), total bilirubin 15.44, direct 0.54 mg/dL. Total bilirubin on day 5 was 11.45 mg/dL. The infant was transferred to a higher center of care for treatment of intermittent hypoglycemia and jaundice. He remained stable in the hospital and was discharged after his examination and work-ups were normal.

He was seen about 2-3 times after discharge at the local clinic but was lost to follow-up after 2 weeks of life. Then the patient presented to our emergency department at 2 months and 3 weeks of age for concerns of jaundice and scleral icterus. Mother reported that he has been jaundiced since birth and it never fully resolved. The infant was exclusively breast-fed. His Bowel movements were reported to be yellowish-gold in color and 2-3 times a day and had dark-colored urine. She denied any fevers, lethargy, feeding difficulties, nausea and vomiting. No sick contacts reported.

He had not yet received his 2-month immunizations; however he did receive Hepatitis B vaccination at birth. He was not on any medications and no allergies were reported. Milestones were consistent with chronological age. Family history was remarkable for maternal depression. No history of liver disease, birth defects, or thyroid disease. The infant lived with his mother and maternal grandparents. Father was deployed in the military. No smokers were reported.

On examination, the infant appeared alert, active, well hydrated but icteric and not in any distress. Vital signs were unremarkable, his head circumference was at the 25th percentile, and his weight and height were both at the 5th percentile. General appearance was not dysmorphic. His eyes were with bilateral scleral icterus. He was normocephalic, with open flat anterior fontanelle. Normal appearing

external ears without skin tags, normal oropharynx, and supple neck without lymphadenopathy. Lungs were clear bilaterally with good air exchange. Heart sounds were normal with no murmur. Good peripheral perfusion was observed. Abdomen was soft and non-tender. The liver edge was palpable 2 cm below the right costal margin. Splenomegaly was not appreciated. The examination of genitalia showed bilaterally descended testes and normal scrotal skin. His spine was normal with no sacral dimple. The neurological exam revealed good head control, normal tone, good suck, and cry.

His developmental skills were appropriate for age. The work up in the emergency department was normal except for potassium of 5.8mEq/L (high), chloride of 98 mEq/L (low), bicarbonate of 20mEq/L (low), glucose of 68 mg/dl, total bilirubin of 16 mg/dL, direct bilirubin 9.9 mg/dL, AST 425 IU/L, ALT1454 IU/L, and PT 14.9 seconds.

Urinalysis was remarkable for a specific gravity of 1.005, pH of 6.5, bilirubin was positive, with trace hemoglobin. His blood type was A negative. Ultrasound study was limited with non-visualization of common bile duct, contracted gallbladder but showed no intra-hepatic duct dilatation. Our differential for conjugated hyperbilirubinemia included extra-hepatic biliary atresia, inborn errors of metabolism and galactosemia, Hypopituitarism, infections, and other common causes of direct hyperbilirubinemia. He was noted as clinically stable with risk of hepatic dysfunction and failure. He was switched to soy-based formula for possible galactosemia. Ursodiol was started at 30 mg/kg/day divided BID (75mg BID) for treatment of possible cholestasis.

An endocrine consult was obtained and further work up was done. This included total cholesterol 258 mg/dL (high), LDL 205 mg/dL (high), Triglycerides 216 mmol/L (high), TSH 6.76 uU/ml (high),

T4 6 ug/dL, Free T4 0.78 ng/dL, Alkaline Phosphatase 624 IU/L, and ammonia 60 mcg/dL. An early morning (9 AM) cortisol was <1.5 mcg/dL (with glucose: 27mg/dL), and insulin <2 uU/mL 1 mcg. The cosyntropin stimulation test did cause the cortisol to increase to 3.2 mcg/dL. Other hormone levels were obtained including ACTH 8 pg/mL, IGF-1 <25 ng/mL (ref: 25-248), LH 4.1 mU/mL, FSH 0.6 ng/dL, prolactin 25.3 ng/mL, and testosterone 5ng/dL.

HIDA scan was done to evaluate for biliary atresia, however it was not definitive due to lack of pre-treatment with Phenobarbital. Serologic testing for Hepatitis A, B and C, EBV, CMV and rubella were negative for recent infection. Alpha-1 Antitrypsin serum level was 154 mg/dL (normal). Urine reducing substances was negative. Newborn screen was negative and he was switched back to breast milk.

Diagnosis of hypopituitarism was made based on the evaluation. The patient was started on levothyroxine and hydrocortisone. A MRI of the pituitary was obtained which showed size of anterior pituitary to be at the lower limits of normal. The patient had persistent intermittent hypoglycemia, necessitating the addition and initiation of growth hormone treatment. The liver function tests responded to this treatment and normalized after several months.

