Revised 3rd Case Presentation for the Course in Clinical Nutrition

GESKES/ SSNC

Case of Congenital Cholestasis due to Congenital Syphilis and its Nutritional Approach

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1. Summary

Congenital cholestasis is a considerable differential diagnostic challenge, necessitating rapid work-up to rule out potentially life threatening conditions and conditions that might require urgent surgical repair or nutritional modifications. Our infant presented with early congenital syphilis. This was marked by an early hepatopathy, transient hypoglycaemia and lactacidosis which was managed conservatively with initial partial parenteral nutrition and rapid introduction of regular enteral nutrition.

2. Key Words

Cholestasis; early congenital syphilis; hypoglycaemia; oral vitamin supplementation; Ursodeoxycholic Acid.

3. Abbreviations

PPHN: persistent pulmonary hypertension of the newborn; VDRL Venereal Disease Research Laboratory; TPHA Treponema pallidum Hemagglutinations Assay; INR international normalized ratio;

4. Introduction

Jaundice, ***requiring treatment (for example phototherapy),*** occurs in 2-15% of newborn infants. [1,2,3] Most often it is due to an elevation in indirect bilirubin, respectively unconjugated bilirubin because of a yet immature enzymatic processing of bilirubin. Neonatal cholestasis, however, is far rarer and estimated to occur in 1:1500-2500 cases. [2,3,4,] Cholestasis needs to be sought in very early hyperbilirubinaemia and in cases of prolonged jaundice. Neonatal cholestasis encompasses a large differential diagnostic list, one that is greater than at any other time in life and poses a diagnostic challenge. [1,2,3,4,5,6,8] In a first approach, one should differentiate extrahepatic from other cholestatic entities.[4,5,6] Clinical signs other than jaundice should help direct further investigations. In the presence of growth restriction and thrombocytopenia, congenital infections need to be considered first. Clinical signs of a bacterial infection, on the other hand, will make an acquired infection more likely. Metabolic disturbances such as acidosis or persistent hypoglycaemia could point to an inherited metabolic disease.

Once the diagnosis has been established, the focus remains on the infant's growth through supportive measures in light of the cholestasis and the potential ensuing complications. [2,3,4,7]

5.1. Case Presentation

MK, born vaginally at 38 4/7 weeks gestation with a birth weight of 2980 g (percentile 7) to a healthy 22 year old G2P1 mother of Central African origin, adapted well with Apgar scores of 8, 9, 10 at 1, 5 and 10 minutes, respectively. Timely antibiotic prophylaxis for positive Group B Streptococcus screen had been applied before delivery. So the baby was transferred to the regular postnatal ward.

He presented at 8 hours of age with a dusky colour, subtle signs of respiratory distress, SaO2 at 88 % on room air, with prompt response to the hyperoxia test, capillary refill time < 2 seconds, hypothermia (35.8 °C), hypoglycaemia of 1.4 mmol/L (defined as glucose < 2.5 mmol/L [17, 18, 20]) and listlessness. His abdomen was slightly distended with discrete organomegaly but non-tender with normal bowel sounds. His skin showed multiple erythematous maculae on the palmo-plantar surfaces, maximally with a 5 mm diameter, a blueish center and hyperpigmented border and with some desquamation. The mother's serologies drawn during the first trimester were negative for lues, HIV, hepatitis B and C, and showed immunity for rubella and toxoplasmosis. We admitted the infant with suspected early onset sepsis for further investigations and immediate intravenous antibiotic treatment with amoxicillin and amikacin as well as intravenous glucose.

The CRP was highly elevated (178 mg/l), Interleukin-6 was not detectable and his white blood cell count of 25.3 G/l (Norm at birth 5-25 G/L) showed a marked left shift (53%). Chest-X-ray and cerebrospinal fluid were normal. He received oxygen via nasal canula at 2 L and maintained saturations of 92 % and above. An extended biochemical panel, drawn because of possible septic complications, revealed biochemical signs of cholestasis (an elevated direct bilirubin, with normal transaminases, γ-GT), normal coagulation screening, normal total protein with Albumin decreased to 23 g/L (Norm 28-44 g/L). The hypoglycaemia normalized within 3 hours with an initial intravenous glucose load of 3.6 mg/kg/Min, supplemented with enteral feeds at 30 ml/kg/day every 3 hours with maternal breast milk and regular infant formula and remained stable thereafter. The initial lactic acidosis of 6.6 mmol/L spontaneously dropped to 2.5 mmol/L with the partial parenteral nutrition and with supplemental enteral feeds within 24 hours of admission. Our infant was always normotonic and never showed signs of seizures nor vomiting, making a metabolic disease or intestinal obstruction less likely.

