CASE REPORT

Prolonged, but transient, elevation of liver and biliary function tests in a healthy infant affected with breast milk jaundice

Dimitri Poddighe,¹ Lucia Castelli,¹ Gian Luigi Marseglia,² Paola Bruni¹

¹Department of Pediatrics, Ospedale di Circolo di Melegnano, Vizzolo Predabissi, Italy

²Department of Pediatrics, IRCCS Policlinico Fondazione San Matteo, Pavia, Italy

Correspondence to

Dr Dimitri Poddighe, dimimedpv@yahoo.it

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SUMMARY

Unconjugated hyperbilirubinaemia is a common finding in newborns. When it is exaggerated, it is usually investigated in order to exclude several diseases, such as newborn's haemolytic diseases, infections or hypothyroidism. Breast milk jaundice is a form of neonatal jaundice related to breast feeding and it is not usually associated with any clinical issue and/or other laboratory abnormalities. We describe a case of breast milk jaundice being associated, unexpectedly, to significant elevation of plasmatic liver and biliary enzymes. Despite the infant's good clinical condition and growth, several investigations were performed and these ruled out metabolic, infectious and autoimmune liver diseases. All liver function tests normalised by 6–7 months of life. We suggest that the finding of hypertransaminasaemia and hyper- γ -glutamyl transpeptidase in a benign clinical context (similar to what we described) should be followed for 6–7 months before performing sophisticated and expensive diagnostic investigations which aim at excluding some unlikely and severe diseases in a completely asymptomatic infant.

BACKGROUND

Unconjugated hyperbilirubinaemia is defined by a direct fraction <20% of total bilirubin. It is a normal finding in the neonatal period and about 60% of term and late preterm newborns develop so-called 'physiological' jaundice. Indeed, in the first week of life, there is an increased bilirubin production (due to a physiological reduction of red blood cells number): the consequent catabolism of heme, leading to bilirubin production, must be drained by the liver, where actually the enzymatic systems committed to the uptake, the conjugation and the excretion of the bilirubin are functionally immature.¹

The occurrence of jaundice is more frequent in breast fed than in formula-fed newborns. This association between breast feeding and jaundice is explained by two distinct clinical entities. Breast feeding jaundice is due to relative dehydration before lactation onset, when milk intake of breast-fed newborns is limited, promoting an exaggerated enterohepatic circulation of bilirubin. As soon as the breast feeding is stable, jaundice regresses and usually resolves before 10 days of life. Breast milk jaundice usually occurs later and it is due to a poorly understood component of human breast milk, which would increase serum bilirubin levels, remaining elevated for as long as 6–12 weeks.²

The occurrence of exaggerated and/or prolonged unconjugated hyperbilirubinaemia raises the suspicion of non-physiological jaundice, namely due to a pathological condition, such as haemolytic, infectious or metabolic diseases. Despite the jaundiced aspect, newborns with breast milk jaundice appear healthy, grow normally and exhibit no laboratory signs suggesting an underlying disease. However, the presence of abnormalities of laboratory tests consistent with hepatobiliary dysfunction, such as an elevation of aminotransferases and/or γ -glutamyl transpeptidase (GGT), usually prompts to search an ongoing pathological process.³

Although hepatocytes are functionally specialised at birth and bile secretion can start early during intrauterine life (at around 12 weeks' gestation), the liver actually only acquires the fullness of its metabolic properties by 2 years of age. At birth, as soon as the umbilical supply is interrupted, there is a rapid induction of several enzymatic functions, synthesis of coagulation factors and bile production/transport. Therefore, a rise of serum GGT from a low baseline value (of around 30 IU/L) up to 120 IU/L is seen during the first few months of life.⁴ Similarly, as regards alanine aminotransferase (ALT) and aspartate aminotransferase (AST), clinical guidelines on laboratory tests recommend higher reference values for infants compared to older children, being the 97th centile greater than an adult's upper limit.⁵

We report the case of a healthy newborn affected with unconjugated hyperbilirubinaemia (probably because of breast milk jaundice) characterised by a significant and unusual elevation of liver aminotransferases and GGT, which persisted for several months. However, despite several diagnostic efforts, it did not seem to be associated with any definite liver disease.

CASE PRESENTATION

A male full-term newborn was evaluated at our department of paediatrics, because of the onset of jaundice at 15th day of life. Total bilirubin was 18.7 mg/dL and the direct component was 1.2 mg/dL.

The patient was born by vaginal delivery after a regular pregnancy; adaption to extrauterine life was physiological: Apgar scores were 9 (at 1 min) and 10 (at 5 min). At birth, weight (3.730 kg), length (51 cm) and head circumference (35 cm) were appropriate for gestational age. No signs of chronic or acute fetal distress were evident and the only

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abnormal clinical finding at birth was the occurrence of delivery-related cephalohaematoma. He was breast fed and was discharged from the nursery on the third day of life, in the absence of any clinical issue. Family history was not significant and the newborn was the first son.

