

Congenital adrenal hyperplasia with cholestatic jaundice

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Nisreen Feroz Ali, Areeb Sohail Bangash (Fifth Year Medical Students, Ziauddin Medical University, North Nazimabad, Karachi, Pakistan.)

Farhana Zafar, Abdul Malik, Karimunnisa Mohammedi (Department of Paediatrics, Ziauddin Medical University, North Nazimabad, Karachi, Pakistan.)

Abstract

Congenital Adrenal Hyperplasia describes a group of autosomal recessive disorders characterized by a decrease in Cortisol production. 11 beta hydroxylase deficiencies is the second most common form. However, its presentation with cholestatic jaundice is extremely rare. We present a case of a 29-day-old infant who came to us with unusual dark complexion, persistent jaundice, and electrolyte imbalance. On investigation he was diagnosed as a case of congenital adrenal hyperplasia. Treatment with hydrocortisone and fludrocortisone cleared his jaundice and complexion with subsequent improvement in electrolytes. The aim of this report is to illustrate an unusual presentation of CAH with Cholestatic jaundice. This is the first case to be reported from Pakistan. The case outlines the difficult workup that was encountered in the diagnosis and management of the patient.

Keywords: Congenital Adrenal Hyperplasia, 11 beta hydroxylase deficiency, Cholestatic jaundice, Infant, Hyponatraemia, Hyperkalaemia, Hypocortisolism.

Introduction

The term Congenital Adrenal Hyperplasia (CAH) describes a group of autosomal recessive disorders with a defect in the biosynthesis of Cortisol, and presents with consequent over production of adrenocorticotrophic hormone (ACTH) and secondary adrenal hyperplasia. An enzymatic defect in 11-beta-hydroxylase is the second most common variant of CAH,¹ and accounts for less than 5% of cases.² Patients with this enzymatic defect present with features of androgen excess, which include virilization in females and precocious puberty in male children.³ Approximately two thirds of the patients also present with hypertension, which may or may not be associated with mineralocorticoid excess, hyperkalaemia and metabolic alkalosis.^{2,4}

Case Report

A 29-day-old male infant was presented to the clinic in December 2011, with jaundice since the third day of life, vomiting by the end of 15 days and developed a reluctance to feed for the next four days. The neonate was an outcome of consanguineous marriage, born at term through a normal vaginal delivery, with a birth weight of 3.15 kg. He developed persistent jaundice since the third day of life and vomiting at the end of second week of life. He was exclusively breastfed and contents of vomitus were only ingested milk, it was non projectile and non-bilious. The child was afebrile throughout with normal appetite, but progressively decreased activity. There were no complaints of diarrhoea but his stools were intermittently clay coloured. On the 25th day of life he developed reluctance to feed, for which he was referred to the hospital. No similar presentation or family history of other features of liver or endocrine disease was reported.

On examination, child was noticed to have a dark complexion in comparison to the parents and was icteric. Weight at the time of presentation was 2800 gm, length 54 cm and Occipital Frontal Circumference of 36 cm; blood pressure was 68/46mmHg (90th centile). Systemic examination showed

some dehydration, but was otherwise normal with no visceromegaly appreciated. External genitalia were darkly pigmented, with normal phallus (3cm in length) and bilaterally descended testis. On laboratory workup his septic screening was negative and the infant had persistent hyponatraemia (123mEq/L) and hyperkalaemia (7.5mEq/L) with normal urea and creatinine values hence adrenal work up was done that is shown in Table-1.

Table-1: Adrenal workup.

Test Name	Test Result	Normal Value
ACTH	237pg/ml	Normal upto 46pg/ml
Plasma Renin	2.9ng/ml/h	Normal upto 3.5ng/ml/h
Serum Aldosterone	59ng/ml	Normal upto 31ng/ml
Cortisol	2.8µg/dl	Normal A:M: 3.7-19.4 µg/dl
17 hydroxy progesterone	20 ng/ml	Normal 0.03-0.90ng/ml

Short Synacthen Stimulation Test was done shown in table 2,

Table-2: Short synacthen stimulation test.

