Neonatal cholestasis and hypopituitarism

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SUMMARY The diagnosis of optic nerve hypoplasia and hypopituitarism must be entertained in infants who present for evaluation of cholestatic jaundice, particularly if there is associated hypoglycaemia and wandering nystagmus. Although the hepatic dysfunction seems to resolve, the long term prognosis of liver disease in optic nerve hypoplasia remains unknown.

Optic nerve hypoplasia with hypopituitarism and intact septum pellucidum is a variant of septo-optic dysplasia or deMorsier's syndrome.[1] Although neonatal jaundice has been seen with this syndrome, the association with severe prolonged cholestatic jaundice has not been emphasised. We describe three patients who presented with cholestatic jaundice and were found to have optic nerve hypoplasia and hypopituitarism.

Case reports

Patient 1. A 2 month old girl was evaluated for prolonged jaundice, hepatomegaly, and hypoglycaemia; her length and weight were at the 10th centile. She had scleral icterus, wandering nystagmus, bilateral optic nerve hypoplasia, and hepatomegaly. Liver function tests showed cholestasis (Table) and an open liver biopsy was performed. An

Table *Results of liver function tests*

	Age				
Patient 1	*1 day*	*2 months*	*4 months*	*1 year*	*2 years*
Lactate dehydrogenase (IU/l)	291	432	256	270	251
Serum glutamic oxalo-acetic transaminase (IU/l)	1416	1414	211	55	29
Serum glutamic pyruvic transaminase (IU/l)	528	526	186	54	23
Total bilirubin (μmol/l)	1·4	0·9	0·2	0·01	0·01
Direct bilirubin (μmol/l)	0·2	0·2	0·06	ND	ND
Alkaline phosphatase (IU/l)	270	291	185	18	86
Prothrombin time (sec)	ND	10·9	ND	ND	ND
Cholylglycine (μmol/l)	ND	40·9	ND	2·7	ND
Serum glucose (mmol/l)	ND	1·4	1·2	3·8	4·6
Patient 2	*2 weeks*	*2 months*	*4 months*	*1 year*	
Lactate dehydrogenase (IU/l)	310	262	268	225	
Serum glutamic oxalo-acetic transaminase (IU/l)	78	53	49	28	
Serum glutamic pyruvic transaminase (IU/l)	45	32	51	21	
Total bilirubin (μmol/l)	0·9	0·2	0·01	0·01	
Direct bilirubin (μmol/l)	0·2	0·05	ND	0·005	
Alkaline phosphatase (IU/l)	220	419	251	132	
Prothrombin time (sec)	10·4	ND	ND	ND	
Cholylglycine (μmol/l)	39·9	66·3	ND	3·1	
Serum glucose (mmol/l)	1·6	3·2	4·6	4·6	
Patient 3	*1 week*	*2 months*			
Lactate dehydrogenase (IU/l)	260	280			
Serum glutamic oxalo-acetic transaminase (IU/l)	131	123			
Serum glutamic pyruvic transaminase (IU/l)	146	37			
Total bilirubin (μmol/l)	0·4	0·4			
Direct bilirubin (μmol/l)	0·3	0·3			
Alkaline phosphatase (IU/l)	525	363			
Prothrombin time (sec)	10·6	ND			
Serum glucose (mmol/l)	ND	2·8			

All patients had a negative workup for congenital infection and hepatitis. Sweat chloride and α_1 antitrypsin values were normal. Cerebral computed tomograms were normal and the septum pellucidum was identified. There was no biliary excretion on PIPIDA liver scans.

Normal ranges for lactate dehydrogenase 150 to 360 IU/l, serum glutamic oxalo-acetic transaminase 20 to 55 IU/l, serum glutamic pyruvic transaminase 3 to 37 IU/l, total bilirubin less than 0·07 μmol/l, direct bilirubin less than 0·03 μmol/l, alkaline phosphatase 80 to 270 IU/l, prothrombin time 10 to 11 sec, cholylglycine random values 0 to 2·5 μmol/l.

ND, not done.

intraoperative cholangiogram showed normal extrahepatic bile ducts. Because results of a thyrotrophin releasing hormone stimulation test and a combined arginine-insulin tolerance test were consistent with hypothalamic hypothyroidism, growth hormone and partial adrenocorticotrophic hormone deficiencies, L-thyroxine and hydrocortisone were prescribed. Follow up liver function tests showed an improvement (Table) but a repeat percutaneous liver biopsy was performed at 2 years of age because of persistent hepatomegaly.

Patient 2. A 2 week old boy was referred for hypoglycaemia and prolonged jaundice. His length and weight were at the 80th centile; he had scleral icterus, wandering nystagmus, bilateral optic nerve hypoplasia, and hepatomegaly. Liver function tests were abnormal (Table) and a percutaneous liver biopsy was performed. Results of a thyrotrophin releasing hormone stimulation test and a glucagon tolerance test showed hypothalamic hypothyroidism and growth hormone deficiency, and evaluation during spontaneous hypoglycaemia showed adrenocorticotrophic hormone deficiency. The patient was treated with L-thyroxine and hydrocortisone. Repeat liver function tests showed an improvement (Table).

