Archives of Pediatrics
Pinto RB, et al. Arch Pediatr 7: 212.
www.doi.org/10.29011/2575-825X.100212
www.gavinpublishers.com

Review Article

Cholestatic Jaundice with Hypoglycemia as a Manifestation of Congenital Endocrine Disorders: A Case Series

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Citation: Pinto RB, Ramos ARL, Santos BJ, Puñales M, Bressiani M, et al. (2022) Cholestatic Jaundice with Hypoglycaemia as a Manifestation of Congenital Endocrine Disorders: A Case Series. Arch Pediatr 7: 212. DOI: 10.29011/2575-825X.100212

Received Date: 01 July, 2022**; Accepted Date:** 06 July, 2022**; Published Date:** 11 July 2022

Abstract

Background: Cholestasis in newborns is a great challenge due to many different etiological factors. Endocrine disorders are an uncommon but important cause of neonatal cholestasis.

Methods: A retrospective review of the medical records of newborns with cholestasis and endocrine disorders was carried out in a tertiary hospital from October 2012 to March 2018.

Results: Six of the 360 patients (1.7%) were included in the study period. The diagnoses were congenital hypopituitarism (2), hypothyroidism (2), and hyperthyroidism (2). The onset of cholestasis occurred with a median age of 10.5 days, and the patients did not have hepatosplenomegaly except for two cases born with fetal hydrops. None of the cases presented acholia. Biochemical tests showed cholestasis associated with a discrete elevation in transaminases and gamma-glutamyltransferase (levels below 300 mg/dL) and no changes in albumin or coagulation tests. A significant finding of the study was the presence of hypoglycaemia in all patients. The median time for the resolution of cholestasis was 96.4 days.

Conclusion: Although uncommon, endocrine disorders should be investigated in neonatal cholestasis. We emphasize the importance of monitoring the presence of hypoglycaemia in patients with neonatal cholestasis and highlight the need to collect a critical sample during the period of hypoglycaemia.

Keywords: Hyperthyroidism; Hypoglycaemia; Hypopituitarism; Hypothyroidism; Neonatal cholestasis

Introduction

Cholestatic jaundice in newborns is very challenging due to many different etiological factors and may be classified as biliary or hepatocellular. Biliary cholestasis results from structural abnormalities and obstruction of extrahepatic or intrahepatic bile ducts, while hepatocellular cholestasis results from impairment in bile transport or genetic or metabolic abnormalities [1]. The most frequent causes of neonatal cholestasis are biliary atresia and a significant number of genetic and metabolic diseases [2]. Cholestasis is defined by the stagnation of bile in the liver resulting from the obstruction of bile flow with the consequent retention of substances normally excreted by bile [1]. Cholestatic jaundice (characterized by increased direct bilirubin) is uncommon, yet it is a potentially serious condition. From a clinical point of view, the child may present with jaundice, choluria, and hypocholia or acholia. Prolonged jaundice (newborns aged over fourteen days) is always pathological and requires careful evaluation [2]. Endocrine disorders are uncommon causes of neonatal cholestasis, and the incidence of this association is unknown. This study aimed to describe clinical and laboratory manifestations as well as the treatment and follow-up of six cases of newborns with cholestasis associated with different endocrine disorders, discussing the importance of considering endocrine disorders in the differential diagnosis of neonatal cholestasis.

Subjects and Methods

A retrospective review of the electronic medical records of all patients with neonatal cholestasis hospitalized at Hospital Criança Conceição (HCC) from October 2012 to March 2018 was carried out. The HCC is a tertiary hospital of the Conceição Hospital Group (GHC), considered the largest pediatric public hospital in the south of Brazil. Each case was individually reviewed, and the inclusion criteria were the presence of neonatal cholestasis during the first three months of life and the diagnosis of endocrine disorders. Neonatal cholestasis was defined as a conjugated (direct) bilirubin of more than 1.0 mg/dL (if total bilirubin was < 5.0 mg/dL) or a direct bilirubin fraction of over 20% of the total (if total bilirubin was > 5.0 mg/dL) [3], confirmed in more than one measurement and/or clinical signs of cholestasis (jaundice, choluria, hypocholia, or acholia). Haematological and biochemical tests were performed at the Central Laboratory of Hospital Nossa Senhora da Conceição (HNSC). Bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT) were analysed by the colorimetric method (MODULAR ANALYTICS test, Roche Diagnostics, Mannheim, Germany). Transaminases were evaluated by the UV optimized kinetic method (MODULAR ANALYTICS test, Roche Diagnostics, Mannheim, Germany). Albumin was analysed by the bromocresol green method (MODULAR ANALYTICS test, Roche Diagnostics, Mannheim, Germany). Glycaemia was performed by the enzymatic UV method (MODULAR ANALYTICS test, Roche Diagnostics, Mannheim, Germany). INR was analysed by the automated coagulometer ACL method (Milan, Italy). Total cholesterol and triglycerides were analysed by the enzymatic colorimetric method (MODULAR ANALYTICS test, Roche Diagnostics, Mannheim, Germany). Reference values of normality were used according to age [4].