Test Name	Test Reult	Normal Value
Basal Plasma Cortisol	2.8 µg/dl	>6.2 µg/dL
Stimulated P.Cortisol 30min	2.9 µg/dl	>21.0 µg/dL
Stimulated P.Cortisol 60min	3.1 µg/dl	>21.0 µg/dL
ACTH	207.0 pg/dl	Upto 46 pg/mL

which was suggestive of primary adrenal failure. As 17 hydroxy progesterone was elevated, >20ng/ml, (normal 0.03-0.9ng/ml) diagnosis of congenital adrenal hyperplasia (CAH) was made.

Due to the persistent jaundice, workup done showed a total bilirubin of 13.28mg/dl (normal 0.3-1.9mg/dl) with a conjugated bilirubin of 8.89mg/dl seen. Mother's blood group was A positive and the child's blood group was AB positive. Coombs test was negative. His SGPT (ALT) was 235IU/L, Alkaline Phosphatase 242IU/L (normal 117-390IU/L) and Gamma Glutaryl Transferase 84IU/L. The markers for viral hepatitis were negative. Thyroid profile was normal. Urine for non-glucose reducing sugar and amino acid chromatography were sent to exclude inborn errors of metabolism, and illustrated negative results. Random blood sugar levels were 77mg/dl.

Keeping in mind his conjugated hyperbilirubinemia of the cholestatic type and persistent vomiting, HIDA scan was done, which showed normal uptake by liver but hepatobiliary tract and gall bladder were not visualized and there was no excretion of dye into the gut (Figure-1),