3- DISCUSSION

The association of liver dysfunction with hypopituitarism has been suggested since 1956. Since that time there have been several case reports of cholestasis with hypopituitarism (3-5). Anterior hypopituitarism may present in the newborn period with recurrent hypoglycemia and cholestatic jaundice. Many patients may have midline defects such as cleft palate or cleft lip, microphallus, cryptorchidism and ocular

manifestations. Although congenital hypopituitarism is a well-recognized entity on the differential list for cholestatic jaundice of infancy, it is often missed and unnecessary liver biopsies are done before the diagnosis comes to light. Several factors may be responsible for late diagnosis including ambiguity at presentation, lack of any morphologic abnormalities and lack of detection of recurrent hypoglycemia.

In the reported case, no abnormal physical findings were noted. We emphasize that it is important to consider congenital hypopituitarism even in the absence of features like micropenis, pendular nystagmus and other ocular abnormalities. We recommend that hypoglycemia must be looked for and GH, insulin and cortisol levels measured during the episode.

MRI findings aid in the diagnosis and an ectopic hyper-intense T1 signal or bright spot is predictive of anterior pituitary hormone deficiencies. Attenuation of the stalk is associated with anterior pituitary hormone deficiencies limited to GH and thyrotropin and an inconstant age of onset. Non-visualization of the stalk has been associated with pan-hypopituitarism and an inconstant age of onset 5. In the reported patient, MRI revealed an ectopic neurohypophysis located within the stalk. Thus, we conclude that the anterior pituitary hormone deficiencies were less severe and probably evolved over time. This may explain the course of cholestasis and liver enzyme elevations.

Karnsakul et al. (7), published data on eight infants who presented between the ages of 2 days to 30 days of life. A number of them were noted to have hepatomegaly with other clinical and radiographic findings including Septo-optic dysplasia (SOD), and Holoprosencephaly (HPE). Binder et al. (8), looked at retrospective data from nine infants on the course of cholestasis. The infants appeared to have indirect hyperbilirubinemia at birth

requiring phototherapy that resolved. Direct hyperbilirubinemia presented at 5 to 31 days of life. At and after the patient's maximum elevated direct bilirubin, the authors noted elevation in serum enzymes, 5 days (AST range: 68-432 IU/L), 25 days (ALP range: 360-1918 IU/L), and 50 days (ALT range: 44-329 IU/L). In these cases, normal GGT, Albumin and coagulation studies have been described.

In our patient, the peak direct bilirubin was 9.9 mg/dL noted at presentation on day 86 of life. At that later age, the liver enzymes were elevated (AST was 1454 U/L, ALP 32 U/L, ALT 425 U/L and GGT 48 U/L). The ALP in our patient was comparable to the ALP in the one child described by Binder et al (8), who was diagnosed at school age. The AST and ALT values are among the highest reported.

Extrapolation of the available data and prior case studies, it appears that direct hyperbilirubinemia is seen first in untreated state, followed by a rise in liver enzymes (AST, ALP and then ALT), and a gradual return to baseline. The initiation of treatment with hormone replacement appeared to restore the bilirubin values towards normal quickly with a more gradual fall in liver enzyme levels. The course of cholestasis in our infant correlates with the prior reported case study by Binder et al (8). Larger studies with longer periods of follow-up are needed to plot the course of cholestasis.

The mechanism of cholestasis is not well understood. Leblanc et al. suggested the role of cortisol deficiency (9). In some cases persistent liver dysfunction seen despite adequate hydrocortisone resolved with growth hormone replacement. Giacoia and Macgillvary (10) and Poley et al. (11), supported the role of growth hormone in bile acid secretion. However Hodges and Buckler reported that despite replacement with growth hormone and hydrocortisone, the transaminase level did not resolve for seven months (12). On the

contrary, Binder et al. (8), described a tendency to spontaneous improvement at the age of 2-3 months when hormonal therapy is delayed. In our case, we needed to replace GH for persistent hypoglycemia despite cortisol replacement. Karnsakul et al. (6), pointed out that some children who developed cholestasis eventually were diagnosed as GH deficient. Further studies are needed to definitively prove causality for the cholestasis. However, hormone replacement should be done without delay. There does not seem to be much evidence for permanent liver damage. However, longer follow-up studies are needed to confirm that.

4- CONCLUSION

We conclude that congenital hypopituitarism is an important entity in the differential diagnosis of cholestatic jaundice of infancy even in the absence of morphologic or ocular abnormalities as evidenced from our case. The hormone deficiencies may not be apparent at birth and may evolve gradually. Larger studies are needed to describe the cause and course of cholestasis, resolution of elevated transaminases and long-term effects on the liver.

5- ABBREVIATIONS

ALT: Alanine Aminotransferase Test,
 AST: Aspartate Aminotransferase Test,
 ALP: Alkaline Phosphatase,
 B.i.d: bis in die (twice a day),
 GGT: Gamma-Glutamyl Transferase,
 IU/L: International Units/Liter,
 T4: Total Thyroxine,
 GH: Growth Hormone,
 GGT: Gamma-Glutamyl Transferase,
 EBV: Epstein-Barr virus.
 CMV: Cytomegalovirus.

6- CONFLICT OF INTEREST

The authors did not have any financial relationship with other people or organizations during the study. Hence, there was no conflict of interest in this case.

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