Diagnosis criteria for endocrine disorders

In congenital hypopituitarism, growth hormone (GH) deficiency was diagnosed in the presence of hypoglycaemia (reference value < 47 mg/dL) [5] by a serum GH concentration below 5 µg/L (chemiluminescence, SIEMENS, Munich, Germany) and change in at least one additional pituitary hormone and/or the classic triad: ectopic neurohypophysis, hypoplasia, and abnormality of the pituitary gland by magnetic resonance imaging (MRI). In suspect cases, confirmation was obtained through provocation tests [6]. Congenital hypothyroidism was diagnosed by low levels of the thyroid hormone: Total T4 (reference values: 5.1 µg/dL to 14.1 µg/dL) and free T4 (reference values: 0.93 µg/dL to 1.70 µg/dL) via electrochemiluminescence (competitive technique, Roche Diagnostics, Mannheim, Germany). TSH levels may be within the reference values, reduced, or slightly increased (biologically inactive TSH). The TSH reference values were under 15 µUI/mL for the first week of life and 0.80 µUI/mL to 6.3 µUI/mL after the first week of life to eleven months, performed by the electrochemiluminescence method (sandwich assay, Roche Diagnostics, Mannheim, Germany). Neonatal hyperthyroidism was diagnosed by high levels of the thyroid hormone (free T4, total T4) with suppressed levels of TSH. Transplacental antibodies for the TSH receptor (TRAb) are usually present. The TRAb reference value was over 1.75 UI/L, performed by electrochemiluminescence (Roche Diagnostics, Mannheim, Germany). The analyzed data included general information (demographic data, clinical history, follow-up until the resolution of the cholestasis), investigative findings (laboratory, radiology, and pathology tests), treatment, and clinical evolution. The data processing and statistical analysis were performed by creating a database in Excel 6.0 and SPSS software version 15.0 for Windows. A descriptive analysis of the continuous variables was performed through medians and interquartile ranges.

Table 1: Demographic, clinical and radiological data; endocrinological investigation; treatment and outcome of children with neonatal cholestasis and endocrine disorders

Case	Onset of cholestasis (days)	Clinical and radiological manifestations	Hypoglycemia	T4L (RV 0.93 to 1.7 ng/dL)	TSH *	Cortisol (RV 6.2 to 25 mcg/dL)	GH (RV > 5 µg/L)	IGF-1 (RV 15 to 150 ng/dL)	ACTH (RV < 46pg/ml)	Endocrine diagnosis	Treatment outcome (age of resolution of cholestasis)
1(F)	17	BW: 3kg; GA: 38.3 weeks; Apgar 10. Cholestasis, hyponatremia, suspected sepsis, optic nerve atrophy. MRI: brain alterations**.	Yes	0.9	5.92	0.32	1.26	<25	18.6	congenital hypopituitarism	UDCA, prednisolone and levothyroxine. (49 days)
2(M)	57	BW: 3.2kg, GA: 42 weeks, Apgar not available. Transferred at 45 days; dehydrated, hypoactive, anemia and cholestasis. Micropenis. MRI: brain alterations**.	Yes	0.56	10.16	0.43	1.29	< 15		congenital hypopituitarism	UDCA, levothyroxine and prednisolone. (96 days)
3(M)	8	RH incompatibility; intrauterine transfusion; hydrops fetalis. BW: 2.1 kg; GA: 34.5 weeks; Apgar 3. Phototherapy and exchange transfusion; neonatal asphyxia; hepatosplenomegaly; seizures; sepsis; acute renal failure. Brain US: grade 2 hemorrhage.	Yes	1.67	10.14	35				Hypothyroidism	UDCA and levothyroxine.(53 days)
4(F)	2	IUGR. BW: 1.7kg; GA: 36 weeks; Apgar 9; hydrocephalus; cholestasis; congenital toxoplasmosis; microphthalmia in the right eye. Transfontanelar US, Supratentorial hydrocephalus, and periventricular encephalomalacia.	Yes	1.02	10.11					Hypothyroidism	UDCA, levothyroxine and toxoplasmosis treatment. Resolution of jaundice. No laboratory controls for bilirubin. Patient developed West syndrome and died at 15 months.
5(M)	13	Mother presented thyroid storm during pregnancy; obstetric US: hydrops fetalis. BW: 2.2kg; GA: 36 weeks; Apgar 7; cholestasis and hepatosplenomegaly.	Yes	1.18	0.01					Hyperthyroidism	UDCA, methimazole, prednisolone and Lugol's solution. (138 days)
6(F)	2	Gestational maternal hyperthyroidism. Treatment: methimazole, metoprolol and methyldopa. Obstetric US: fetal tachycardia. Fetal MRI: increased uptake in fetal thyroid. BW: 1.7kg; GA: 31.4 weeks; Apgar 7. Newborn with early respiratory dysfunction, hypoglycaemia, suspected sepsis, thrombocytopenia, persistent tachycardia (improvement with propranolol), and sepsis.	Yes	1.25	0.01					Hyperthyroidism	UDCA, Hydrocortisone, propranolol, methimazole and methimazole. (146days)

