Research Article

AFP and liver diseases in AT and AOA

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Is high AFP associated with liver diseases in ataxia-telangiectasia and ataxia-oculomotor apraxia?

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Abstract

Background and Aim: Ataxia-telangiectasia (AT) and ataxia-oculomotor apraxia type 2 (AOA2) are both autosomal recessive cerebellar ataxias characterized by elevated serum alpha-fetoprotein (AFP) levels. However, the source and clinical implications of this increase, as well as its relationship with liver diseases are unknown. In this study, we investigated the frequency of liver diseases and their relationship with high AFP in patients with AT and AOA2.

Materials and Methods: The study involved 19 adult patients (13 patients with AT and 6 patients with AOA2) who were followed between January 1992 and March 2023. The demographic and clinical characteristics, serum levels of liver enzymes and AFP, liver imaging, and survival data were retrospectively reviewed.

Results: The mean age of patients was 26.8±5.1 years (11 men and 8 women).While 69% (9/13) of AT patients had elevated liver enzymes and 56% (5/9) had abnormal liver imaging, both were normal in all AOA2 patients.Liver enzyme elevation was associated with the presence of comorbid disease (p=0.007), but not with AFP level (p=0.33) in AT patients. Hepatosteatosis was not associated neither with comorbidity (p=0.524) nor AFP level (p=0.905) in this group. During a median follow-up of 17 (1–29) years, 5 AT patients passed away due to cancer (4 patients) and sepsis (1 patient). AFP level was not associated with the occurrence of cancer (p=0.382).

Conclusion: This study found a high prevalence of liver disease (69%) in AT, unlike in AOA, independent of AFP levels. Since comorbid diseases, especially cancer, were associated with elevated liver enzymes, adult AT patients with abnormal liver functions should be screened for the development of cancers.

Keywords: Ataxia-telangiectasia; ataxia-oculomotor apraxia; liver.

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Introduction

Ataxia-telangiectasia (AT) is an autosomal recessive cerebellar ataxia (ARCA) characterized by cerebellar degeneration, oculocutaneous telangiectasia, immunodeficiency, and cancer predisposition.[1] The estimated prevalence of the disease worldwide is one in 40,000–100,000 live births.[2] The classic type of AT occurs at an earlier age and has a more aggressive course than the mild type. The disease develops due to an ATM gene mutation located on chromosome 11q22-q23. ATM protein is mainly involved in the repair of dsDNA breaks, genotoxic stress response, cell cycle checkpoints, and apoptosis. Therefore, a mutation in the ATM gene causes genetic instability and cancer predisposition. Lifetime cancer incidence increases by approximately 25% in AT patients. The most common malignancies are lymphoma and leukemia, while breast, stomach, esophagus, or liver cancers are also encountered.[3] In addition, the incidence of immunodeficiency, chronic pulmonary diseases, growth retardation, gonadal dysgenesis, diabetes, and autoimmune diseases increases in AT. The most common causes of mortality in AT patients are recurrent respiratory tract infections and malignancies.[1]

In the ARCA spectrum, AT and ataxia-oculomotor apraxia type 2 (AOA2) are known to be associated with an increase in serum alpha-fetoprotein (AFP) level, but its origin and consequences are unclear.[4] Data showing the relationship between AFP level and clinical course are very limited.[5,6] There is also limited data on the frequency of liver diseases in AT and AOA patients. Underlying immunodeficiency, recurrent infections, or insulin resistance may predispose to liver diseases. In this study, we aimed to investigate the frequency of liver diseases and their relationship with AFP levels in patients with AT or AOA.

Materials and Methods

The study included all adult patients without any exclusion, followed up at our tertiary center with the clinically and/or genetically confirmed diagnosis of AT or AOA2 between 1992 and 2023. Approval for the study was obtained from the institutional ethics committee (date: 19.10.2021, decision number: 2021/17-09). The study was conducted in accordance with the Declaration of Helsinki. Demographic and clinical data of the patients were retrospectively obtained from hospital records and if possible by interviewing with the patients. Age, gender, age at diagnosis, body mass index (BMI), history of alcohol use or viral hepatitis, clinical signs, comorbid diseases, brain and liver imaging, liver biopsy findings, the occurrence of malignancy, and survival data

