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Alpha-l-antitrypsin deficiency in babies with prolonged jaundice

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Abstract

Over a three-year-period, 310 babies with prolonged jaundice admitted to GHKL were studied, to determine the incidence of alpha-l-antitrypsin deficiency as a cause of the problem. Ninety-two babies (29.7%) were found to be alpha-l-antitrypsin deficient. The percentage incidence was found to be highest in Indians (33.3%), followed by Malays (31.9%) and Chinese (26.7%). There was a male preponderance with a M:F ratio of 1.6:1. Most of these babies presented at the hospital at the age of more than two weeks but less than one month. Apart from the problem of prolonged jaundice and alpha-l-antitrypsin deficiency, 2 had associated bleeding problems, 11 associated infections and 3 respiratory problems. Two babies had clinical features of Down's syndrome, 2 had G6PD deficiency and 1 had congenital hypothyroidism. AST, ALT and ALPO, were high in 20, 26 and 3 babies respectively.

Key words: Alpha-l-antitrypsin deficiency, neonatal jaundice.

INTRODUCTION

Alpha-1-antitrypsin (A1AT) is an important serum protease inhibitor and accounts for approximately 90% of the total inhibitory capacity of human serum. This protease inhibitor is of hepatic origin and shows affinity to and inhibits a variety of serine proteases such as trypsin, chymotrypsin, thrombin, plasmin, kallikerin, elastase and collagenase.[1,2] Deficiency of these glycoproteins lead to predominantly lung as well as liver diseases. Previous workers showed that in 10 to 20% of children with A1AT deficiency, clinical liver diseases manifested initially as neonatal hepatitis, sometimes followed by juvenile cirrhosis especially in infants who suffered from prolonged jaundice in the first few months of life.'

Clinical jaundice is defined as plasma total bilirubin level of more than 100 umol/L. Babies presented with jaundice before two days of life or with jaundice which persisted for more than a week underwent further clinical and biochemical investigations.

The main objective of our study was to determine the frequency of A1AT deficiency as a cause of neonatal jaundice. Early diagnosis will allow appropriate measures to be taken in preventing the morbidity and, subsequently, mortality caused by the disease. Such a study has not been previously carried out in Malaysia.

MATERIALS AND METHODS

Over the three years from 1986 to 1988, we conducted a study of three hundred and ten children below 2 years of age who were admitted for jaundice to the General Hospital Kuala Lumpur. The clinical presentations and results of various investigations during admission were recorded. Laboratory investigations included serum total protein, albumin, serum bilirubin, liver enzymes - aspartate amino transaminase (AST), alanine amino transaminase (ALT) and alkaline phosphatase (AST) - serum T_4, TORCHES studies and haematological studies. Glucose-6-phosphate dehydrogenase enzyme results which were already obtained as part of our routine screening tests in newborn babies were also looked at. All the above investigations were done at the hospital laboratory.

Serum samples were also taken for the measurement of A1AT levels. The specimens were initially screened by serum electrophoresis for the alpha-1 band, and subsequently the A1AT levels were quantified by Laurell's rocket electroimmunoassay technique. Both of these methods have been described elsewhere.[3,4] Patients were considered to have A1AT deficiency when the level of A1AT was below 2.0 g/L. Repeat estimations were performed on follow-

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up specimens of these patients for confirmation.

RESULTS

The race and sex distributions of all jaundiced babies studied are as shown in Table 1 and Figure 1.

Out of these, 92 babies (29.7%) were found to be A1AT deficient. The frequency, according to ethnic origin, of A1AT deficiency in the jaundiced babies were 31.9%, 26.7% and 33.3% in Malays, Chinese and Indians respectively. The clinical presentations and results of laboratory investigations in these babies are summarized in Table 2.

