Neonatal Hepatitis in Premature Infants Simulating Hereditary Tyrosinosis

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Yu, J. S., Walker-Smith, J. A., and Burnard, E. D. (1971). *Archives of Disease in Childhood*, 46, 306. Neonatal hepatitis in premature infants simulating hereditary tyrosinosis. Three premature infants are reported who developed obstructive jaundice in the first 3 months of life, with a chemical and histological picture consistent with neonatal hepatitis. The disease was complicated by gross generalized aminoaciduria, rickets, and anaemia. Serum tyrosine levels were raised to $0.28-1.64 \mu\text{mole/ml}$ in 2 infants, and did not fall in response to ascorbic acid given orally. The infants recovered over the next 3 to 5 months without specific therapy. Many features of the illness in the 3 infants are suggestive of hereditary tyrosinosis, but the transient nature of the illness excluded this diagnosis.

It is suggested that the infants had neonatal hepatitis and that the aminoaciduria and rickets were complications of the hepatitis and the prematurity. The recognition of this syndrome of neonatal hepatitis simulating tyrosinosis is important, if unnecessary and possibly dangerous therapy directed at hereditary tyrosinosis is to be avoided.

A high serum tyrosine level may be found in the neonate (Wong, Lambert, and Komrower, 1967; Partington, 1968) in liver disease (Levine and Conn, 1967) and more specifically in hereditary tyrosinosis (Sakai and Kitagawa, 1957; Gentz, Jagenburg, and Zetterström, 1965; Halvorsen *et al.*, 1966). Hereditary tyrosinosis is an inherited metabolic disorder characterized by hepatocellular liver damage which may progress to cirrhosis, hypophosphataemic rickets, renal tubular defects, skin pigmentation, and a moderately raised serum tyrosine. When recognized early, the clinical course can be modified by a restriction of phenylalanine and tyrosine in the diet (Sass-Kortsak *et al.*, 1967; Fairney *et al.*, 1968). The case histories of 3 premature infants with neonatal hepatitis are described in whom complications produced a clinical picture like hereditary tyrosinosis.

Reports

Case 1. This infant was delivered at 30 weeks' gestation with a birthweight of 1600 g. He developed the respiratory distress syndrome. Jaundice developed

on the third day and by the fourth day the serum bilirubin reached 14.1 mg/100 ml , of which 12.9 mg was conjugated. There were no reducing sugars in the urine. A routine urine chromatogram showed a generalized aminoaciduria, with a pattern similar to that seen in prematurity. The jaundice faded slowly but reappeared at 5 weeks when he was noted to be pigmented and unwell. The haemoglobin was 9.6 g/100 ml and the serum bilirubin 4.1 mg/100 ml , with 2.4 mg direct reacting. The stools were pale and hepatosplenomegaly was noted. On admission to the Royal Alexandra Hospital for Children, his bilirubin had risen to 8.8 mg/100 ml (direct 7.1 mg/100 ml), the serum alkaline phosphatase was 134 K.A. units , and the serum aspartate aminotransferase (SGOT) was 235 Karmen units . Serological tests for syphilis, rubella, and cytomegalovirus were negative. A generalized aminoaciduria persisted and a Millon's test was strongly positive for tyrosine and its metabolites, but a ferric chloride test was negative. Serum tyrosine level was raised ($0.28 \mu\text{moles/ml}$) and this did not fall after oral ascorbic acid 100 mg 3 times a day. The serum methionine and serum phenylalanine were normal ($0.044 \mu\text{moles/ml}$ and $0.118 \mu\text{mole/ml}$ respectively). X-rays of the long bones showed well-developed rachitic changes at 15 weeks, with a serum calcium 7.4 mg/100 ml , serum phosphorus 4.6 mg/100 ml , and serum alkaline phosphatase $70 \text{ K.A. units/100 ml}$.

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Up to this time he had received the routine amounts of vitamin D, 400 IU per day. A liver biopsy showed neonatal hepatitis with giant cells and prominent hepatocellular damage. An operative cholangiogram was normal.