* TSH: Reference value: up to 1 week – up to 15 mUI\ml; 1 week to 11 months – 0.7 to 6 mUI\mL.

BW: birth weight; GA: gestational age; IUGR: Intrauterine growth restriction; UDCA: ursodeoxycholic acid;

**Reduced sella turcica; ectopic neurohypophysis; no identification of the pituitary stalk.

Results

During the study period, 360 patients were diagnosed with neonatal cholestasis. Six Caucasian patients (1.7%) had diagnoses of associated endocrine disorders: central hypopituitarism (2), hypothyroidism (2), and hyperthyroidism (2), and three were male. The onset of cholestasis occurred with a median age of 10.5 days (2 to 27 days), and the patients did not have hepatosplenomegaly, except for Cases 3 and 5, who were born with fetal hydrops. None of the cases presented hypocholia or acholia. Four cases were premature, and one presented an APGAR score lower than seven (Case 3). The summary of each case is shown in Table 1.

Hematological and biochemistry tests

Regarding the hematological tests, none of the patients presented anemia. Leukopenia was found in two patients (Cases 1 and 4), leukocytosis in one patient (Case 5), and the others were normal. Thrombocytopenia was found in three patients (Cases 3, 4, and 6). The mean (range) levels of liver function tests measured at the baseline were the following: total bilirubin, 10.3 mg/dL (5.9 mg/dL to 19.4 mg/dL); direct bilirubin, 4.0 mg/dL (2.22 mg/dL to 7.73 mg/dL); alanine aminotransferase (ALT), 41.5 U/L (14.2 U/L to 151.75 U/L); aspartate aminotransferase (AST), 138.5 U/L (49.5 U/L to 225.5 U/L); alkaline phosphatase, 246.0 U/L (207.0 U/L to 358.0 U/L); gamma-glutamyl transpeptidase (GGT), 40.0 U/L (38.5 U/L to 269.0 U/L). The prothrombin time (PT) and serum albumin measurements were within the normal ranges in all cases. Transitory hyperlipemia was observed in three patients. The mean cholesterol and triglyceride levels were 155 mg/dL (142 mg/dL to 291 mg/dL) and 165.5 mg/dL (65 mg/dL to 236 mg/dL), respectively.

Serological tests

Serological tests for Toxoplasma gondii, rubella, herpes simplex virus (HSV), syphilis, and cytomegalovirus (CMV), as well as PCR for CMV in urine, were negative in most cases, except for Case 4, which was IgM positive for toxoplasmosis. Serological tests for hepatitis B and C were negative in all cases. Alpha-1-antitrypsin was normal in five cases. The metabolic evaluation included the following: newborn screening (measurement of galactose, plasma amino acid chromatography, immunoreactive trypsin, hemoglobin electrophoresis, TSH, and 17-OH progesterone); chromatography of sugars, amino acids, and oligo- and sialosaccharides; hexosaminidase and chitotriosidase assays; and metabolic profiling (gasometry, lactate, ketonemia, glycemia, electrolytes, cholesterol, triglycerides, and uric acid).

Complementary tests

Abdominal ultrasounds were performed for all patients and showed no hepatosplenomegaly. The magnetic resonance imaging of the hypothalamic-pituitary region was performed on two patients (Cases 1 and 2), with the images showing a reduced size sella turcica, ectopic neurohypophysis, and no pituitary stalk. In Case 4, a brain ultrasound showed ventricular dilatation and leukomalacia. Liver biopsies were performed for two patients to exclude biliary atresia and other liver diseases. In one (Case 1), there was a reduction in the number of bile ducts, but it was not possible to confirm ductopenia due to the insufficient number of portal spaces for immunohistochemical analysis. The other case showed a pattern of neonatal hepatitis with fibrosis with a nodular pattern (Case 5). All patients underwent additional tests for the exclusion of biliary atresia. A slit lamp eye exam was performed in all cases and detected optic nerve atrophy (Case 1) and microphthalmia (Case 4).

