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Ataxia-Telangiectasia: Case Report of Two Siblings

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Abstract
Characterized by progressive cerebellar ataxia, cutaneous and conjuctival telangiectasia, ocular apraxy, immunodeficiency, and increased risk of malignancy, ataxia-telangiectasia is a rare neurodegenerative disorder that shows signs of autosomal recessive transmission. The ataxia-telangiectasia gene is located in chromosome 11q22-23. Various degrees of abnormalities in T and B cell immunities have also been described. It is known that the incidence of both T cell and B cell leukemia and lymphoma increased compared with the general growth of the population in Turkey. T cell malignancy can be seen at any age though B cell malignancy is more common at older ages. This report presents the case of two siblings who were diagnosed with ataxia-telangiectasia. The two siblings formerly had another sibling who was diagnosed with ataxia-telangiectasia and died from leukemia. Taking these two cases as the staring point, this study focuses on the clinical manifestations, affected systems and treatment of ataxia-telangiectasia.
Key Words: Ataxia-Telangiectasia; Immunodeficiency; Cerebellar Atrophy.

Ataksi-Telenjiektazi: İki Kardeş Olgunun Sunumu

Özet
Ataksi-telenjiektazi ilerleyici serebellar ataksi, kutanöz ve konjunktival telenjiektaziler, oküler apraksi, immün yetmezlik ve artmış malignensi riski ile karekterize nadir görülen otozomal resesif geçiş gösteren nörodejeneratif bir hastalıktır. Ataksi-telenjiektaziden sorumlu gen 11q22-23 de lokalizedir. Humoral ve hücresel immünitede değişik derecelerde bozukluklar bildirilmiştir. Hem T hücreli, hemde B hücreli lösemi ve lenfoma sıklığı genel popülasyona göre artmıştır. T hücreli tümörler hastalığın seyri sırasında herhangi bir yaşta görülürken, B hücreli tümörler daha çok ileri yaşta görülür. Bu sunumda daha önce ataksi-telenjiektazi tanısı konulup lösemi nedeniyle ölen kardeş öyküsü olan ataksi-telenjiektazili iki kardeş olgusu tartışıldı. Bu olgular nedeniyle ataksi telenjiektazinin klinik bulguları, etkilenen sistemler ve tedavisi üzerinde duruldu.
Anahtar Kelimeler: Ataksi Telenjiektazi; İmmün Yetmezlik; Serebellar Atrofi.

INTRODUCTION

The clinical findings of ataxia-telangiectasia (AT) were first defined in 1926 by Syllaba and Henner, and, in 1957, named AT syndrome by Boder and Sedgwick (1). Characterised by cerebellar ataxia, cutaneous and conjunctival telangiectasia, ocular apraxia, immune deficiency, and increased risk of cancer, ataxia-telangiectasia is a neurodegenerative disease with autosomal recession, which itself is rare (2). It has been found out that the mutant gene responsible for the disease is in the long arm of chromosome 11 (11q22-23) (3).

The humoral and cellular immunity of ataxia-telangiectasia patients are affected in different degrees. Therefore, as a result of the developing immune deficiency, serious recurrent sinopulmonary infections are seen in these cases and this constitutes the most common cause of mortality. In this paper, we intend to report the cases of two siblings from the same family with the diagnosis of AT.

CASE REPORT

Patient 1: 7 year-old male patient was admitted to our clinic with ongoing cough for 4 days and fever. His medical history revealed that he was born through normal vaginal way, with 3200 g of birth-weight, and had frequent upper respiratory tract infections in winters. The patient had undergone lung infection for the first time at 2 years of age and, up until now, had been hospitalised six times due to lung infection. The family history further evinced that the parents were first cousins and that one of the brothers was diagnosed with AT at the age of 4 and then died of leukemia at the age of 5. Initial examination gave the following results: body weight: 16 kg (<3p); height: 105 cm (3 <p); heart rate: 90 beats/min; respiratory rate 36/min; and body temperature: 38.7 C, respectively. Head and neck examination provided the following details: eyes had oculomotor apraxia and there was telangiectasia in bulbar conjunctiva, auricle of the ear, and on the face (Figure 1).