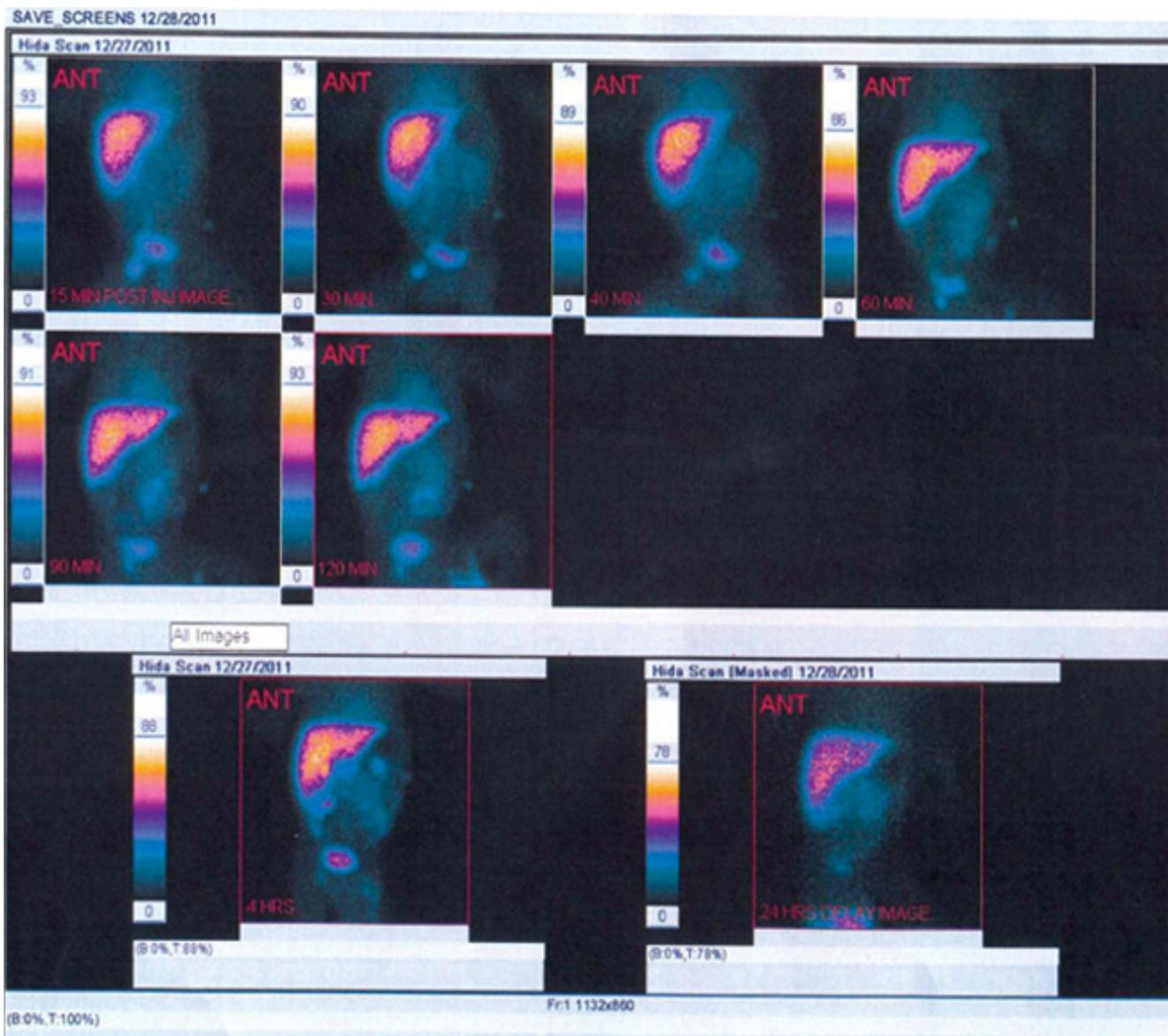


Figure-1: HIDA scan before treatment.

suggestive of biliary atresia, however, the Ultrasound abdomen showed a well outlined gall bladder which made the diagnosis doubtful.

As aldosterone level was elevated, 21-hydroxylase deficiency was excluded and provisional diagnosis of 11-beta hydroxylase deficiency with cholestatic jaundice was made. Treatment was started with hydrocortisone and fludrocortisone at the dose of 15 mg/m²/day and 0.2mg/kg/day in divided doses respectively. This improved the symptoms including complexion, jaundice and vomiting. A drop in bilirubin from 13.2mg/dl to 4.0mg/dl was appreciated in 3 weeks time. Repeat HIDA scan of the patient showed complete excretion of the dye, (Figure-2).