DISCUSSION

Out of 310 babies studied (Table 1 and Fig.1), 92 babies (29.7%) were found to be AlAT deficient. The percentage incidence was highest in Indians (33.3%), followed by Malays (31.9%) and Chinese (26.7%). There was a male preponderance with male to female ratio of 1.6:1. A study done by Sveger also showed a male preponderance with male to female ratio of 2:1.[5]

The clinical presentations and laboratory findings of these 92 babies are summarized in Table 2. Sixty-two babies first presented at the hospital at less than one month of age. Another 25 cases presented at the age of more than 1 month but less than 1 year and the remaining 5 cases at the age of more than 1 year. Apart from the problem of prolonged jaundice, 23 of them had either an enlarged liver and/or spleen; 5 cases were suspected to have biliary atresia. Another 2 babies were found to have bleeding problems; in 1 case this was due to Factor X deficiency, and, in the other, to disseminated intravascular coagulation (DIVC) complicating septicaemia. The causes of infection in 11 babies were neonatal hepatitis (6), congenital syphillis (1), urinary tract infection (1), umbilical sepsis (1), conjunctivitis (1) and septicaemia (1). Three babies had respiratory distress due to lung prematurity. It was noted that another 2 babies had clinical features of Down's syndrome while two had Glucose-6-phosphate dehydrogenase deficiency and one had congenital hypothyroidism.

The laboratory findings of these 92 babies (Table 2) showed that 77 babies (83.7%) had serum bilirubin levels below 170 umol/L and 15 (16.3%) above 170 umol/L. Interpretation of liver enzymes were based on the previous study by Sveger.[5] The cut-off normal level for aspartate amino transaminase (AST) was ≤ 50 IU/L, alanine amino transaminase (ALT) ≤30 IU/L and alkaline phosphatase (ALPO,) ≤700 IU/L. AST was high in 20 (21.7%) and ALT in 26 cases (28.3%) and most of these babies were diagnosed either as having neonatal hepatitis or

TABLE 1: Race and sex distribution of 310 jaundiced babies

Race	Male	Female	Total
Malay	118 (39)	73 (22)	191 (61)
Chinese	49 (13)	37 (10)	86 (23)
Indian	14 (5)	10 (3)	24 (8)
Others	6 (0)	3 (0)	9 (0)
Total	187 (57)	187 (35)	310 (92)

( ) = Number of babies with A1AT deficiency

TABLE 2: Clinical presentation and laboratory findings in 92 A1AT deficient babies

Time of presentation at hospital	*No of babies*
< 2 weeks	24
> 2 weeks – < 1 month	38
> 1 month – < 1 year	25
> 1 year	5
Clinical presentation (in addition to prolonged jaundice)	
Hepatosplenomegaly	23
Biliary atresia	5
Bleeding problems	2
Infections	11
RDS	3
Congenital hypothyroidism	1
Down's syndrome	2
G6PD deficiency	2
Laboratory results	
Serum bilirubin	
< 170 umol/L	77
> 170 umol/L	15
Aspartate transaminase	
< 50 IU/L	72
> 50 IU/L	20
Alanine transaminase	
< 30 IU/L	66
> 30 IU/L	26
Alkaline phosphatase	
< 700 IU/L	89
> 700 IU/L	3