He required 3 platelet transfusions for thrombocytopenia (minimal value of 27'000 G/L). Echocardiography revealed a moderate pulmonary hypertension, a finding that can be physiological at that postnatal age. His circulatory function remained stable, never requiring vasopressors.

At this stage the working hypothesis was that of neonatal early onset sepsis with concomitant hepatopathy, suggestive either of an antenatal infection, hereditary liver disease or of congenital thalassemia.

Family history was noteworthy for the mother having arrived in Switzerland at the age of 12 years and who had a homozygous alpha+ thalassemia. No information was available from the father, who was also of Central African origin and who had abandoned the mother during pregnancy.

Pregnancy was uneventful and follow up exams including routine serology testing during the first trimester with the gynaecologist described as normal. Upon further questioning the mother remembered a non-pruritic bronze-coloured flat rash on her forearms one month prior to delivery, which is compatible with secondary syphilis. The repeat maternal syphilis serology revealed a seroconversion beyond the first trimester. Reevaluation of the infant confirmed metaphyseal osteitis on long bone x-rays. The repeat cerebrospinal fluid showed no pleocytosis, but slightly elevated TPHA antibodies. The cranial ultrasound images and hearing test were normal, thus neither confirming nor ruling out the diagnosis of neurosyphilis. The infant received penicillin iv. for 10 days for confirmed early congenital syphilis.

In retrospect the palmo-plantar lesions with the hepatopathy, splenomegaly and thrombocytopenia are pathognomonic of early congenital syphilis.

Diagnosis: Term infant with early congenital syphilis

- moderate cholestatic hepatopathy
- transient hypalbuminaemia
- metaphyseal osteitis
- intrauterine growth restriction (small for gestational age)
- ***transient hypoglycaemia***
- possible central nervous involvement
- transient thrombocytopenia

Heterozygous alpha +Thalassemia

Transient Persistent Pulmonary Hypertension of the Newborn

5.2. Further Clinical Course

The PPHN resolved spontaneously within days of admission with just supplemental oxygen via nasal canula. His general condition also returned to normal within 72 hours of admission. Blood cultures remained negative. His cholestatic liver parameters increased over the next few weeks, without the infant developing any liver failure. We were able to wean him off of supplemental intravenous glucose within 72 hours and maintain him on maternal breast milk with an estimated enteral glucose load of 8 mg/kg/Min, for a total of 170 ml/kg/day of breast milk. He was noted to be hyperphagic and thus breastfeeding with satisfactory weight gain. He developed hypocholic stools and was supplemented with Ursodeoxycholic Acid as of the 6th day of life and is currently still under that medication.

Since the hepatopathy did not encompass liver failure, defined as a prothrombin time INR ≥ 1.5 with clinical hepatic encephalopathy or INR ≥ 2 regardless of hepatic encephalopathy [(9)]

and that the liver function parameters were partially normal with albumin spontaneously increasing to normal values, we continued enteral feeds with breast milk and proceeded to supplement the infant with extra vitamins, namely vitamin K 2 mg po weekly, multivitamins as Oranol® 2 x 6 drops daily (with 1500 IU ≈ 450 ug Retinol Palmitate; 450 IU Ergocalciferol; 7 mg Tocopherol; 0.7 mg vitamin B2; 1 mg Pyridoxin; 7 mg Nicotinamid; 5 mg Dexpanthenol; 0.1 mg Biotin; 40 mg ascorbic acid) as well as 1 drop of Oleovit® (400 IU Cholecalciferol) vitamin D daily.