Initially, unconjugated jaundice was supposed to be linked to the reabsorption of extensive cephalohaematoma, as blood tests, including liver function tests, were normal (AST 74 U/L and ALT 41 U/L). Moreover, baby's clinical aspect was definitely healthy and his growth was regular (4.400 kg). Therefore, the neonate was first discharged from the emergency department and a clinical follow-up programme of jaundice was established with the parents and home paediatrician. Actually, the latter re-evaluated plasma aminotransferases, in addition to checking plasma bilirubin levels in the following days, although jaundice showed an ameliorating trend (plasma bilirubin 17.5 mg/dL at 16th day, 15 mg/dL at 19th day and 12 mg/dL at 22nd day): so doing, a progressive increase of plasma aminotransferases was detected (at 22nd day AST 121 U/L, ALT 60 U/L and GGT 192 U/L). Despite newborn's well-appearing aspect, the paediatrician planned to check laboratory parameters again 1 week later and, surprisingly, he found further increase of liver function parameters (at 29th day of life AST 213 U/L, ALT 132 U/L and GGT 273 U/L) and, therefore, he asked for the admission to our department of paediatrics, in order to perform further investigations. When the patient was admitted, all vital parameters were normal, the growth was regular and no clinical issue emerged through the colloquium with parents, including any drug intake. Moreover, the baby was regularly breast fed.

INVESTIGATIONS

No impairment of liver biosynthetic function was evident: ammonium was normal (105 µg/dL; n.v. 40–120) as well as coagulation parameters (prothrombin time 102%, n.v. 70–120%; activated partial thromboplastin time 35.8 s, n.v. 26–32; fibrinogen 230 mg/dL, n.v. 200–400) and serum albumin levels (5.3 g/dL). Lactate dehydrogenase was increased (884 mU/mL, n.v. 220–450), but no signs of haemolysis were found and the blood count was normal and balanced (white cell count 11 100/mm³, platelet count 357 000/mm³, haemoglobin 14.7 mg/dL, reticulocytes 65 000/mm³). C reactive protein was negative (0.04 mg/dL; normal values 0–0.5). The urinary output was conserved and the urinary dipstick was normal. No changes of stool aspect were detected.

Abdominal ultrasound scan (US) did not show any abnormality of liver, spleen, gallbladder or biliary tract. Although infectious serology panel during pregnancy was not significant, some tests were repeated and they ruled out infections by hepatitis A virus (HAV), HBV and HCV, HIV, Epstein-Barr virus (EBV) and cytomegalovirus (CMV); as for the CMV, urine p72 antigen resulted negative too. Moreover, mother's infectious serology (including rubella virus, characterised by the presence of IgG protective titre and absence of specific IgM) was not consistent with any intrauterine infection.

Urinary copper was low (6.8 µg/24 h, n.v. 3–37) and serum ceruloplasmin was normal (21.3 mg/dL, n.v. 20–60); moreover, there was no family history of Wilson's disease. Thyroid function was conserved. α -1-Antitrypsin deficit was excluded by its measurement in the serum (133 mg/dL, n.v. 90–200). Urinary excretion of fructose (0.20 mg/dL, n.v. 0–4) and galactose (8.09 mg/dL, n.v. 0–60) was in the normal range and other metabolic diseases were excluded by blood measurement of amino acids, succinylacetone and acylcarnitines, through mass spectrometry. Finally, markers of autoimmune hepatitis were all negative (ANA, AMA, ASMA, LKM, p-ANCA).

DIFFERENTIAL DIAGNOSIS

Although the clinical picture and the biochemical panel, in this case of protracted neonatal jaundice, were not consistent with serious liver diseases, the diagnostic work-up aimed at definitely excluding viral illnesses (HAV, HBV, HCV, CMV, EBV, rubella virus), autoimmune hepatitis, metabolic liver diseases (eg, α -1-antitrypsin deficiency, Wilson disease, tyrosinaemia, galactosaemia, progressive familial intrahepatic cholestasis, etc), hypothyroidism and drug-induced hepatitis.

TREATMENT

The patient did not require any therapy. The baby was followed by a 'wait and see' approach, as he was always asymptomatic and all the investigations did not support any definite diagnosis of liver disease.

