Report of a Family with Fanconi Anemia and Ataxia-Telangiectasia

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ABSTRACT

We diagnosed two boys with two different chromosomal instability disorders such as Fanconi anemia (FA) and ataxia-telangiectasia (AT) in the same family. The phenotype of the first sibling supports the diagnosis of ataxia-telangiectasia. He had ataxia, telangiectasias on bulbar conjunctivas, a high level of alpha-fetoprotein, low levels of IgA and IgE, and a defective cell-mediated immunity. Cytogenetic studies of the peripheral lymphocytes revealed a chromosomal sensitivity to ionizing radiation. His 8-years-old brother had pancytopenia but had no ataxia and telangiectasia. He had a normal level of immunoglobulins and alpha-fetoprotein. His cell-mediated immunity was also normal. Cytogenetic studies showed no evidence spontaneus chromosome aberrations; however, there was a mild increase in the rate of diepoxybutane (DEB) and also an increased chromosome aberrations in the mitomycin C (MMC) treated samples than the control. The parent of the boys and 5^{th} child were healty. The first child had normal hematological and immunological features, but he had a mild increase in the rate of DEB. The 4^{th} child had an increased rate of DEB-induced chromosome aberrations.

To our knowledge, this is the first family with FA and AT in Turkey and it is reported because of its rarity.

Key Words: Fanconi anemia, Ataxia-telangiectasia.

ÖZET

Aynı Ailede Ataksi-Telanjektazi ve Fanconi Anemisi Birlikteliği

Aynı ailenin iki erkek çocuğunda ataksi telanjektazi (AT) ve Fanconi anemisi (FA) gibi iki farklı tip kromozomal kırılma bozukluğu olduğu tanımlandı. Fenotipik olarak AT tanısı konulan ilk hastada bulbar konjunktivada telanjektazi, alfa-föto protein yüksekliği, IgA ve IgE'nin eksikliği, hücresel immünitenin bozukluğu tanıyı desteklemekteydi. Sitogenetik çalışmada periferal kan lenfositlerinin iyonize radyasyona karşı hassasiyeti saptandı. Pansitopenisi olan sekiz yaşındaki erkek kardeşinde immünglobulin, alfa-föto protein değerleri ve hücresel immünite normal bulundu. Sitogenetik çalışmada spontan kırık gözlenmemesine rağmen diepoksi bütan (DEB) ile hafif, mitomisin-C ile fazla miktarda kromozomal kırılma saptandı. Ailenin beşinci erkek çocuğu sağlıklı idi ancak normal hematolojik ve immünolojik bulgulara sahip olan ilk çocukta DEB testinde hafif bozulma varken dördüncü çocukta DEB testi bozuk olarak saptandı. Bilgilerimize göre Türkiye'deki FA ve AT beraberliği olan ilk aile olması nedeniyle bu ender durum rapor edildi.

Anahtar Kelimeler: Fanconi anemisi, Ataksi-telanjektazi.

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INTRODUCTION

Genetic instability disorders of humans include ataxia-telangiectasia (AT), Bloom syndrome (BS), Fanconi anemia (FA), xeroderma pigmentosum and Nijmegen breakage syndrome, all of which are very rare and inherited in a recessive manner. These syndromes associated with an increased sensitivity to certain DNA damaging agents where no defect in DNA repair has been defined include FA (sensitivity to DNA croos-link agents), hereditary dysplastic nevus syndrome (sensitivity to ultraviolet) and AT (sensitivity to ionizing radiation)[1]. The production of DNA damage by physical or chemical agents is dose-dependent. The error free enzymatic repair process including excission resynthesis of base damage or of altered nucleotides allow reinstitution of intact DNA. Absence of repair leads to cytotoxicity and programmed cell death cycle control lead to a pretumoral state[2]. The incidence of cancers or malignant blood disease is high[3].

We present here the cases with two different chromosomal instability disorders such as FA and AT among members of the same family because of its rarity.

CASE REPORTS

Case 1

A 12-years-old boy was admitted to the pediatric department because of progressive pulmonary infection and diarrhea. His parents were first cousins. His past history releaved that he had recurrent respiratory infection, he walked at three years of age and had ataxia. He was not vaccinated. Physical examination showed a severly malnourished boy weighing 17.5 kg (< 3rd percentile) and height 121 cm (< 3rd percentile). He had bilateral nystagmus, strabismus and telangiectasias in the bulbar conjunctivas, on the bridge of the nose and on the ears. He had suppurative otitis media and rales on the lung. He had choreoatetoid movements and dysconjugate gaze. With striking hypotonia and generalized muscle weakness.