Treatment and follow-up

All patients received protein hydrolysate formula, fat-soluble and water-soluble vitamins, and ursodeoxycholic acid at a dose of 15 mg/kg/day until approximately thirty days after the resolution of the cholestasis.

Hormone replacement therapy (HRT) was initiated in both cases with congenital hypopituitarism. Levothyroxine was administered at an initial dose of 50 mcg/m2/day and subsequently adjusted for thyroid function tests (TSH and free T4). Hydrocortisone was administered orally at a dose ranging from 10 mg/kg/m²/day to 15 mg/kg/m2/day. The assessment of possible growth hormone deficiency was postponed because it was not possible to evaluate the GH levels in the presence of hypoglycaemia, but it was confirmed later in the cases with congenital hypopituitarism, and replacement treatment was administered.

Levothyroxine was also administered to the patients with hypothyroidism, and methimazole was initiated at a dose of 0.25 mg/kg/day for patients with hyperthyroidism and used temporarily. The medication was withdrawn as the TSH levels increased due to the elimination of stimulatory transplacental antibodies (TRAb).

In the patient with congenital toxoplasmosis, the specific treatment for the infection was performed.

The median time for the resolution of the cholestasis was 96.4 days, except for Patient 4, in which case there was a loss of follow-up and who died due to a cause unrelated to cholestasis. None of the patients developed chronic liver disease.

Discussion

Neonatal cholestasis may be caused by different etiological factors such as obstructive, infectious, and genetic/metabolic factors, hypoxic-ischemic injuries, and eventually by endocrine disorders. This study identified six patients out of 360 (1.7%) with neonatal cholestasis associated with endocrine disorders. These

findings are similar to the results of the meta-analysis that examined seventeen published studies including 1692 newborns with conjugated hyperbilirubinemia in childhood, of which 33 cases (1.95%) had hypopituitarism or hypothyroidism. The most common etiologies of neonatal cholestasis in this study were idiopathic neonatal hepatitis (26.0%), biliary atresia (25.89%), infection (11.47%), cholestasis associated with parenteral nutrition (6.44%), metabolic disease (4.37%), alpha-1-antitrypsin (4.14%), and perinatal hypoxic-ischemic injury (3.66%) (7). Although cholestasis caused by endocrine disorders is uncommon, it should be evaluated to provide adequate treatment and avoid complications such as mental disabilities in some cases.

The relationship between cholestasis and endocrine disorders may be explained by different mechanisms. Cholestasis in neonates was an important finding in seven out of twenty children (35%) diagnosed **with congenital hypopituitarism** (8). The pathogenesis of cholestasis in hypopituitarism may be related to the deficiency in one or more of the trophic hormones (thyroxine, cortisol, and growth hormone), which may cause the inhibition of the bile acid synthesis, or to a reduced hepatocellular expression of canalicular transport proteins in infants with congenital hypopituitarism (9). The presence of cholestasis and **hypothyroidism** is well documented and seems to be caused by a reduction in the secondary bile flow due to a thyroid hormone deficiency (10,11). On the other hand, in neonatal **hyperthyroidism** affecting the infants of mothers with Graves' disease, which is associated with the transplacental passage of stimulating the antibodies of the mother (TRAb), particularly during the second half of pregnancy (12), the cause of cholestasis is unclear. Cholestasis may be related to the excessive demands of oxygen delivery and free radical generation (13) and may even cause liver failure secondary to high output congestive heart failure (14).

Regarding the anamnesis and physical exam of the newborn with neonatal cholestasis, some clues suggest associated endocrine disorders. In both cases with hyperthyroidism in our study, the maternal history of Graves' disease was important in defining the etiologic diagnosis of neonatal hyperthyroidism. In one of the patients with congenital hypopituitarism (Case 2), the presence of micropenis was observed during the physical examination. This finding in newborns with neonatal cholestasis is highly suggestive of congenital hypopituitarism. In the other patient with this diagnosis (Case 1), optic nerve atrophy was identified through ophthalmoscopy, another frequent finding in congenital hypopituitarism that may be related to central nervous system malformations (15). Thus, a complete anamnesis, physical examination, and ophthalmologic examination are fundamental in evaluating patients with neonatal cholestasis.