By the time a diagnosis of hereditary tyrosinosis was entertained, he was showing considerable clinical improvement without specific therapy, and his amino-aciduria and raised serum tyrosine level had disappeared (see Table II). This excluded a diagnosis of hereditary tyrosinosis.

He was last seen at 30 months when he was thriving and clinically normal. His liver function tests were normal, his rickets healed, and his urinary amino acid pattern was normal.

Case 2. This child was born at 28 weeks' gestation with a birthweight of 1021 g. He was the second of non-identical twins and at 2 minutes his Apgar rating was 8/10. He had severe recurrent apnoea. At 10 days of age, a routine test on the urine with Millon's solution was strongly positive and his serum tyrosine was raised ($1.16 \mu\text{moles/ml}$), but serum methionine and serum phenylalanine were normal ($0.012 \mu\text{moles/ml}$ and $0.097 \mu\text{moles/ml}$, respectively). The level of serum tyrosine did not fall following the use of ascorbic acid, and reached a peak of $1.64 \mu\text{moles/ml}$ (see Table II).

At 6 weeks of age he looked slightly jaundiced, pigmented, and his liver was enlarging. The serum tyrosine was $0.54 \mu\text{moles/ml}$, bilirubin 1.3 mg/100 ml , SGOT 45 Karmen units, SGPT 40 Karmen units. A month later the bilirubin had risen to 3.5 mg/100 ml , SGOT 106 Karmen units and SGPT 56 Karmen units. Serological tests and cultures for cytomegalovirus, mycoplasma, toxoplasmosis, and rubella were all negative.

The infant was discharged aged 5 months, still jaundiced and still with hepatomegaly. He was admitted to the Royal Alexandra Hospital for Children for liver biopsy at 6 months. This showed the histological picture of neonatal hepatitis. There was a focal inflammatory reaction with some multinucleated giant cells but little bile stasis. Serum bilirubin 3.3 mg/100 ml (direct 2.2 mg/100 ml), SGOT 360 Karmen units, and SGPT 200 Karmen units. When last seen at $2\frac{1}{2}$ years a slightly palpable liver was the only anomaly detected.

The other twin had a birthweight of 906 g, and after an episode of the respiratory distress syndrome which was less severe than that of our patient, settled without any complication. She had an early period of mild transient jaundice which settled in 3 days. Her tyrosine was higher than that of her twin at 10 days ($1.64 \mu\text{moles/ml}$).

Case 3. This aboriginal infant was seen at 2 days because of jaundice and weighed 1520 g. Over the next 3 months he was nursed in a country hospital because of his small size, persistent jaundice, and recurrent chest infections. At 3 months he was transferred to the Royal Alexandra Hospital for Children. On admission he was jaundiced with a liver palpable

1 cm below the costal margin. Serum bilirubin was 4.5 mg/100 ml (direct 3.7 mg/100 ml), SGPT 120 Karmen units, Hb 8.0 g/100 ml , with reticulocytes 5% and a film suggestive of haemolysis. He had a gross generalized aminoaciduria. The tyrosine spot was noted to be particularly heavy, but no quantitation was performed. There was no glycosuria. X-ray of the long bones showed rachitic changes, serum calcium was 7.7 mg/100 ml , phosphorus 2.9 mg/100 ml , (phosphorus result repeated), and a serum alkaline phosphatase 83 K.A. units. Serological tests for toxoplasmosis, rubella, syphilis, and cytomegalovirus were negative.

Liver biopsy showed some giant cell transformation and bile retention, but with minimal alteration to liver architecture, i.e. the picture of neonatal hepatitis of mild degree.

He improved slowly on a normal diet with normal vitamin supplements. The jaundice and hepatomegaly resolved over the next 2 months. When seen at 5 years of age there was no clinical or chemical evidence of liver disease. His serum and urinary amino acids were normal and there were no sequelae to his earlier rickets.

Discussion

Neonatal or giant cell hepatitis is characterized by obstructive jaundice in the first 3 months of life. Its clinical picture, histology, and prognosis have been well described (Craig and Landing, 1952; Brent, 1962; Gellis and Kibrick, 1964; Thaler and Gellis, 1968). The 3 infants described (Table I) fulfil the criteria of the syndrome of neonatal hepatitis.