The hemoglobin was 11.6 g/dL; white blood cell (WBC) count 23.300/mm^3; platelets 470.000/mm^3; mean corpuscular volume 67 fl. Urine analysis, liver and renal function tests were normal. He had a high level of alpha-fetoprotein (217.4 mg/dL). The level of IgG in the serum was 949 mg/dL; IgA was 6.4 mg/dL; IgM was 152 mg/dL; IgE was 8 mg/dL. He had no IgG subclass deficiency. His chest radiography showed infiltrates in the both lungs. PPD reaction was negative. He had diminished response of peripheral blood lymphocytes to PHA. Cytogenetic studies of the peripheral lymphocytes releaved a chromosomal sensitivity to ionizing radiation when compared with the normal control, no increase in the rate of DEB and MMC-induced chromosome aberrations (Table 1).

Case 2

A 8-years-old boy was admitted to the pediatric hematology department because of severe ecchymosis, epistaxis and weight loss for two months. His past history releaved

Table 1. Hematologic, immunologic and cytogenetic features of case 1 and 2

	Case 1	Case 2
Hemoglobin (g/dl)	11.6	**4.3**
WBC (/mm^3)	12.300	**2.200**
Platelets (/mm^3)	470.000	**26.000**
MCV (fl)	67.9	**112.3**
MCH (pg)	21.7	36.5
RDW (%)	16.1	17.2
α-FP (ng/mL)	**217.4**	9.5
Hb F (%)		**13.8**
IgG (mg/dL)	949	574
IgA (mg/dL)	**6.4**	131
IgM (mg/dL)	152	35
IgE (mg/dL)	**18**	169
Diepoxybutane	(-)	**Borderline**
MMC-induced breakage	(-)	**(+)**
Sensitivity to ionizing radiation	**(+)**	(-)

that he had no recurrent sinopulmonary infection. Physical examination showed that he was pale and he had cafe-au-lait spots and hyperpigmentation on his skin. He weighed 22 kg (< 3rd percentile) and was 120 cm (< 3rd percentile). His head circumference was 48.5 cm (< 3rd percentile). He had bilateral microcornea and no hepatosplenomegaly and lymphadenopathy. It was revealed that he had no cardiac and renal abnormality.

The hemoglobin was 4.3 g/dL; WBC count 2200/mm^3; platelets 26.000/mm^3; MCV 104 fl; MCH 35.7 pg; MCHC 34.2 g/dL. Peripheral blood and bone marrow smears showed no blastic cells. He had a hypoplastic bone marrow. Alpha-fetoprotein level was 9.5 mg/dL. He had a normal level of IgG, IgA, IgM and IgE. His cell-mediated immunity was also normal. Cytogenetic studies showed that higher frequency of spontaneous chromosome aberrations in the untreated cultur and of induced aberration in the mitomycin C treated samples, than the normal control and also there was a mild increase in the rate of diepoxybutane (DEB). The patient was given 3 mg/kg of oxymethalone and is still prepared for bone marrow transplantation (Table 1).

As the two boys of the same family had two different chromosomal instability disorders such as FA and AT, we investigated other members of the family. The parent and 5th child were healthy. The first boy had a normal level of hemoglobin, WBC count, platelets, immunoglobulins and alpha-fetoprotein, but he had a mild increase in the rate of DEB. The 4th child had an increased rate of DEB-induced chromosome aberrations, a normal level of α-FP and she had 4400/mm^3 leukocyte count and 144.000/mm^3 of platelets (Table 2) (Figure 1).

DISCUSSION

Genetic instability syndromes are defined by either an increase of chromosomal breakage or increase of sister chromatid exchange number, or by an increase of the two. Bloom's syndrome, AT and FA are the main components of this group[3].

The AT gene (ATM) is involved in a variety of signal transduction patways that regulate

Table 2. Hematologic, immunologic and cytogenetic features of other family members

	Mother	Father	1st child	4th child	5th child
Hemoglobin (g/dL)	12.4	16.4	12.0	11.9	11.9
WBC (/mm^3)	5000	5800	7040	**4400**	5600
Platelets (/mm^3)	307.000	264.000	315.000	**144.000**	392.000
MCV (fl)	81.3	87.0	81.6	**100**	78.3
MCH (pg)	26.9	28.3	26.7	34.5	25.9
RDW (%)	13.0	11.6	12.6	12.0	14.6
α–FP (ng/mL)	3.9	1.9	3.8	6.2	
Hb F (%)			0.5	**10.5**	0.5
IgG (mg/dL)			1318	**638**	690
IgA (mg/dL)			180	**53.4**	35
IgM (mg/dL)			150	**22.2**	116
IgE (mg/dL)			43	**304**	75
Diepoxybutane			**Borderline**	**(+)**	(-)
Abdominal ultrasonography				Normal	