There were cafe-au-lait spots on the body, the largest being 2×2 cm in size. System examinations showed that

the bilateral lungs were equally ventilated though there were rales at the basilar of the right lung. Neurological examination showed signs of ataxic gait while cerebellar tests such as tests for dysmetria and dysdiadochokinesia revealed abnormalities. Further findings concerning patient's unsteady gait history pointed out that the unready gait was first observed when he was 3 years old; the family related that they noticed the telangiectasia in the eyes when he was 4 years old. Laboratory test results were as follows: WBC: 7,100/mm3; absolute lymphocyte count: 1,500/mm3; absolute neutrophil count: 4,500/mm3; total eosinophil count: 120/mm3 (1.6%); hemoglobin 12.7 g/dL; hematocrit: % 40; MCV: 88.2 fl; Plt: 573,000/mm3; AST: 12 U/L; ALT: 13 U/L; ALP: 210 U/L; BUN: 16 mg/dL; creatinine: 0.67mg/dL and creatinine kinase: 57 U/L (30-200), respectively. Immunoglobulins were lower for his age; the results were as follows: Ig A: 9 mg/dL (70-300); Ig G: 380 mg/dL (764-2134); Ig M: 112 mg/dL (69-382); Ig E: 1.7 IU/ml (0-50, and alpha-fetoprotein: 405 IU/ml (0.5-5.5), respectively. The investigation of lymphocyte subset provided us with the results below: CD3 [48.7% (55-78)]; CD4 [26.1% (27-53)], and CD19 [4.3% (10-31)], which were below the normal values for his age; similarly, CD8 [35% (19-34)] and CD16-56 [24% (4-26)] were also lower for his age. Chest radiographs showed infiltration in the right lower lobe. The patient was consulted to child neurology and cranial magnetic resonance imaging (MRI) showed cerebellum to be atrophic (Figure 2).

As a result of these clinical and laboratory tests, the patient was diagnosed with AT. Once the lung infection was treated, the patient was given an IVIG treatment (400 mg/kg) with intervals of 4 weeks and the prophylaxis (5 mg/kg) with trimethoprim-sulfamethoxazole. As a precaution for probable malignancies and sinopulmonary infections, the patient was followed closely.

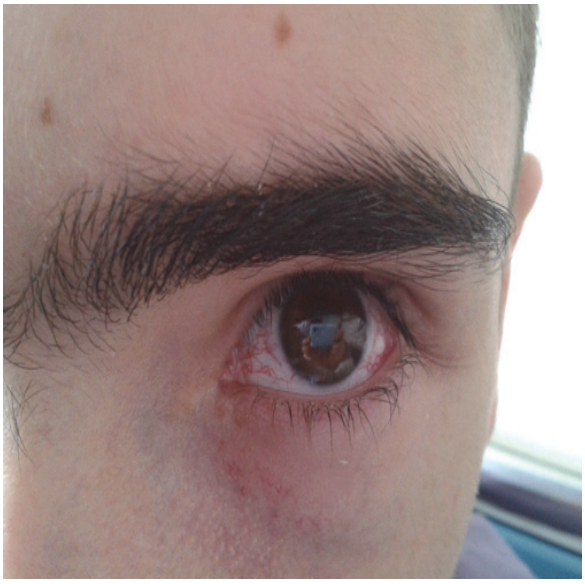

Figure 1. Bulbar conjunctiva and telangiectasia on the face of patient 1

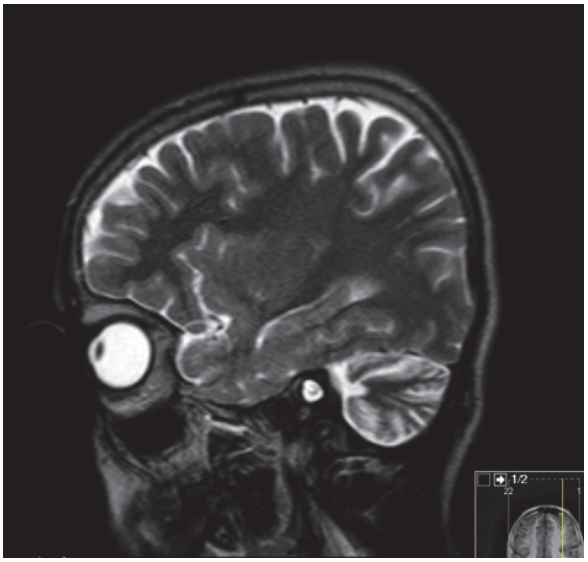

Figure 2. Cerebellar atrophy in cranial magnetic resonance imaging (MRI) of patient 1