were recorded. The complete blood count, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), triglyceride, and AFP levels at the last visit were analyzed. Fibrosis-4 score (FIB-4) and hepatic steatosis index (HSI) were used to predict liver fibrosis and fatty liver disease, respectively. FIB-4 was calculated as: age (years) × AST (U/L)/(platelets [10^9/L] × ALT [U/L]1/2), with AST and ALT measured on the same day and platelets within ±30 days. The score was categorised as low (<1.3), indeterminate (1.3-2.7), or high (>2.67) risk of advanced fibrosis.[7] HSI was calculated using the formula HSI = 8 × ALT/AST ratio + BMI + 2 (if diabetic) + 2 (if female). In recognizing non-alcoholic fatty liver disease the index has high sensitivity and specificity at cutoff values of <30 and >36, respectively.[8]

Since there was no specific curative treatment for AT or AOA2, patient-based symptomatic supportive treatment was given including management of infections, intravenous immunoglobulin replacement, antiepileptics, antioxidant agents, anti-inflammatory hormonal therapy, and physical therapy.

Statistical Analysis

All analyses were performed with the Statistical Package for Social Sciences, version 28 (IBM Inc., Armonk, NY) and GraphPad Prism 9 softwares. Descriptive statistics were presented as frequency (percentage), mean±SD, or median (min-max). Categorical groups were compared with Fisher's exact tests. Continuous variables were analyzed with the Mann-Whitney U test for two independent samples. The correlation between two non-parametric variables was examined with the Spearman test. Overall survival was defined as the time from diagnosis to death from any cause or last follow-up visit. The survival analyses were done using the Kaplan-Meier method, and the comparisons between sub-groups were made with the log-rank test. An overall type-1 error level was used to infer statistical significance.

Results

Baseline Characteristics

The mean age of 19 patients included in the study was 26.8±5.1 years (range, 19 to 40), and there were 11 (58%) men and 8 (42%) women. The diagnosis was AT in 13 patients and AOA2 in 6 patients (Table 1). The median age at diagnosis was 8 years (range, 2 to 23). The mean BMI was 20.5±4.1 kg/m^2 (range, 12.7 to 26.1). The most frequent neurologic finding was gait ataxia (79%), followed by limb ataxia (58%), nystagmus (47%), dysarthria (47%), posture disorder (32%), and sitting problem (21%). The brain magnetic resonance imaging was examined in 9 patients, and all of them had cerebellar atrophy. The comorbidities in AT patients were as follows; 4 malignancies (1 pancreatic cancer, 1 gastric cancer, 1 acute leukemia, and 1 glioblastoma multiforme), 3 autoimmune diseases (1 hypothyroidism, 1 rheumatoid arthritis, 1 Crohn's disease), 2 chronic lung disease, 1 growth retardation, and 1 gonadal dysgenesis. There was no comorbidity in the AOA2 patients. None of the patients in this series had a history of viral hepatitis or alcohol use.

Laboratory Investigations

The median serum AFP level was significantly higher in AT patients [226.2 ng/ml (range, 40.9 to 913.8)] than in AOA2 patients [20.2 ng/ml (range, 12.1 to 52.2)] (p<0.001, Fig. 1). AOA2 patients had normal AFP levels, except 2 patients with 2 SETX mutation having mildly elevated AFP (41.6 and 52.2 ng/ml). All AOA2 patients had normal liver enzymes, while 9 (69%) of 13 AT patients had an elevation in them; 8 (62%) in GGT, 7 (54%) in ALP, 3 (23%) in ALT and 1 (8%) in AST. In AT patients, liver enzymes elevation was not associated with AFP level (p=0.33), but with the presence of comorbid disease (p=0.007). However, AFP was not correlated with ALT (r=0.118; p=0.7), AST (r=0.099; p=0.748), ALP (r=-0.011; p=0.972), or GGT (r=-0.094; p=0.761).

The platelet counts and serum triglyceride levels were normal in all AOA2 patients, although out of 13 AT patients, 1 (8%) patient had thrombocytopenia and 4 (31%) patients had hypertriglyceridemia. The median FIB-4 score was similar in AT patients (0.51 and range, 0.15 to 1.59) and AOA2 patients (0.39 and range, 0.17 to 0.42), (p=0.152). The median HSI of AT and AOA2 patients were respectively 28.1 (range, 22.7 to 41.4) and 30.1 (range, 28.9 to 35.4), (p=0.521).