Regarding the laboratory tests, the alterations in liver tests were transitory, and none of the patients presented coagulopathy or hypoalbuminemia, which shows that hepatic synthesis was preserved. A significant finding of the study was the presence of hypoglycaemia in all patients, although prematurity and low birth weight may have contributed to the low glycemia in some cases. Therefore, it is very important to monitor the presence of hypoglycaemia in patients with neonatal cholestasis. If confirmed, a critical sample collection (measurement of insulin, cortisol, GH, glucagon, ketone bodies, total CO2, etc.) should be performed at the time of the spontaneous presentation of hypoglycaemia and before treatment (5). Thus, it is possible to evaluate several hormonal parameters involved in the hypothalamic-pituitary axis that may contribute to the occurrence of cholestasis. An important differential diagnosis in newborns with cholestasis who present hypoglycaemia is genetic-metabolic diseases, which should be evaluated (5). Hyperlipidemia was found in three patients although no familial hyperlipidemia was found, but it was transitory. It has also been found in one of eight patients with congenital hypopituitarism, but, in such cases, it was persistent despite the resolution of the cholestasis (15).

A complementary investigation with liver biopsies was necessary to exclude biliary atresia and other causes of cholestasis for two patients. We observed a reduction in the number of bile ducts in one case with congenital hypopituitarism (Case 1). In contrast to our finding, three studies of patients with cholestasis associated with congenital hypopituitarism who underwent liver biopsies observed moderate to severe degrees of cellular and canalicular cholestasis and giant cell transformation of hepatocytes (8,9,15). In one study, fibrosis was found in four of ten patients with congenital hypothyroidism (9), and there was a case report of a child who presented neonatal cholestasis and a late diagnosis of hypopituitarism at five years old that developed into cirrhosis and portal hypertension (16). We also observed a pattern of neonatal hepatitis with fibrosis in one patient with hyperthyroidism (Case 5), but the clinical evolution was excellent.

Although molecular diagnostics is currently considered an important part of the investigation of neonatal cholestasis after excluding biliary atresia, alpha-1-antitrypsin deficiency, and treatable causes of cholestasis (such as choledochal cyst, galactosemia, tyrosinemia, urinary tract infection), the investigation of endocrine disorders is still included in the initial standard battery of tests (17,18). The importance of investigating endocrine disorders in neonates and children with cholestasis is related to the possibility of treatments that avoid important sequelae such as cerebral damage due to unrecognized hypoglycaemia and intellectual deficits due to the late treatment of hypothyroidism or eventually complications of chronic liver disease (8).

This study had some limitations. It was a retrospective study with a small number of patients, and the molecular diagnosis of cholestatic diseases was not carried out because it was not avail-

able at the institution. Another limitation was that, in some cases, other diseases possibly related to cholestasis were also identified: sepsis, severe hemolytic disease, congenital toxoplasmosis, and prematurity. Determining the cause of neonatal cholestasis is a real challenge because the etiology consists of numerous causes, and different etiological factors may occur in the same patient (multifactorial) (15). The most important thing is to define which cause is treatable, such as biliary atresia, galactosemia, sepsis, and endocrine disorders. Indeed, our results contributed to understanding the importance of investigating endocrine disorders in newborns with neonatal cholestasis, given they are treatable causes that must be considered as a differential diagnosis of neonatal cholestasis.

In conclusion, although uncommon, endocrine disorders should be considered in the differential diagnosis of neonatal cholestasis, especially in neonates who have episodes of hypoglycaemia, allowing the treatment of the endocrine disorders and preventing the development of complications. Cholestasis in children with endocrine disorders was transient and there was complete resolution within the first months of life, even in the case with fibrosis with a nodular pattern in the liver histopathological assessment.

Financial Support: No financial support

Disclosure Statement: The authors declare no competing interests

Category of study: Clinical

Consent Statement: Not required

Author Contributions

Study design: R.B.P., A.R.L.R, M.P., O.A.

Sample and data acquisition: R.B.P., A.R.L.R, B.J.S, M.P., M.B., M.M.D., F.N.,O. A.P.A

Data interpretation: All authors

Draft manuscript: R.B.P, M.P., O.A.P.A.

Review and approve manuscript: All authors

Accountability for work: All authors

Conflicts of interest: The authors declare that there is no conflict of interest regarding the publication of this paper

Acknowledgments: The authors would like to thank Valentina de Oliveira Provenzi, MD, for the careful anatomopathological analysis of the liver biopsies and Vânia Naomi Hirakata for the help in the statistical analysis.

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