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Serum Alpha Fetoprotein in Childhood*

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Serum alpha fetoprotein (AFP) is a normal plasma protein component in human fetuses older than six weeks, reaches maximal concentration between 12-16 weeks of fetal life. Around 13 weeks the level reaches 300 mg/100 ml. and at birth levels range between 2.5-15 mg/100 ml. A few weeks after birth it disappears from the circulation and it is absent in healthy children and adults.[1-3] It reappears in patients with primary carcinoma of liver and embryonal cell carcinoma of testis and its presence is considered to be diagnostic of these conditions.[4,5] AFP is reported to be positive in hepatopathies in the first year of life,[4] in some cases of Indian Childhood cirrhosis[6] and in some gastric carcinomas with metastases to the liver.[7-9] It is also found in mice and rats in experimentally produced hepatomas.[10,11]

Here we will report our findings for AFP in children with various clinical disorders.

Material and Method

428 children aged between 1 day and 16 year were studied by double diffusion agar technique using the anti AFP serum of Behring-Werke. An AFP positive serum was used as control. Development of pricipitation lines were checked at 24 hours and later. Fig 1 shows those lines on the 4 AFP positive patients and a positive control. As seen these lines are identical.

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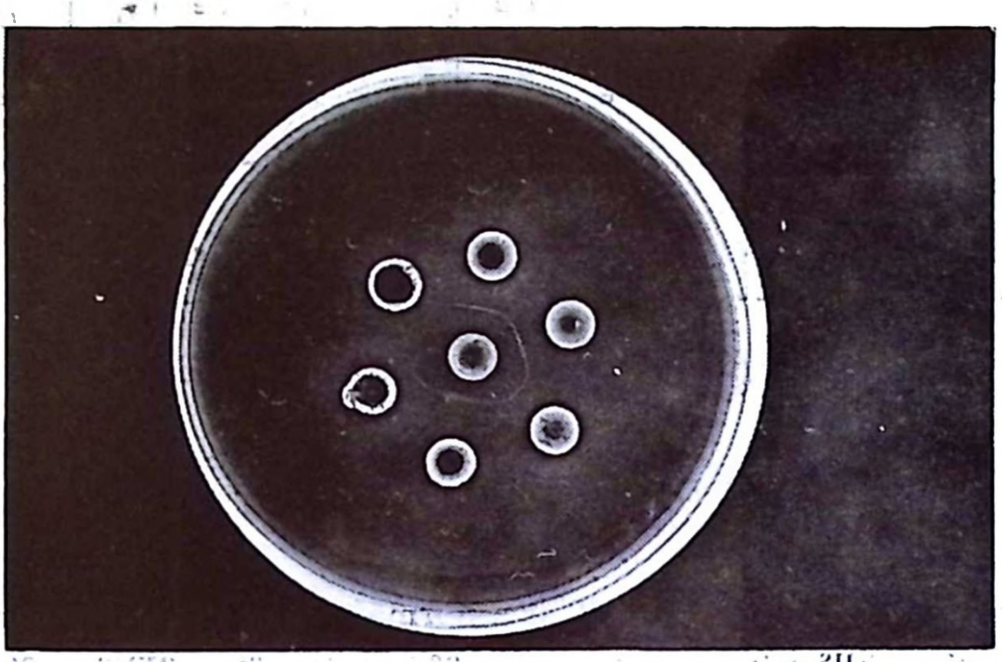

Figure 1

Identical precipitation lines for alpha-fetoprotein on 4 patients and a positive control serum.

Diagnosis of patients are summarized in Table 1.

In some positive cases such as tumors and newborns, determinations were repeated at certain intervals. For the quantitative test, immunodiffusion plates of Behring-Werke were used.

Findings

AFP was positive in 32 out of 428 examined. As seen from the Table 1 it was negative in the following: 46 cases of liver cirrhosis, 14 cases of malnutrition, 31 cases of various liver conditions, 13 cases of hydatid disease of liver, 18 cases of Hodking's disease, 59 cases of various tumors, 6 cases of ataxia telangiectasia, 29 cases of acute leukemia and 118 cases miscellaneous diseases. In 19 out of 30 newborns a positive precipitation line was seen. Their ages ranged between 1 day and 6 days. Case No 10 had a 4 cm. palpable liver. (See Table II).

We found positive precipitation lines in 4 out of 16 patients who had clinical diagnosis of hepatoma or hepatoblastoma. In three cases (case No. 2,6 and 31, 7 months, 11 year and 11 months old) diagnosis was confirmed histologically. AFP levels were 56 mg and 75 mg/100 ml in cases cases No. 6 and No. 31 and it became undetectable 1 month after chemothrapy in the former.