Liver Imaging and Pathology

Twelve of the patients underwent abdominal ultrasonography. While 3 AOA2 patients had normal findings, 5 (56%) of 9 AT patients had pathology, namely 3 hepatosteatosis, 1 hemangioma, and 1 hepatosteatosis with fibrosis. The presence of hepatosteatosis in patients with AT was not associated with the presence of comorbidity (p=0.524), median BMI (p=0.413), FIB-4 score (p=0.556), HSI (p=0.998), or AFP level (p=0.905); however, AT patients with hepatosteatosis had a significantly higher triglyceride level (289 mg/dL and range, 182 to 381) than those without hepatosteatosis (96 mg/dL and range, 75 to 112), (p=0.016). The liver biopsies were done in 2 AT patients for evaluationof increase in cholestatic enzymes, and revealed granulomatous hepatitis and chronic active hepatitis with biliary tract injury in each patient.

Survival

Five AT patients passed away over a median follow-up of 17 years (range, 1-29); 4 died of cancer (1 pancreatic cancer, 1 gastric cancer, 1 acute leukemia, and 1 glioblastoma multiforme) and 1 died of sepsis. Pancreatic cancer, gastric cancer, acute leukemia, and glioblastoma multiforme were diagnosed at the ages of 26, 23, 25, and 26 years, with respective survival times of 6, 12, 8, and 15 months. Overall survival was highly associated with the emergence of malignancy in patients with AT (p=0.002, Fig. 2). However, serum AFP level was not related with cancer development (p=0.940, Fig. 3).

Discussion

In this study, we examined the frequency of liver diseases and their relationship with AFP levels among patients with ARCA. ARCA constitutes a broad spectrum of diseases, led by Friedreich's ataxia, also includes AT and AOA that are characterized by an increase in AFP.[9,10] At least 90% of AT patients experience a significant rise in AFP exceeding 100 ng/ml.[5] However, the AFP level is mildly elevated in AOA, with a various rate depending on the subtype. AOA1 is often detected under the age of 10, and a slight increase in AFP (15 to 20 ng/ml) is observed in approximately 40% of patients. AOA4 has also an early-onset with varying degrees of AFP elevation. On the other hand, AOA2 develops between the ages of 12 and 20, and always has distinguisingly high AFP (15 to 65 ng/ml).[11]

AFP, produced by the fetal liver and yolk sac, replaces albumin as the predominant plasma protein in fetal life. Although AFP has an affinity for estrogen, bilirubin, fatty acids, as well as the ions Cu^{2+} and Ni^{2+}, its

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Table 1. Clinical and demographic characteristics of patients

No	Age /sex	Age at diagnosis /follow-up time, years	Comorbidity	AFP, ng/ml (0–40)	ALT /AST, U/l (<40)	ALP/ GGT, U/l (30–120/<40)	Liver imaging	Liver biopsy	Cancer	Outcome
Ataxia-telangiectasia										
1	40/F	9/29	No	913.8	38/29	96/14	Normal	–	No	Alive
2	26/F	6/19	GD, DM	562.3	34/33	228/234	HS£	–	Pancreas and thyroid cancer	Exitus
3	26/F	3/23	CPD	226.2	28/21	138/86	Hemangioma	–	No	Alive
4	27/F	6/21	DM, CPD, AD	594.1	46/52	135/132	–	–	No	Exitus
5	24/M	7/17	No	656.4	27/22	260/240	HS, fibrosis£	Granulomatous hepatitis	Gastric cancer	Exitus
6	26/M	17/3	GR	89.9	38/37	164/73	–	–	ALL	Exitus
7	28/M	2/21	No	197.0	10/27	64/75	Normal	–	GBM	Exitus
8	28/M	3/25	No	426.8	51/24	107/73	HS	–	No	Alive
9	28/M	4/24	AD	40.9	61/32	207/231	HS£	Chronic active hepatitis	No	Alive
10	33/M	6/26	No	155.6	13/13	79/34	–	–	No	Alive
11	23/M	7/16	No	673.0	37/28	94/21	Normal	–	No	Alive
12	33/M	23/10	AD	121.0	25/23	132/28	–	–	No	Alive
13	28/M	16/8	No	225.0	12/18	63/21	Normal	–	No	Alive
Ataxia-oculomotor apraxia type 2										
14	28/F	17/7	No	12.1	19/20	68/22	–	–	No	Alive
15	21/F	16/4	No	18.1	11/17	70/15	Normal	–	No	Alive
16	30/M	8/10	No	52.2	30/23	113/26	–	–	No	Alive
17	19/F	18/1	No	19.6	25/28	102/29	Normal	–	No	Alive
18	23/E	18/5	No	41.6	19/13	66/13	Normal	–	No	Alive
19	19/F	18/1	No	20.9	8/14	86/15	–	–	No	Alive