Patient 3. An 8 week old boy was referred for jaundice. His length and weight were at the 90th and 50th centile respectively. He had scleral icterus, wandering nystagmus, bilateral optic nerve hypoplasia, and hepatomegaly. Results of liver function tests were abnormal (Table). An open liver biopsy was performed (Figure) and an intraoperative cholangiogram showed a normal gallbladder and extrahepatic bile ducts. The serum thyroxine concentration was below normal for age. The patient moved from the area and further evaluation was not possible.

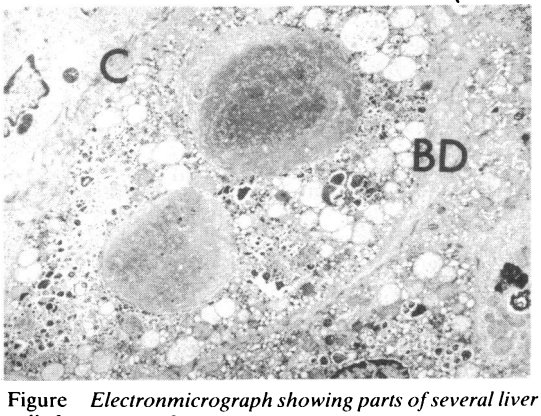

Figure *Electronmicrograph showing parts of several liver cells from patient 3.*

The central liver cell contains several large inclusions and multiple small inclusions. Both are assumed to be due to deposition of bile. A sinusoid with collagen in the space of Disse is noted.
C=collagen; BD=bile duct. Uranyl acetate and lead citrate stained×5800.

Biopsy results

Liver biopsy specimens showed appreciable bile stasis in liver cells and Kupffer cells and dilatation of bile canaliculi on light microscopy. Typical giant cell hepatitis was present in patients 1 and 3; patient 1 had focal areas of necrosis and extramedullary haematopoesis. On electron microscopy, large granular inclusions considered to be bile deposits were present in Kupffer cells, hepatocytes, and bile canaliculi. Collagen fibrils were present in the space of Disse in patients 1 and 3. The second liver biopsy in patient 1, performed at 2 years of age, showed prominent fibrosis with distortion of the lobular architecture due to inter- and intralobular fibrosis producing a micronodular pattern.

Discussion

The three patients described presented with early and persistent direct hyperbilirubinaemia. The diagnosis of neonatal cholestasis was made by the finding of raised serum cholylglycine, transaminase, and alkaline phosphatase concentrations, and failure of biliary excretion on PIPIDA liver scan. An extensive evaluation excluded infectious, metabolic, and anatomic causes of neonatal cholestasis. The presence of severe hypoglycaemia and wandering nystagmus suggested the diagnosis of optic nerve hypoplasia and hypopituitarism.

The association of liver dysfunction with hypopituitarism was first suggested in 1956.[2] Since that time a few reports have associated neonatal hepatitis with idiopathic hypopituitarism,[3–6] but this has not been emphasised in septo-optic dysplasia or optic nerve hypoplasia. In reports of patients with septo-optic dysplasia,[3 6] prolonged unconjugated hyperbilirubinaemia has been mentioned and in a few reports[4 5] cholestatic jaundice and giant cell hepatitis were documented. All of these patients had growth hormone and adrenocorticotrophic hormone deficiencies and 20% had thyroid stimulating hormone deficiency. All patients had resolution of jaundice and in some this occurred after glucocorticoid supplementation and thyroid hormone replacement. In our patients evidence of appreciable cholestasis was present in the initial liver biopsy specimens and in two patients giant cell hepatitis was noted. Resolution of jaundice and normalisation of liver function tests occurred in our two

patients after hormone replacement. The presence of persistent fibrosis on repeat liver biopsy in patient 1, however, makes the long term prognosis of the liver damage unknown.

The aetiology of the liver dysfunction in optic nerve hypoplasia and hypopituitarism is not well understood. Although hypothyroidism may present with prolonged neonatal jaundice, it is generally associated with unconjugated hyperbilirubinaemia rather than direct conjugated hyperbilirubinaemia, as was seen in our patients. It has been suggested that growth hormone and cortisol deficiencies may be responsible for the development of hyperbilirubinaemia since these hormones seem to modulate bile acid synthesis and bile flow. Since our patients and those described by others improved without growth hormone replacement treatment and only half received glucocorticoids,[3–6] it is unlikely that these hormone deficiencies alone could have accounted for liver dysfunction. It is also possible that the liver dysfunction and the central nervous system abnormality leading to hypopituitarism and optic nerve hypoplasia are secondary to a common environmental, toxic, or infectious insult and that the improvement in liver function reflects the natural history of this still undefined disease process.

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