Age	**DOL 1**	**DOL 2**	**DOL 3**	**DOL 4**	**DOL 12**	**4 weeks**	**6 weeks**
Haemoglobin g/l (95-150)	147	141		151	127		98
Platelets	122 (100-400)	34	27	162	240 (150-450)		315
WBC *10^9/l (from DOL2 :3-15)	23.1 (N: 5-25)	25.3	30.3				10.6
Left-shift	53%		<5%				<5%
CRP mg/L (<5)	178	194	111	49	13		
Fe umol/L (10-28)					46	27	16
Transferrin g/L (1.4-4.3)					2.28		1.96
Transferrinsaturation % (20-50)					80		32
Ferritin ug/L (20-250)					2248	1731	676
α-Foetoprotein kU/L					8961	21524	
Albumin g/L (28-44)		23	28		28	32	33
total Protein g/L (46-73)		53					
Prothrombin INR	1.5 (0.7-2.2)	1.3		1.28	1.2 (0.7-1.4)	1	1
total Bilirubin		124	180	104	203	181	117
direct Bilirubin		104	152	84	166	144	100
ASAT U/L (<50)		109	74	389	443	186	168
ALAT U/L (<50)		23	23	192	321	135	87
γ-GT U/L (8-61)		62	43	45	41	58	126
LDH U/L (<1732)		1028					
Ammoniak umol/L (<100)		31					
Lactate mmol/L (0.5-1.7)	6.2	2.6	2.2	2.5	2.8		

Table 1: Laboratory values during the course of the hospital stay and two out patient follow-up values. Abbreviations: WBC white blood cell count; DOL day of life; CRP C-reactive protein; Fe iron; ASAT aspartate aminotransferase ; ALAT alanine aminotransferase; γ-GT gamma glutamyl transpeptidase; LDH lactate dehydrogenase.

Age	Day of life 1	2 weeks	4 weeks
Weight g (Percentile)	2910 (7)	2980 (10)	3620 (10)
Head circumference cm (Percentile)	33.5 (10)	34 (10)	35.3 (10)
Length cm (Percentile)	48 (<3)	49 (3)	51.5 (10)

Table 2: anthropometric data with corresponding percentiles according to Voigt M et al 2010 and Swiss Society of Paediatrics 2011.

6. Discussion

Our patient presented within hours of birth with congenital syphilis, which is unusual. Syphilis, an illness known from antiquity, having humans as sole reservoir, is easily diagnosed and treated, yet still poses a global health threat. Sadly, transmission of syphilis to the fetus results in far greater morbidity and mortality than the primary infection of the adult does. [10,11,14,15,16] Early syphilis is diagnosed before the age of 2 years. [10,15,16] As many as 65% of infants with congenital syphilis will be asymptomatic at birth. The clinical presentation in most cases is non-specific and can encompass signs of a congenital infection (as also seen with other pathogens), typical skin rash in 10-70%, hepatomegaly in 25-70%, central nervous system involvement in about 25 % and long bone involvement in 60-80% as periostitis or osteochondritis. [10,11,12,13] The most frequent skin manifestation is that of small copper coloured maculopapular lesions very similar to the secondary syphilitic lesions, as in our case. [10,11, 12,15] Liver function may be normal despite hepatomegaly, but cholestatic jaundice is common, sometimes accompanied by partial, and most often transient, disease. Typically liver disease will resolve only slowly and sometimes transiently even worsen after treatment begins, as seen in our infant. [10]

Within hours of the clinical course our differential diagnosis rapidly expanded to include first and foremost a congenital infection, because of organomegaly, thrombocytopenia and hepatopathy. What could have led to liver failure in light of the presenting hypoglycaemia, the lactic acidosis and hypalbuminaemia subsequently turned out to be a transient hepatopathy in association with the congenital syphilis. ***Since the infants cholestatic laboratory parpameters were beyond the values stated in the literature in the context of congenital syphillis, we proceeded to rule out some differential diagnoses that would have had immediate therapeutic consequences,*** namely cholestasis due to extrahepatic obstruction and certain metabolic diseases, which would have necessitated rapid nutritional or pharmacological treatment. [1,2,3,4,5] There were no clinical signs, nor further exams suggestive of a syndromal disorder.