AD: Autoimmune disease; AFP: Alpha fetoprotein; ALL: Acute lymphoblastic leukemia; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CPD: Chronic pulmonary disease; DM: Diabetes mellitus; GBM: Glioblastoma multiforme; GD: Gonadal dysgenesis; GGT: Gamma-glutamyl transferase; GR: Growth retardation; HS: Hepatosteatosis; £: Indicates magnetic resonance imaging. The rest was done by ultrasonography.

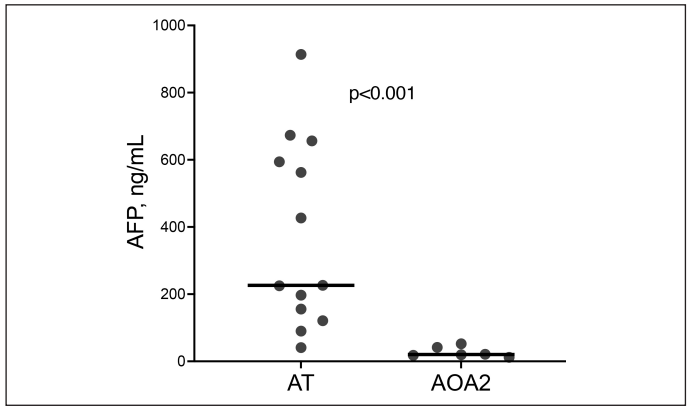

Figure 1. Serum alpha-fetoprotein (AFP) levels in ataxia-telangiectasia (AT) and ataxia-oculomotor apraxia type 2 (AOA2) patients.

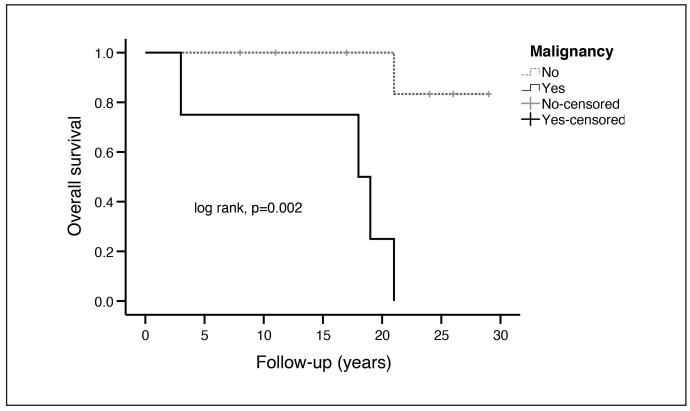

Figure 2. Association of cancer presence and overall survival in patients with ataxia-telangiectasia - Kaplan Meier analysis.

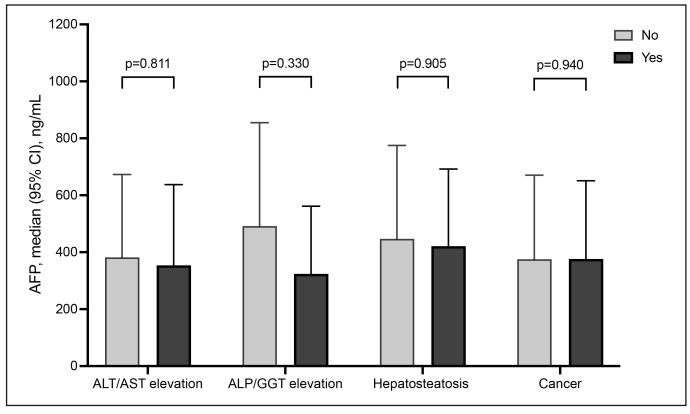

Figure 3. The median alpha-fetoprotein (AFP) levels in ataxia-telangiectasia patients according to the presence of alanine transaminase (ALT) and/or aspartate aminotransferase (AST) elevation; alkaline phosphatase (ALP) and/or gamma-glutamyl transferase (GGT) elevation; hepatosteatosis; and cancer.

role in adulthood is yet unknown. AFP is used to predict neural tube defects and chromosomal diseases such as Down syndrome in the intrauterine period. In postnatal life, increased AFP is encountered in hepatocellular cancer, acute hepatitis, cirrhosis, germ cell tumors, or AT.[12,13] The exact mechanism of AFP increase in AT patients has not been elucidated. Studies indicate that the increased AFP in these patients is of hepatic origin.[14] The common view is that it may be due to dysregulation of transcription in the liver secondary to DNA damage.[11] It has also been shown that the level of AFP increases by aging in AT patients.[5] However, the association of increased AFP level with prognostic outcomes has not been demonstrated.[3,12] Similarly, there was no correlation between the level of AFP and the emergence of malignancy in our series.