Patient 2: The 5-year-old sister of the first case was called to our clinic because of her unsteady gait complaint. Her medical resume manifested that she was delivered by way of normal vaginal delivery with 2900 g of birth-weight and that she was hospitalized for lung infection when she was 7 months-old and, again, at the age of 2. Telangiectasia in the eyes of the patient was noticed at the age of 3.5, and her unsteady gait was first noticed when she was 4. The findings at the initial examination were as follows: body weight: 12 kg (<3p); height: 97 cm (3<p); heart peak rate: 84/min; and respiratory rate 24/ min, respectively. There were telangiectasia in the eyes and ears (Figure 3), and abnormalities in the cerebellar test results following the neurological examination.Other system examinations showed no abnormalities. The laboratory test results were as follows: WBC: 6,100/mm3; absolute lymphocyte count: 1,200/mm3; absolute neutrophil count: 4000/mm3; total eosinophil count: 160/mm3 (2.6%); hemoglobin 11.6 g/dL; hematocrit: 37; MCV: 81 fl; Plt: 380,000/mm3; AST: 21 U/L; ALT: 8 U/L; ALP: 180 U/L; BUN: 12 mg/dL; creatinine: 0.27 mg/dl, and creatine kinase: 37 U/ (30-200), respectively.Immunoglobulins were lower for her age [Ig A: 14 mg/dL (57-282); Ig G: 529 mg/dL (745-1804); Ig M: 98 mg/dL (78-261); Ig E: 1.9 IU/ml (0-50)], and alpha-fetoprotein count was 173 IU/ml (0.5-5.5). The analysis of lymphocyte subset manifested the following results: CD3 [37.1% (55-78)] and CD4 [23.8% (27-53)], which were low for her age; CD8 [22.5% (19-34)], CD19 [9.9% (10-31)], and CD16-56 [32% (4-26)] were normal for her age. The case was consulted to paediatric neurology department and cranial MRI revealed cerebellar atrophy. Taking the her sibling's resume along well with the clinical and laboratory findings into consideration, the patient was diagnosed with AT. The patient, having no complaints other than unsteady gait, was followed for possible malignancies and sinopulmonary infections.

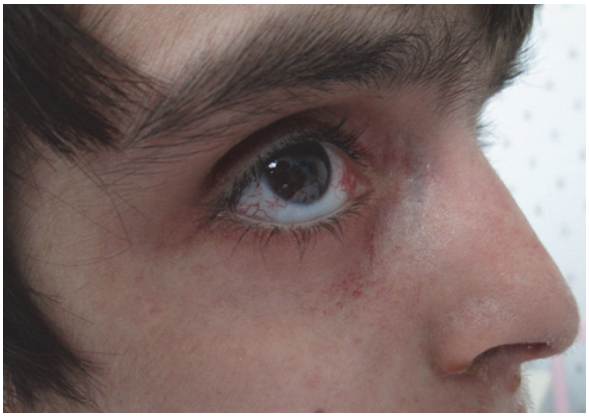

Figure 3. Bulbar conjunctiva and telangiectasia on the face of patient 2

DISCUSSION

Usually emerging in early childhood, ataxia-telangiectasia is an autosomal recessive disease with progressive cerebellar ataxia, sclera, and telangiectasia and cutaneous findings on the skin (vitiligo, acanthosis nigrigans, seborrheic dermatitis, hypertrichosis), and finally developing immune deficiencies (4). It is considered to be a rare disease with the estimated rate of incidence of 1/40000-100000 (5). Its etiology is unknown, but the responsible mutant gene (ATM) has been found to be on the long arm (11q 22-23) of chromosome 11. For the diagnosis of disease, "European Society for Immunodeficiencies" (ESID) diagnostic criteria are used (Table 1) (6).