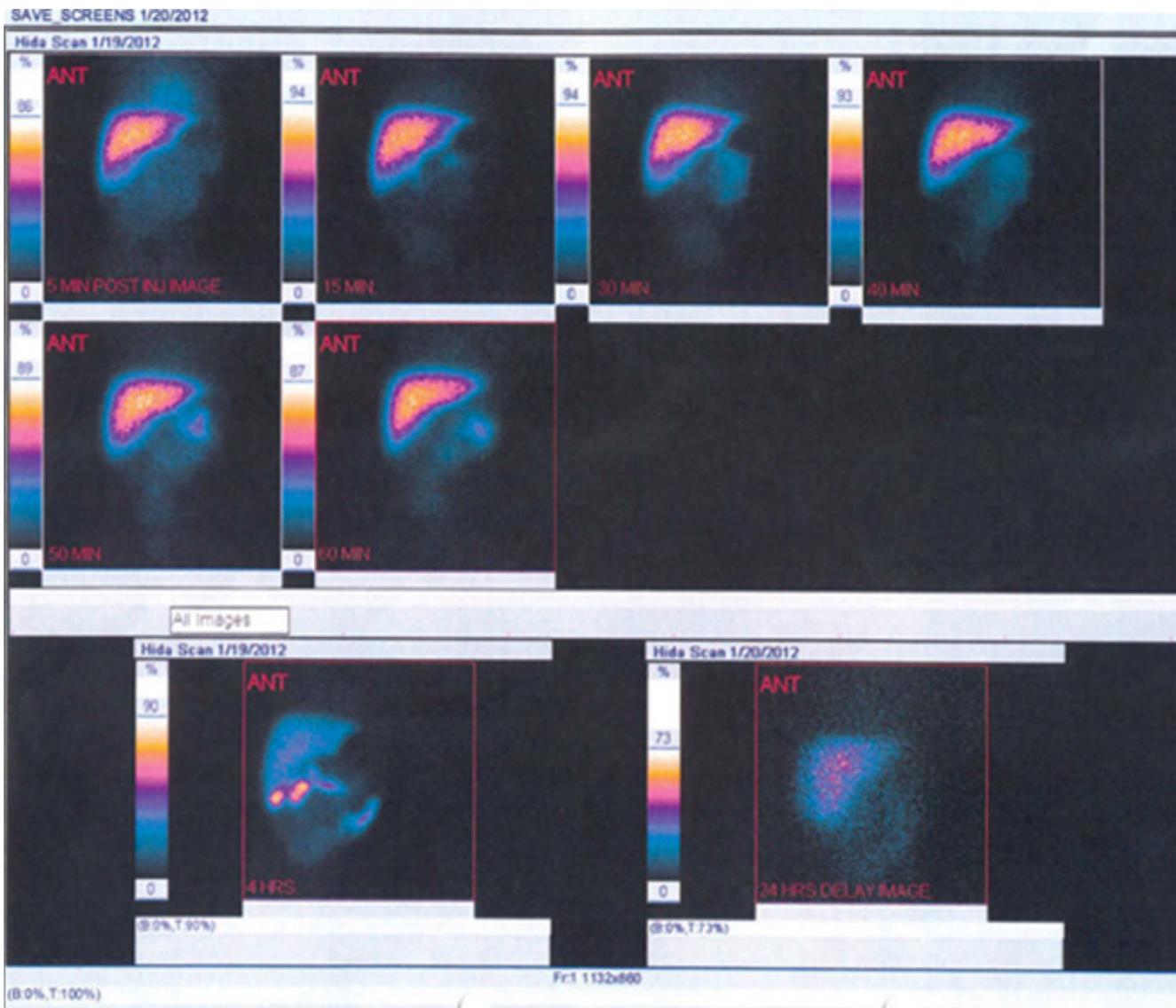


Figure-2: HIDA scan after treatment.

Discussion

Congenital Adrenal Hyperplasia is a rare disease with an incidence of common variety of CAH of only 1:16000 to 1:20000 live births.¹ Five kinds of various enzyme deficiencies are recognized for CAH, we present one of the rarer forms; 11-beta hydroxylase deficiency. With an incidence of 1: 100,000 live births¹ this is due to the mutation of the CYP 11 beta 1 gene on the 8q21-q22. 11-beta hydroxylase mediates the final step in the glucocorticoid pathway and the conversion of 11-deoxycorticosterone (DOC) into corticosterone. Deficiency of the enzyme results in excessive levels of 11-deoxycorticosterone and Dehydroepiandrosterone (DHEA) causing hypertension and virilization in females and precocious puberty in males. The mineralocorticoid manifestations are biphasic. Salt wasting in early infancy followed later by hypertension in mid childhood, due to extreme over production of deoxycorticosterone.⁵

To the best of our knowledge, this is one of the first case reports of CAH with cholestatic jaundice, from Pakistan, with only one case of "Lipoid Congenital Adrenal Hyperplasia Presenting with Cholestasis" reported from Iran.

Neonatal cholestasis is defined as prolonged conjugated Hyperbilirubinemia, typically lasting more than two weeks^{6,7} and affects approximately 1 in 2500 births.^{8,9}

The evaluation of neonatal Cholestasis may appear complicated because of the large number of potential diagnosis such as, biliary atresia, congenital panhypopituitarism, congenital adrenal hyperplasia, neonatal lupus and pseudohypoaldosteronism.

Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations more than 1,000 ng/dL. For the few patients with levels in the range of >630ng/dL (upper limit of reference range for newborns) to 2,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of Cortisol will be low where as in CYP11B2 deficiency, serum Cortisol concentrations are usually normal. Due to the presence of intact 11 beta-hydroxylase 2 (CYP11B2), serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range.¹³ The final diagnosis is based on genetic testing which is not available in Pakistan. The pathophysiology of cholestasis in CAH is unclear, but a lack of glucocorticoid may result in decreased bile secretion into the canaliculi.^{5,10,11} Research based on animal models suggests that Cortisol influences bile formation, furthermore bile flow was reduced in adrenalectomized rats.¹² Hence any alteration in either synthesis or secretion of bile combined with the relative immaturity of the infantile liver could set the stage for cholestasis. Interestingly enough, adrenal insufficiency with cholestasis is limited only to the early infantile period; hepatic manifestations beyond infancy include hypertransaminasemia but not cholestasis.^{14,15}

Furthermore, hyperbilirubinaemia and cholaemia are shown to be associated with hypovolaemia and hyponatraemia. Retained bile acids can reduce fluid reabsorption in the proximal tubule causing volume depletion and hyponatraemia,^{16,17} which in turn causes secondary hyperaldosteronism. In most cases (classical type) mineralocorticoid deficiency explains the electrolyte imbalance.

Conclusion

Rarely, CAH may present itself with persistent conjugated hyperbilirubinaemia leading to difficulty in its diagnosis, with an extensive workup or even surgical intervention required. However, apt identification can lead to the treatment, which is uncomplicated and results in rapid recovery of the patient.

Consent

Written informed consent was obtained from the parents of the patient for publication of this case report.

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