The literature about the liver diseases and their relationship with serum AFP levels among AT patients are limited. Caballero T et al.[15] first reported a 22-year-old AT patient with nonalcoholic steatohepatitis. In a study conducted in 53 pediatric AT patients in 2016, elevated liver enzymes were detected in 23 (43.4%) patients, and 9 of them (39%) had fatty liver.[16] A link between dyslipidemia and increased liver enzymes was revealed, and sugested that liver damage may be associated with increased oxidative stress due to ATM protein inactivation. Paulino TL et al.[17] reported 64.7% hepatosteatosis and frequent metabolic disorders in AT patients. We observed an increased incidence of liver enzymes elevation and hepatosteatosis in our series of AT patients (respectively 69% and 44%).Liver enzymes was significantly higher in patients with comorbid diseases including cancer, diabetes, autoimmune disease, chronic lung disease, and gonadal dysgenesis.

Donath H et al.[4] found that levels of AFP and liver enzyme, as well as rate of hepatosteatosis were higher in AT patients older than 12 years in comparison to youngers. They also recently evaluated 31 AT patients with transient elastography (TE). Rates of hepatosteatosis was higher in patients older than 12 years (10% vs. 90%). The hepatosteatosis was significantly correlated with steatotest, AFP, HbA1C, and triglyceride levels. The presence of hepatosteatosis was also associated with increased triglyceride levels in our series. However, we couldn't show any relationship between hepatosteatosis and AFP level. Additionally, liver stiffness measurement was significantly increased in the older group in comparison to the younger group (8.9±6.9 kPa vs. 4.5±0.93 kPa, $p<0.001$).[18] The data for TE was not available in our center for the study period. Increasing oxidative stress and metabolic dysfunction by aging might lead to the development of hepatosteatosis in AT patients. Since there was not a consistent association between AFP and hepatosteatosis among reports, the increase in AFP levels and rates of hepatosteatosis with age may be a confounding factor. Multiple regression models are required to demonstrate the independent association of AFP with hepatosteatosis.

Although few studies on liver diseases in AT have been published in the last decade, there is no data on AOA patients. Among the AOA patients included in our study, 2 patients with SETX mutation (AOA2) had mild AFP elevation. AOA patients had a milder clinical course than AT patients without evidence of liver damage.

The majority of the AT patients reported in the literature are coming from the pediatric age group. However, AT patients can survive longer due to easy access to health services and improvements in treatment methods, and are now more frequently encountered in adult practice. It is noteworthy that only patients aged ³18 years were included in our study, and we first reported their prognosis from the point of the liver. Nevertheless, the most important limitation of our study was the small number of patients which did not allow to analyze age-dependent correlation between AFP and liver enzymes increase or hepatosteatosis. Other limitations were retrospective and single-centered design and the lack of ultrasonography evaluation in all patients.

Conclusion

This is a frontier study showing that unlike AOA2, AT adult patients had significantly increased liver disease, mainly hepatosteatosis. The liver disease was not associated with AFP, but with comorbidities. Therefore, increased oxidative stress, aging-related metabolic dysfunctions, and/or comorbid diseases might lead to liver diseases in AT patients. We strongly recommend periodic screening of adult AT patients with liver enzymes and hepatobiliary imaging to early identify liver diseases or comorbidities, especially cancers.

Ethics Committee Approval: The Hacettepe University Non-interventional Clinical Research Ethics Committee granted approval for this study (date: 19.10.2021, number: 2021/17-09).

Author Contributions: Concept – HYB, RI; Design – RI; Supervision – HYB, GYC; Materials – SI, NA; Data Collection and/or Processing – RI, TO, EE; Analysis and/or Interpretation – RI; Literature Search – RI; Writing – RI; Critical Reviews – HYB, GYC, BE.

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