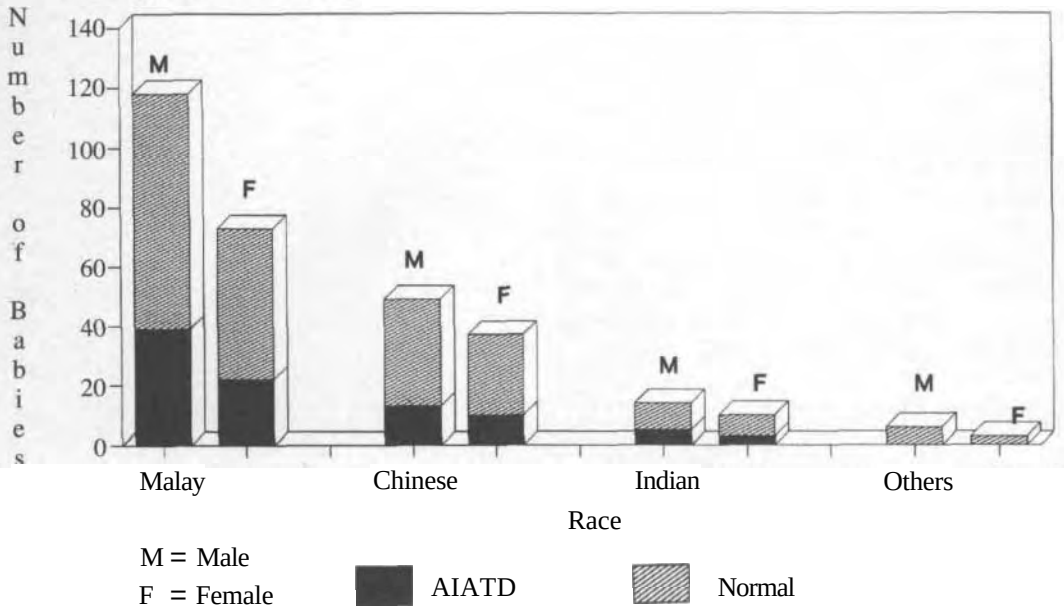

FIG. 1: Race and sex distribution of alpha-l-antitrypsin deficiency in 310 jaundiced babies.

biliary atresia. The ALPO, were high in 3 (3.3%) babies and all of them had biliary atresia. The diagnoses of the above conditions were based on liver biopsies. The basis of prolonged jaundice in A1AT deficiency is believed to be due to liver cell damage. Isherwood and Fletcher[1] indicated that 10-20% of A1AT-deficient babies, especially those with the PiZZ phenotype, present with liver damage in the neonatal period and with prolonged jaundice. In this study, the problem of prolonged jaundice in some of the babies can be explained by associated problems including biliary atresia, infection, congenital hypothyriodism, Down's syndrome and G6PD deficiency (a total of 21 babies), whereas in the remaining 71 jaundiced babies, this could be due to A1AT deficiency alone. Of these 71 babies, 8 had elevated liver enzymes (both AST and ALT), 9 had elevation of either AST or ALT. The remaining 54 babies had normal liver enzymes. The pathophysiology of liver damage in A1AT deficiency is controversial.[2,5] It is still not clear here whether the clinical presentation of prolonged jaundice was due to A1AT deficiency or merely incidental. Prevalence or case control studies may help to clarify the picture. However, previous studies in other countries[2,5,6] have shown that prolonged jaundice is a clinical presentation of A1AT deficient babies.

A1AT is one of acute phase proteins. All the above associated clinical presentations can cause the levels of acute phase proteins to be increased. However, in these 92 babies the A1AT levels were lower than 2.0 g/L, whereas other acute phase proteins including those moving in the alpha-l globulin position were increased in response to the patients' acute conditions. This was supported by the presence of a normal alpha-1 band in the electrophoresis pattern in some of the patients' sera. This finding supports that of other researchers[2]."(' that A1AT deficiency is significant in causing prolonged jaundice. Studies on the phenotypes of the A1AT deficiency may be helpful in clarifying its causative role in clinical jaundice.[1,2,5,6]

This study showed that the percentage incidence of A1AT deficiency in babies with prolonged jaundice was 29.7%. There was a male preponderance with a male to female ratio of 1.6:1. These findings are comparable to results from other studies.' We would like to suggest that screening for A1AT be carried out on all newborns and not only for jaundiced babies. Screening for A1AT in patients with various kinds of respiratory problems may be worthwhile since many researchers from other countries have described the association of A1AT deficiency with respiratory diseases.[2,5-7] Unlike in patients with liver problems, the pathophysiology of A1AT in respiratory diseases is already established.[2-7] Among the Caucasian population, A1AT deficiency is one of the common lethal hereditary disorders especially for those with certain uhenotvues. The incidence is as

high as 1 in 7,700 among white Northern Americans, and, in some Northern European populations, it is as frequent as 1 in 2,000 to 3,000.' However, there has been no study so far to determine the incidence of this disease in Asians or in Malaysians. Early diagnosis of this problem is important so that cirrhosis can be avoided or minimised by reducing exposure to a precipitating environment such as smoke and air pollution. Genetic counselling may be possible for those couples with certain A1AT phenotypes to avoid having affected children.

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