OUTCOME AND FOLLOW-UP

At 35th day of life, plasma bilirubin levels were significantly decreased (5.75 mg/dL), but liver function test was not changed (AST 285 U/L, ALT 165 U/L and GGT 298 U/L). However, as the baby was always asymptomatic and all the diagnostic investigations did not lead to any suspicion of diagnosable disease, accounting potentially for above abnormalities of liver function tests, a simple follow-up programme was instituted. Therefore, we agreed with parents to repeat the tests monthly, obtaining the results reported in [table 1](#). Basically, bilirubin plasma levels continued to decrease and completely normalised by the second month of life. On the contrary, aminotransferases and GGT levels maintained increased levels for several months and showed a progressive reduction starting from third to fourth month of life, when the baby was weaned. Of course, during all the follow-up period, the parents did not report any symptom and the baby grew up very well. Liver function tests returned to the normal range by sixth to seventh month of life, when the breast milk intake was significantly reduced.

DISCUSSION

We describe the unusual elevation of the plasmatic activity of liver and biliary enzymes in a newborn investigated because of the occurrence of exaggerated unconjugated jaundice. The jaundice became clinically relevant at around 2 weeks of life and was not associated with any symptom and/or growth issue. After an accurate diagnostic work-up, it did not seem to be associated with any disease, such as neonatal infectious illnesses, haemolytic syndromes or congenital hypothyroidism. Thus, the main diagnostic hypothesis was breast milk jaundice. Owing to the finding of abnormal elevation of liver function tests (ALT, AST and GGT), compared with the reference range for age, further diagnostic investigations were prompted, even if baby's clinical condition was optimal and no symptoms were reported. Therefore, a series of laboratory tests were performed and excluded most metabolic diseases that cause those abnormalities of plasmatic liver enzymes.

Viral causes which are usually associated to neonatal hepatitis (HAV, HBV, HCV, CMV and rubella virus) have been excluded, as the related serology was negative in the newborn and mother's analyses during pregnancy were not consistent with any prenatal infection. Moreover, the research of serum auto-antibodies was negative too. Therefore, atypical and mild forms of infectious and autoimmune hepatitis resulted to be unlikely, also because they actually manifest through jaundice characterised by a significant direct component of plasmatic bilirubin, in addition to a concomitant elevation of GGT.⁶ Moreover, idiopathic neonatal hepatitis usually leads to more profound

Table 1 Patient's liver biochemistry (follow-up)

	2 weeks	3 weeks	4 weeks	6 weeks	12 weeks	16 weeks	24 weeks
Liver function tests							
AST (U/L)	76	121	218	285	95	93	42
ALT (U/L)	43	62	139	185	77	64	33
GGT (U/L)	97	192	284	298	140	71	23
Total bilirubin (mg/dL)	17.5	12.7	10.69	5.85	0.97	0.60	0.44
Direct bilirubin (mg/dL)	0.9	0.75	0.85	0.72	0.22	0.14	0.12

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transpeptidase.

abnormalities of liver function tests, including protein synthesis dysfunction. Wang *et al* collected a retrospective series of 103 infants less than 3 months of age with idiopathic hepatitis: almost all patients were affected by conjugated jaundice, although AST and ALT increases were variable with median values ranging between 170 and 210 U/L. In this study, children with idiopathic neonatal hepatitis resulted in having milder disease if their GGT levels were greater than 100 U/L, as it occurred in our patient.⁷ Although our patient showed plasmatic aminotransferases and GGT levels similar to above values (suggesting maybe mild form of idiopathic hepatitis), the jaundice was exclusively indirect and the US findings of the liver were completely normal. Therefore, a diagnosis of idiopathic neonatal hepatitis was ruled out too.

In our case, jaundice ameliorated spontaneously by the first 4–6 weeks of life and plasmatic bilirubin levels were normal at 3 months of age, although the breast feeding was maintained during this period of time, as it is recommended by recent available guidelines. Actually, significant breast feeding was maintained until 6 months of age. Breast milk jaundice is defined as the onset or the prolongation of unconjugated hyperbilirubinaemia in a breastfed baby with regular weight gain and normal production of urine and stools, with no signs or symptoms of disease.⁸ In our opinion, the patient satisfies the above definition, despite bilirubin level exceeding 12 mg/dL, which is seldom described in this clinical context.

The diagnosis of breast milk jaundice is supported by the above definition and by the benign clinical course. What is not common or, at least, not sufficiently investigated or described so far (as regards the features of breast milk jaundice), is the abnormality of liver function tests. Indeed, our patient showed aminotransferases levels being significantly greater than the upper limit of accepted reference range for an infant below 1 year of age. Jorgensen *et al*⁵ studied how feeding mode affected liver biochemistry, including AST, which resulted to be higher in breastfed infants during the first months of life. Similarly, a previous study by Landaas *et al*⁹ found elevated AST and ALT levels, in breastfed infants, up to 75 and 85 U/L, respectively. Even fewer data are available for plasmatic concentration of GGT in children, although it is well known that its value is significantly higher in newborns than older infants: levels up to 120–130 U/L are considered normal in this paediatric population.⁴ No study evaluating plasmatic GGT in breastfed infants is currently available. However, GGT activity of breast milk resulted to be very high during the first weeks of lactation (>3000–7000 U/L) and it showed a 10-fold decrease by 6 months post partum. It is speculated that plasmatic GGT in breastfed infants can be increased also by absorption of GGT from breast milk.¹⁰ GGT is considered an index of cholestasis and it can be useful to detect some paediatric liver disease. While plasmatic GGT can be elevated from 10-fold to 50-fold in biliary atresia, Alagille syndrome or sclerosing cholangitis,