AFP was positive in only 1 out 27 cases of infectious hepatitis (case No. 18), 2 cases of neonatal hepatitis (case No 8 and 9) and 2 cases of cholestatic hepatitis (case No. 1 and 5). The infants with cholestatic he-

TABLE I

ALPHA-FETOPROTEIN DETERMINATION IN VARIOUS CLINICAL DISORDERS

Diagnosis	Number of Patients	Number of A.F.P. Positive	% Positive
Testicular Tumors	2	2	100
Hepatoma or Hepatoblastoma	16	4	25.0
Malignant Teratoma	1	1	100
Hodgkin's Disease	18	0	0
Infectious Hepatitis	27	1	3.7
Neonatal Hepatitis	9	2	22
Cholestatic Hepatitis	3	2	66.6
Neuroblastoma	6	1	16.6
Hydatid Disease of The Liver	13	0	0
Liver Cirrhosis	46	0	0
Hepatomegaly and Various Liver Conditions	31	0	0
Ataxia Telangiectasia	6	0	0
Infantile Malnutrition	14	0	0
Acute Leukemia	29	0	0
Newborn	30	19	63.3
Various Tumors	59	0	0
Others	118	0	0
Total	428	32	7.5

patitis were 5 and 14 months old and the AFP levels were 1 and 10.5 mg/100 ml respectively. One of the patients with neonatal hepatitis died and the second patient (case No. 9) still had AFP to be positive in the serum at 6 months of age.

We have seen 2 testicular tumors aged 2, and 5 years with a positive AFP, (case No. 3 and 19) .The AFP level was 25 mg in the former. However we had no chance of follow up for further determinations.

We found AFP to be positive in a 1,5 month old boy with neuroblastoma. An 18 month old girl with malignant sacrococcigeal teratoma (case No. 32) had an AFP level of 34 mg./100 ml.

TABLE II
AGE, DIAGNOSIS AND AU ANTIGEN

Case No:	Age (Yr) and Sex	Diagnosis	Au Antigen	AFP	AFP (mg/100 ml)
1. H.B.	5/12 M	Cholestatic Hepatitis	–	+	1 mg.
2. S.Ç.	7/12 M	Hepatoblastoma		+	
3. E.O.	2 M	Embryonal Adenocarcinoma of Testis		+	25 mg.
4. G.F.	1,5/12 M	Neuroblastoma		+	
5. U.M.	1,2/12 M	Cholestatic Hepatitis	–	+	10.5 mg.
6. İ.A.	11 F	Hepatoblastoma	–	+	56 mg.*
7. Z.A.	8	Hepatoblastoma?	–	+	6 mg.
8. İ.A.	2/12	Neonatal Hepatitis	–	+	
9. H.Ö.	2/12	Neonatal Hepatitis	–	+	
10. D.G.	2 Day	Newborn With Hepatomegaly		+	2.5 mg**
11. Infant D.	2 Day	Newborn		+	
12. Infant K.	1 Day	Newborn		+	
13. Infant A.	6 Day	Newborn		+	
14. Infant A.	1 Day	Newborn		+	
15. Infant Ü.	1 Day	Newborn		+	
16. Infant Ç.	4 Day	Newborn		+	
17. Infant K.	1 Day	Newborn		+	
18. Z.D.	1.1/12	Infectious Hepatitis	–	+	
19. İ.Y.	5	Embryonal Adenocarcinoma of Testis	–	+	
20. Infant A.K.	5 Day	Newborn		+	
21. Infant Ç.	4 Day	Newborn		+	
22. Infant E.	5 Day	Newborn		+	
23. Infant K.Ü.	2 Day	Newborn		+	
24. Infant K.	3 Day	Newborn		+	
25. Infant D.	3 Day	Newborn		+	
26. Infant S.	2 Day	Newborn		+	
27. Infant G.	4 Day	Newborn		+	
28. Infant A.	3 Day	Newborn		+	
29. Infant İ.	4 Day	Newborn		+	
30. Infant S.	3 Day	Newborn		+	
31. G.E.	11/12 y.	Hepatoblastoma		+	75 mg.
32. S.K.	1,6/12 y.	Malignant Teratoma		+	34 mg.