Table 1. ESID* diagnosis criteria for ataxia-telangiectasia (6)

Accurate diagnosis
Increase in radiation-induced chromosome breakage in cultured cells and, in female and male patients with progressive cerebellar ataxia, gene mutations in the ATM gene in each of the two alleles.
Very Probable
The presence of at least three of the following four findings in male or female patients with progressive cerebellar ataxia. 1. Ocular or facial telangiectasia 2. Ig A levels being 2 SD below for the age of the patient 3. † AFP level being 2 SD above for the age of the patient 4. Increase in radiation-induced chromosome breakage in cultured cells
Probable
The presence of one of the following four findings in male or female patients with progressive cerebellar ataxia. 1. Ocular or facial telangiectasia 2. Ig A levels being 2 SD below for the age of the patient 3. † AFP level being 2 SD above for the age of the patient 4. Increase in radiation-induced chromosome breakage in cultured cells

***ESID**: "European Society for Immunodeficiencies", **†AFP**: Alpha fetoprotein

According to these criteria determined for progressive ataxia patients, we have observed the possible disease criteria in both of the cases (these were ocular telangiectasia, that Ig A level being below 2 SD for the patient's age, and that the AFP level was above 2 SD for the patient's age).

First signs to notice in ataxia-telangiectasia patients are generally neurological signs. Although these findings are often marked by more knowledgeable parents in the 9th to 12th months after the birth, the average time to notice the signs is the age of 2. However, in some patients, the emergence of the indications may delay up to 8-9 years (7). The first emerging neurological sign is ataxia but intentional tremor, segmental myoclonus, oculomotor apraxia, progressive dystonia of the fingers, and nystagmus may also occur over time (8). Cerebellar atrophy is observed in the cranial MRIs of these patients. In our cases, ataxia was marked at the age of 3 and 4, respectively; and both cranial MRI results showed cerebellar atrophy.

The most common dermatological findings in ataxia-telangiectasia patients are telangiectasias. Generally noticed at the age of 2, the emergence may delay up to 8-9 years. Bulbar conjunctiva is usually the first place for the disease to show itself but they may often be seen in the canopy of the ear and nose area as well. Though less often, it may be observed on the eyelids, neck, antecubital region, and extensor surfaces of the extremities (2,3,9). In addition to telangiectasia, pigmentary anomalies (such as cafe-au-lait spots, hypopigmented macules, albinism), facial papulo-squamous rash, cutaneous findings such as hypertrichosis can also be observed (9). In the both of our cases, there were the bulbar conjunctiva, and ear and facial telangiectasia. The telangiectasia in our patients were first noticed at the age of 4 and 3.5, respectively. Besides, at the physical examination of ourcase, we noticed a large number of cafe-au-lait spots.

Other major findings in patients with ataxia-telangiectasia are immune deficiency and an increased tendency to infection. Cellular and humoral immonudeficiency in varying degrees are also common in these patients. The most common humoral immune deficiency is the lack of Ig A by 80-90%. In almost all of these patients, Ig E is either too poor or totally absent. These are accompanied by IgG deficiency, and, particularly in almost half of those patients with Ig A deficiency, Ig G2 subclass deficiency (7.10). This deficiency in the immune system manifests itself with recurrent sinopulmonary infections. In our first case, the patient developed both cellular and humoral immunity

deficiency and he had recurrent pulmonary infections. That is why we needed to initiate an IVIG treatment of 400 mg/kg for 4 weeks with intervals and 5 mg/kg/day of prophylaxis with trimethoprim-sulfamethoxazole. In our second case, although she had low Ig A and G levels for her age, there was no recurrent sinopulmonary infection. Therefore, this patient was only followed with routine checks.

There is an increase in malignancy in ataxia-telangiectasia patients compared to normal population. This is explained by the cellular sensitivity reaction these patients show to ionised radiation. 15% of these patients have lymphoid induced malignancies. Both the T-cell, and the B-cell leukemia and lymphoma frequency has increased compared to the state of general population. In addition, non-lymphatic tumours such as disgerminomatous, gastric carcinoma, hepatic carcinoma, pancreatic tumors and solid gynaecological tumours emerge with an incidence rate of 20% during the course of the disease (4). Another sibling of our patients, diagnosed with AT, was lost during leukaemia treatment at the age of 5.

As a result, AT is a rare disease with autosomal recessive transmission that manifests itself through neurological, dermatological and immune deficiency. The principal reasons behind mortality are recurrent sinopulmonary infections and malignancies. Therefore patients with AT should be closely monitored and the emerging infections should be responded timely. In appropriate cases, patients should be given trimethoprim-sulfamethoxazole prophylaxis and/or IVIG treatment.

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