there are other diseases being characterised by milder elevation of this enzyme, as it occurs in some forms of progressive familial intrahepatic cholestasis.¹¹ Finally, transient neonatal cholestasis is described too, particularly in newborns affected by acute perinatal distress and/or intrauterine growth retardation.¹² These clinical entities are different in aetiology and prognosis, but all are invariably characterised by the onset of some degree of direct jaundice. For this reason, those were not considered in the differential diagnosis of our case of neonatal hypertransaminasaemia. Therefore, clinical and laboratory findings are not consistent with cholestatic disease, despite the elevation of plasmatic GGT. It resulted to be higher than usual reference values for age, but milder than expected for diseases leading to important neonatal cholestasis.

In conclusion, we considered a diagnosis of breast milk jaundice. However, in our opinion, the main point arising from this experience is that transient hypertransaminasaemia and hyper-GGT might be an ancillary finding of exaggerated physiological or breast milk jaundice, at least in some cases. We propose that babies showing transient physiological jaundice with mild-to-moderate elevation of liver function test, but no symptoms and/or growth retardation, should be managed by periodical follow-up to ascertain the normalisation of laboratory parameters by 6 months of life. Further sophisticated and expensive diagnostic work-up (namely, specific metabolic and autoimmune investigations) should be reserved to symptomatic infants and/or with progression/persistence of laboratory abnormalities.

Learning points

- ▶ Exaggerated physiological or breast milk jaundice might be associated to abnormalities of liver function tests in some patients.
- ▶ Elevation of liver aminotransferases and γ -glutamyl transpeptidase (GGT) in newborns and infants younger than 6 months can be prolonged, even in the absence of any liver disease.
- ▶ Hypertransaminasaemia and/or hyper-GGT in a well-being and regularly growing infant, in the absence of risk factors, should be observed until sixth to seventh month of life, before performing sophisticated and expensive diagnostic investigation.

Contributors DP conceived and drafted the manuscript. LC contributed to the acquisition and interpretation of clinical data. GLM and PB critically revised the manuscript and provided important intellectual contributions.

Competing interests None.

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REFERENCES

- 1 Lauer BJ, Spector ND. Hyperbilirubinemia in the newborn. *Pediatr Rev* 2011;32:341–9.
- 2 Gartner LM. Breastfeeding and jaundice. *J Perinatol* 2001;21:S21–9.
- 3 Clayton PT. Inborn errors presenting with liver dysfunction. *Semin Neonatol* 2002;7:49–63.
- 4 Beath SV. Hepatic function and physiology in the newborn. *Semin Neonatol* 2003;8:337–46.
- 5 Jorgensen MH, Ott P, Juul A, *et al.* Does breastfeeding influence liver biochemistry? *J Pediatr Gastroenterol Nutr* 2003;37:559–65.
- 6 Brumbaugh D, Mack C. Conjugated hyperbilirubinemia in children. *Pediatr Rev* 2012;33:291–302.
- 7 Wang JS, Tan N, Dhawan A. Significance of low or normal serum gamma glutamyl transferase level in infants with idiopathic neonatal hepatitis. *Eur J Pediatr* 2006;165:795–801.
- 8 Soldi A, Tonetto P, Varalda A, *et al.* Neonatal jaundice and human milk. *J Matern Fetal Neonatal Med* 2011;24:85–7.
- 9 Landaas S, Skrede S, Steen JA. The levels of serum enzymes, plasma proteins and lipids in normal infants and small children. *J Clin Chem Clin Biochem* 1981;19:1075–80.
- 10 Colagiovanni DB, Meyer DJ, Wolf JM, *et al.* High gamma-glutamyl-transferase (GGT) activity in human breast milk confounds interpretation of high serum GGT activity in a nursing infant with liver disease. *Clin Chem* 2005; 51:1750–1.
- 11 Cabrera-Abreu JC, Green A. Gamma-glutamyltransferase: value of its measurement in pediatrics. *Ann Clin Biochem* 2002;39:22–5.
- 12 Jacquemin E, Lykavieris P, Chaoui N, *et al.* Transient neonatal cholestasis: origin and outcome. *J Pediatr* 1998;133:563–7.

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