The presence of hyperpigmentation, amino-aciduria, and high serum tyrosine levels in 2 infants, 1 of whom also had rickets, strongly suggested the possibility of hereditary tyrosinosis. Though a serum tyrosine level was not estimated in the third infant, the similarity of the clinical features, particularly the aminoaciduria with a heavy tyrosine spot, also suggested this diagnosis. However, it was excluded in all 3 infants by the non-progressive nature of the initial illness and the subsequent recovery of the infants.

Raised serum tyrosine levels are often seen in the neonatal age group, particularly in premature infants (Avery *et al.*, 1967). Unlike our infants, tyrosyluria of the newborn usually responds to large doses of ascorbic acid. The infants described here had a positive Millon-reacting urine initially, but abnormal phenolic acids could not be seen in the urine after admission to the Royal Alexandra Hospital for Children. It seems probable that the raised serum tyrosine levels and the amino-aciduria were related to prematurity (Levine and Conn, 1967).

TABLE I
Clinical Data and Investigations

	Case 1	Case 2	Case 3
Birthweight (g)	1600	1021	1520
Initial onset of jaundice	3 days	3 days	2 days
Exacerbation of jaundice	6 weeks	5 weeks	4 weeks
Duration of jaundice	20 weeks	15 weeks	20 weeks
Maximum bilirubin after 3 weeks age	4.4 mg/100 ml (direct 3.5)	8.6 mg/100 ml (direct 6.2)	4.5 mg/100 ml (direct 3.7)
Pigmentation	+	++	None
Maximum SGOT (Karmen units/ml per min)	235	360	67
SGPT (Karmen units/ml per min)	198	200	120
SAP (K.A. units/100 ml)	134	62	83
Minimum Hb (g/100 ml)	8.3	8.0	8.0
X-ray evidence of rickets	Yes	No	Yes
Urinary amino acids	++	++	++
Maximum serum tyrosine (μ mole/ml)	0.28	1.64	Not done

TABLE II
Plasma Amino Acids (μ moles/ml)

	10 Days		17 Days		36 Days		51 Days	
	Case 2	Twin Sib	Case 2	Twin Sib	Case 2	Twin Sib	Case 2	Twin Sib
Taurine	0.039	—	0.040	0.032	0.024	0.022	0.041	0.024
Urea	0.002	—	0.008	0.007	0.004	0.005	0.006	0.004
Threonine	0.370	0.290	0.595	0.373	0.342	0.345	0.278	0.214
Serine	0.381	0.409	0.427	0.335	0.287	0.329	0.337	0.232
Glutamine	0.197	0.264	0.395	0.255	0.275	0.186	0.241	0.176
Proline	0.357	0.291	0.397	0.275	0.253	0.411	0.341	0.457
Glutamic	0.200	0.253	0.101	0.155	0.130	0.175	0.159	0.210
Glycine	0.460	0.458	0.381	0.371	0.294	0.335	0.328	0.304
Alanine	0.390	0.255	0.325	0.300	0.304	0.295	0.344	0.365
Valine	0.247	0.192	0.310	0.229	0.262	0.289	0.228	0.150
Methionine	0.012	0.022	0.027	0.019	0.021	0.017	0.040	0.015
Isoleucine	0.080	0.072	0.090	0.065	0.085	0.098	0.086	0.056
Leucine	0.141	0.129	0.186	0.121	0.158	0.187	0.137	0.101
Tyrosine	1.161	0.817	1.642	0.859	1.231	0.524	0.540	0.229
Phenylalanine	0.097	0.093	0.136	0.081	0.093	0.117	0.100	0.076
Ornithine	0.137	0.218	0.265	0.175	0.190	0.189	0.175	0.092
Lysine	0.241	0.191	0.349	0.223	0.316	0.294	0.250	0.254
Histidine	0.091	0.106	0.133	0.088	0.097	0.083	0.106	trace
Arginine	0.085	0.131	0.146	0.102	0.122	0.097	0.090	0.092
Total amino acids	4.686	4.191	5.953	4.113	4.384	3.993	3.821	3.047