* It became negative after chemotherapy and it reappeared with relapse
** Hepatomegaly disappeared at age of 1 month and AFP became negative
– : Negative
+ : Positive

Discussion

AFP is reported to be positive in some cases of gastric carcinoma with metastases to the liver[7-9] besides usual positivity in hepatoblastoma and testicular tumor. AFP is positive during the first twelve months of life in the serum of children with infectious hepatitis and other hepatopathies.[4] Usually it is present in trace amounts after birth and generally it disappears within 3-4 weeks. With more sensitive methods like radioimmunoassay, AFP levels were found to vary between 2-16 ng/ml.[12] During the course of pregnancy the level increases in the maternal serum and before term it gradually decreases. AFP level is between 103-550 mg/ml. in the last trimestr of pregnancy. With intrauterin death AFP levels in maternal serum exceeds 1000 mg/ml.[12]

This fetal serum protein reappears in the serum of patients with primary liver carcinoma and its presence is considered to be diagnostic for this condition. In neoplasms, the levels show changes between 6 and 90 mg/100 ml. In neonatal hepatitis AFP level is around 3 mg/100 ml. and later it disappears from the serum.

AFP is also detected in pleural exudates, ascitis fluid and organ extracts. A positive reaction during first year of life is not specific for hepatoblastoma because of the above mentioned reasons. We observed an AFP level of 2.5 mg/100 ml. in a newborn with hepatomegaly which became negative within a month. We had no follow up in the other 7 newborn, a case of infectious hepatitis and cases of neonatal and cholestatic hepatitis.

Our 1.5 month of old case of neuroblastoma had also liver metastases.AFP may be positive in this case due to the hepatic incolvement. Actually hepatopathy within the first year of life reported to cause positive AFP in the serum. The same may apply to our 2 cases of cholestatic hepatitis who were younger than 1 year.

Positivity of AFP is reported to be between 29 % and 80 % in cases of hepatoblastoma.[13] This percentage depends upon the sensitivity of the method used for detection and on the racial characteristics. In Africans and Far East population with hepatoblastoma, AFP positivity is higher than other racies.[3] The positivity for AFP in hepatolastoma in different racial groups is reported as follows: In France % 50-60, in England % 40, in Spain % 42, in Greece % 75, in Russia % 60, in South Africa % 75, in Uganda % 50, in Senecal % 80, in Italy % 46.[13]

The exact function of AFP is not known. In a study done among the congenitally malformed infants died within first day of life no AFP, was

found in their serum.[14] In another study done in chickens it is shown that injections of anti-AFP serum cause rachi sichisis partialis in 50%, omphalocele, absence of palpebral fissures and ruffled feathers. In newborn rats it caused meningomyelocel in % 10, maternal mortality in % 6 and abortion in % 20 and maldevelopment of ovum in some. From these studies it is concluded that AFP is necessary for normal organogenesis.[14]

The positivity of AFP in testicular and ovarian tumors (teratoma or embryonic carcinoma) is around % 40.[15] This is lower than that of hepatoblastomas. But AFP determination is usually done once and not repeated. We believe this may affect the incidence of positivity since it may later become positive during the course of the disaese. It is recommended to carry out multiple determinations at certain intervals. It is reported that with chemotherapy AFP becomes negative.[15,16] Multiple determinations may be helpful in deciding on the effectivenses of chemotherapy and on the prognosis. Our patient, an 11 year old girl with hepatoblastoma had negative AFP one month after chemotherapy. However metastases advanced and AFP became positive again and she died within 3 months. Currently we are investigating the relationship betwen the clinical course of the disease and AFP levels.

Recently AFP is reported to be higher in the serum of patients with ataxia telangiectasia in comparison to normal controls. In their study, Waldmann and Mc Intire used the sensitive radioimmunoassay method and the levels over 30 ng/ml. is considered to be abnormal. They concluded that in patients with ataxia telangiectasia there must be a defect in tissue differentiation and the liver is not developed normally. Possibly there is a faulty interaction between ectodermal and mosedermal germ lines.[17]

The mechanism of the AFP being positive in hepatoblastoma and testicular tumors in not adequately explained. There are two views on the synthesis of AFP:

1- AFP is synthesized by the special cells in the liver parenchyma. An alternative type hepatocyte manufacture adult type serum proteins when the fetus matures, can not synthesize AFP.

2- AFP is made by hepatocytes which reach certain degree of differentiation. When they mature AFP production become repressed.

In both views, reproduction of AFP by the adult liver cells denotes that there must be a less mature hepatocyte population than hepatocytes which normally synthesize adult proteins. This suggest either fetal type

hepatocyte matures or hepatocyte redifferentiates into a stage where AFP production begins.

Our presented preliminary data confirm the reported findings in the literature.

Summary

Serum AFP was detected in 428 children of various clinical disorders. Clinical significance of the findings are discussed and the related literature is briefly reviewed.

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