The hypoglycaemia detected upon admission was ***initially*** interpreted in the context of the presumed early onset sepsis of the neonate, since impaired glucose homeostasis can be an early sign thereof. [17,]The mechanisms leading to hypoglycaemia during sepsis of the neonate have not been elucidated, but factors could include increased glucose utilization, depleted glycogen stores, or impaired gluconeogenesis. It is commonly agreed that a glucose value < 2.5 mmol/L requires intervention in the high risk infant and is considered for many an operational threshold. [17, 18, 20]. To date there is insufficient scientific evidence to determine a single, concrete cutoff value for hypoglycaemia, especially when considering the fact that up to 5-15% of healthy normal newborns may have transient glucose values as low as 2.2 mmol/L without developing any sequelae. [17,18,19,20] Nevertheless, guidelines as to best clinical practice have been established to assess and treat the high risk infant in a pragmatic approach since there is evidence of neurological sequelae when glucose values drop to 1.7-2.2 mmol/L (measured with the hexokinase method). [17,18,19,20] In such a case, the initial step is to administer intravenous glucose when the infant is considered to be sick (as in our case). If gluconeogenic capacity of the liver is low, the infant will require at least 5-6 mg/kg/Min intravenously to maintain normal brain function alone, since glucose is the most important energy source for the brain. [17,18,19,20] If the response is not satisfactory, the next step is to titrate intravenous glucose and add intravenous fat and amino acids. Glycerol and amino acids will help induce and stimulate hepatic gluconeogenesis. ***Fortunately, our infant responded well to the first measures, ie a combination of intravenous glucose (limited to 3.6 mg/kg/Min because of peripheral vein access) and enteral supplies at about 2 mg/kg/Min on the first day of life.*** [18,19] ***Our infant presented with a short stature and a low birth weight, but otherwise was normally grown for head circumference. Intrauterine growth restriction leads to low or absent hepatic glycogen reserves. This most likely contributed to the hypoglycaemia observed in our infant. His short stature persisted over the above mentioned observation period and is a frequent feature of congenital syphilis.***

The lactic acidosis on initial presentation was also interpreted in the context of the presumed early onset sepsis. In retrospect, however, this was an expression of liver disease. Within 18 hours, the lactate dropped to quasi-normal values and the infant did not present with acute liver failure. We therefore continued normal feeds and did not suspend protein delivery, nor interrupt milk supply. We did proceed to rule out the most frequent inborn errors of metabolism. The appropriate metabolic screens as well as the newborn screen all returned normal.

Interestingly, our infant was able to feed and showed clear signs of hunger soon after admission, despite his respiratory distress with supplemental oxygen need. Infants with liver disease can be initially hyperphagic. [4] This is in stark contrast to the clinical course with true sepsis, asphyxia or inborn errors of metabolism, where the infant's general condition usually declines and the infant is anorexic.

Over the ensuing days we were able to document biochemical parameters compatible with cholestasis. It was only with established feeds (i.e. within 5 days) that he showed intermittent acholic stools, probably because of the meconium initially staining the stools.

With cholestasis and the appearance of steatorrhea, fat and fat-soluble vitamins may be less readily absorbed and lead to malnutrition as well as vitamin deficiency, hence the need to

increase feeds to about 130% of the recommended dietary allowance and supplement with oral vitamins. [2,3,4,6] Recommendations are based on scarce literature and anecdotal evidence. [2,3,4,7] As long as the infant is growing optimally and not showing signs of progressive cholestasis nor metabolic overload of the liver (i.e. developing hyperammonaemia), enteral nutrition, preferably with breast milk, can be continued. If the infant develops anorexia, enteral feeds need to be given via a naso-gastric tube.

Addition of medium chain triglycerides to either breast milk or formula is recommended on a theoretical basis since their solubilisation does not require bile acid micelles, and thus they are readily absorbed into the portal system and easily metabolized by the liver. [2,5,6,8] Our infant showed satisfactory weight gain with breast feeding alone.

Had the cholestasis increased, we would have had to switch to a specific formula, such as Heparon Junior® (Nutricia). This formula consists of a cow's milk based powder, enriched with branched chain amino acids, but with a lower total protein and copper concentration than that of standard formula to reduce hepatic toxicity as well as glucose syrup as the carbohydrate source (as opposed to lactose in regular formula or breast milk).This formula has been shown to improve weight gain, protein mass, muscle mass, nitrogen balance, body composition and mineral content in an animal model. These results then served to develop this special formula. [21]

Infants with cholestatic liver disease can develop secondary lactose intolerance due to loss of brush border enzymes. The underlying pathophysiology of this still remains elusive and has been shown in an animal model to be related to biliary cirrhosis.[22] Had our infant developed diarrhoe we would have had to consider secondary lactose intolerance and switch him to a glucose-based formula.

With persistent cholestasis and steatorrhea, the infant is at risk of developing hypovitaminosis especially of the fat-soluble vitamins, which is why it is generally recommended to supplement infants with extra vitamins, either enterally or intramuscularly, depending on the degree of cholestasis. [2, 3, 4, 6, 7] We opted to do so with an oral polyvitamin solution.