Rickets occurred in two infants despite routine amounts of vitamin D orally (400 IU daily). Norman, Strandvik, and Zetterström (1969) found no clinical or biochemical evidence of rickets in 4 cases of long-standing neonatal hepatitis with marked intrahepatic cholestasis despite gross steatorrhoea, low bile acid secretion and obvious vitamin A malabsorption. However, De Luca (1969) has shown that vitamin D is hydroxylated to its active biological form in the liver. The impairment of this step in the hepatic parenchymal damage found in neonatal hepatitis may be important in the pathogenesis of the rickets.

The 3 infants reported had neonatal hepatitis, but the clinical picture resembled hereditary

tyrosinosis in many features and, in the acute phase, could have been misdiagnosed as hereditary tyrosinosis and the infants started on a synthetic diet deficient in tyrosine and phenylalanine. With the increasing use of screening tests, infants with high serum tyrosine levels will be recognized more frequently. Caution must be used in interpreting such results, especially in premature infants. Any treatment involving diets deficient in essential food factors should only be prescribed when skilled dietary advice and continuous laboratory control are available.

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REFERENCES

- Avery, M. E., Clow, C. L., Menkes, J. H., Ramos, A., Scriver, C. R., Stern, L., and Wasserman, B. P. (1967). Transient tyrosinemia of the newborn: dietary and clinical aspects. *Pediatrics*, **39**, 378.
- Brent, R. L. (1962). Persistent jaundice in infancy. *Journal of Pediatrics*, **61**, 111.
- Craig, J. M., and Landing, B. H. (1952). Form of hepatitis in the neonatal period simulating biliary atresia. *Archives of Pathology*, **54**, 321.
- DeLuca, H. F. (1969). Vitamin D. *New England Journal of Medicine*, **281**, 1103.
- Fairney, A., Francis, D., Ersser, R. S., Seakins, J. W. T., and Cottom, D. (1968). Diagnosis and treatment of tyrosinosis. *Archives of Disease in Childhood*, **43**, 540.
- Gellis, S. S., and Kibrick, S. (1964). Giant cell hepatitis versus bile duct atresia in the neonate. *Clinical Pediatrics*, **3**, 355.
- Gentz, J., Jagenburg, R., and Zetterström, R. (1965). Tyrosinemia. An inborn error of tyrosine metabolism with cirrhosis of the liver and multiple renal tubular defects. *Journal of Pediatrics*, **66**, 670.
- Halvorsen, S., Pande, H., Løken, A. C., and Gjessing, L. R. (1966). Tyrosinosis. A study of 6 cases. *Archives of Disease in Childhood*, **41**, 238.
- Levine, R. J., and Conn, H. O. (1967). Tyrosine metabolism in patients with liver disease. *Journal of Clinical Investigation*, **46**, 2012.
- Norman, A., Strandvik, B., and Zetterström, R. (1969). Bile acid excretion and malabsorption in intrahepatic cholestasis of infancy ('neonatal hepatitis'). *Acta Paediatrica*, **58**, 59.
- Partington, M. W. (1968). Neonatal tyrosinaemia. *Biologia Neonatorum*, **12**, 316.
- Sakai, K., and Kitagawa, T. (1957). An atypical case of tyrosinosis. *Jikeikai Medical Journal*, **4**, 1.
- Sass-Kortsak, A., Ficici, S., Paunier, L., Kooh, S. W., Fraser, D., and Jackson, S. H. (1967). Observations on treatment of patients with tyrosyluria. *Canadian Medical Association Journal*, **97**, 1089.
- Thaler, M. M., and Gellis, S. S. (1968). Studies in neonatal hepatitis and biliary atresia. *American Journal of Diseases of Children*, **116**, 257.
- Wong, P. W. K., Lambert, A. M., and Komrower, G. M. (1967). Tyrosinaemia and tyrosyluria in infancy. *Developmental Medicine and Child Neurology*, **9**, 551.

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