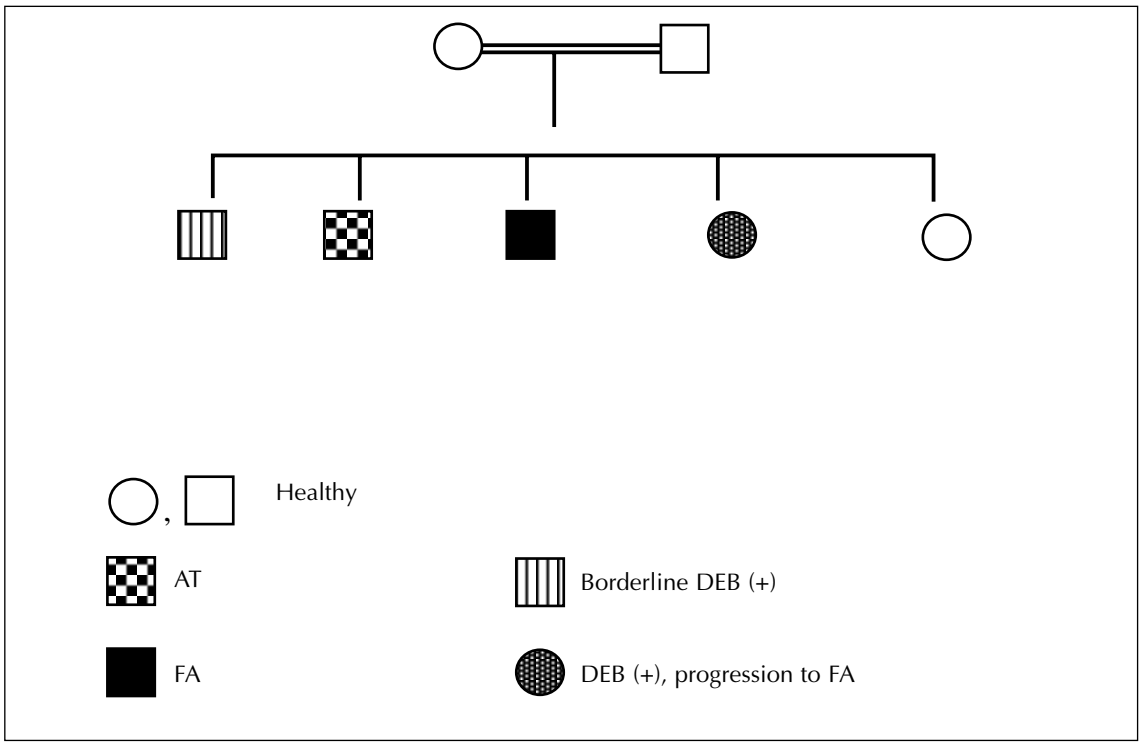

Figure 1. Pedigree of the family.

the cellular response to normal proliferative stimuli as well as the response to DNA damage, and the disruption of these signal transduction pathways provides an explanation for AT characteristics such as ionizing radiation sensitivity, immunodeficiency, and infertility[4]. The peripheral lymphocytes of our first case with AT releaved a chromosomal sensitivity to ionizing radiation. Although the first FA gene (FAC) was cloned over 9 years ago, and a second FA gene (FAA) was cloned in 1996, the biochemical function of FA proteins largerly remains a mystery[5]. The peripheral lymphocytes of our other case with pancytopenia showed a mild increase in the rate of DEB and an increased rate of MMC-induced chromosome aberrations. The eldest brother of our cases had a borderline positivity of DEB test and their sister had an increased rate of DEB-induced chromosome aberrations. DEB tests of the parent and 5th child were negative. All of them did not have the two different mutations (exon 43 deletion and exon 37 3639 deletion T), previously described in Turkish population with FA[6].

Li et al reported the family having major features of two autosomal recessive preleukemic disease, AT and FA in 1978[7]. Then, he diagnosed these family as ataxia-pancytopenia syndrome[8]. Furthermore, a 3-years-old boy with cerebellar ataxia, idiopathic aplastic anemia was reported. Cytogenetic studies of peripheral lymphocytes releaved a previosly described karyotype, 46,XY,t (1;20), (p22;q13.3)[9].

Gonzalez-del Angel et al reported a Mexican girl who developed cerebellar ataxia at age three years and pancytopenia at age 13 years[10].

We diagnosed two brothers with two different chromosomal instability disorders such as FA and AT in the same family according to clinical, immunological and cytogenetic features of these diseases. To our knowledge, this is the first family with FA and AT in Turkey.

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