Vitamin A comprises various compounds of naturally and synthetically derived retinoids with resulting diverse biological activity. Based on the content in human milk the recommended intake is of 400-500 ug/day, twith a tolerated upper level of 600 ug/day. [23, 24] In the context of cholestasis, most clinicians recommend increasing the dose to levels ranging from 1500-3000 ug/day. [2, 3, 4, 5, 6] Vitamin A serum levels can be monitored but do not necessarily reflect the true reserves, since it is stored in the liver, and that the determination requires a considerable amount of blood drawn. Chronic intoxication alone can cause liver disease (Ito cell hyperplasia, fibrosis, cirrhosis), or cause other side effects such as pseudotumor cerebri [(25)], but several studies in premature infants with very high doses, i.e. up to 15'000 ug intramuscularly three times a week (with the aim to reduce the rate of bronchopulmonary dysplasia) have not documented any side effects.[23] Our infant received 450 ug/day in addition to what is found in human milk.

Hepatobiliary disease can predispose to rickets, mainly because of malabsorption of vitamin D, but also because of decreased 25-hydroxylase activity in the liver. Of note too is the fact that added bile salts in the intestinal lumen can lead to formation of complexes between bile salts and ionized calcium and interfere with calcium absorption, so it is advisable to also add calcium. Breastfed infants are already at risk of developing rickets because of low vitamin D

content in milk. The Institute of Medicine of the National Academies, the Canadian Paediatric Society, the Swiss Pediatric Society as well as the European Society for Paediatric Endocrinology all recommend 400 IU/day for infants from ***the second week of life to 12 months of age***. In the case of cholestasis, it is recommended to double the dose, which is what we proceeded to do. Excessive vitamin D supplementation can lead to hypercalciuria and eventually hypercalcaemia and associated consequences, an elaboration of which is beyond the scope of this case discussion. Suffice to say that toxicity is observed at very high (> 40'000 IU/day) doses and that upper limits are determined at 1000-2000 IU. [24, 26]

Vitamin E, actually a collective term for eight naturally occurring compounds, functions essentially as an antioxidant (peroxyl radical scavenger) that, in case of deficiency, can lead to neurological disease (including hyporeflexia , ataxia and cerebellar dysfunction) and haemolytic anaemia in the premature infant.[23, 27, 28] Based on vitamin E content in milk, the infant's basic requirements appear to be around 2-4mg/day, however there is insufficient data to conclude absolute values. [23 , 24]There is scarce data on vitamin E toxicity, mainly derived from studies on premature infants receiving extraordinarily high doses (100-200 mg/day). [29] It is therefore difficult to assess an upper limit. Our infant received double the recommended daily dose of 7 mg of vitamin E, which we deemed well below toxic levels.

We also added extra vitamin K enterally rather than intramuscularly, since our infant's prothrombin time was normal. Of note is the fact that newborn babies are at risk of intracerebral haemorrhage because of vitamin K deficiency, which is why all newborn infants should receive 2mg vitamin K at 4 hours, 4 days and at 4 weeks of age. In case of choelstasis and fat malabsorption the infants require weekly doses. The route of application should be guided by the extent of cholestasis. [23, 30]

Since our infant had regressing cholestatic parameters, the cause of which was treated with antibiotics, we declined to monitor vitamin levels. To do so in light of cholestatic liver disease is recommended in monitoring disease progression, since excessive vitamin A and E levels could per se contribute to additional liver toxicity. [2, 3, 4, 5, 6, 23]

We started the infant on ursodeoxycholic acid, since this treatment has been shown to improve the clinical course of cholestasis. [4, 31]

7. Learning points

1. Serologic screening in early pregnancy should not defer a differential diagnosis of congenital infection.
2. Cholestasis with such an early appearance (within days, respectively hours, of delivery) necessitates careful evaluation and differential diagnostic work-up.

3. Disorders of glucose homeostasis that can lead to hyopglycaemia in the neonate may be transient or due to congenital metabolic disease.
4. Pathophysiological difficulties in defining a concrete value of hypoglycaemia are widely discussed in the literature.
5. Cholestatic hepatopathy requires close anthropometric and laboratory monitoring.
6. Cholestatic hepatopathy is a potentially life-threatening condition.
7. Cholestatic hepatopathy, if synthetic liver capacity is maintained, can be managed on an out patient basis with particular emphasis on avoiding fat malabsorption.
8. A special formula adapted to hepatic insufficiency is available in case of biochemical signs of toxicity with human milk or failure to thrive.
9. Vitamin supplementation is crucial, particularly in light of a growing patient.

8. Literature

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