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Ataxia telangiectasia: report of two cases

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Ataxia telangiectasia (A-T) is a rare autosomal recessive multisystem disease. The diagnosis of A-T is based on the typical clinical picture: ataxia and telangiectasia. However, an increase in α-fetoprotein (AFP) level and the identification of the A-T mutated gene (ATM) assist in an early diagnosis. Here we report two cases of A-T diagnosed in our hospital (case 1: a 7-year-old boy; case 2: an 8-year-old girl). Both of these patients had typical clinical pictures of ataxia and telangiectasia, AFP was also increased (case 1: 471.2 ng/dL; case 2: 196 ng/dL). T-cell dysfunction was noted in both patients. Case 1 had IgG_2 deficiency and case 2 had IgA, IgG_2 and IgG_3 deficiency. Case 2 developed malignant lymphoma at 9 years of age and died of pneumonia with respiratory failure at 10 years of age. Because of rhe rarity of A-T in Taiwan, we report two cases to help pediatricians make an early diagnosis of A-T if they have a patient with progressive ataxia and oculocutaneous telangiectasia.

Key words: α-fetoprotein, ataxia, immunodeficiency, malignancy, telangiectasia

The initial clinical description of ataxia telangiectasia (A-T) was reported by Syllaba and Henner in 1926 and the syndrome was first signed to the term "ataxia telangiectasia" by Boder and Sedgwick in 1957 [1,2]. A-T is a rare, autosomal recessive syndrome characterized by progressive cerebellar ataxia, pathognomonic oculocutaneous telangiectasia, recurrent sinopulmonary infection, variable humoral and cellular immunodeficiency, a high incidence of malignancy and hypersensitivity to ionizing radiation. High serum α-fetoprotein (AFP), retardation of somatic growth, gonadal dysgenesis and defective cell cycle checkpoints are also found. The prevalence of A-T disease has estimated to be one case in 40,000 to one case in 100,000 [3]. While studies of A-T before 1995 had a limited focus, the cloning of the gene mutation responsible for A-T (ATM) on chromosome 11q22-23 in 1995 has led to biological research into the etiology of A-T [4-6]. Here we report two cases of A-T and describe the details needed for pediatricians to make an early diagnosis of A-T when they encounter a patient with progressive ataxia and oculocutaneous telangiectasia.

Case Report

Case 1

A 7-year-old boy had had an unsteady gait from the time he started to walk before 1 year of age. He had a wide-base gait and truncal ataxia. These symptoms progressed. Telangiectasia over the bilateral bulbar conjunctiva was found when he was 2 years old. No members of his family complained of frequent respiratory tract infections.

On physical examination, vertical nystagmus was found. Although the eye movements were full and free but slow and ocular apraxia was noted. Telangiectasia over the ears was also observed in addition to bilateral bulbar telangiectasia (Fig. 1).

On neurologic examination, an ataxic gait was noted, and the Romberg test and tandem gait test were positive. The coordination tests of finger to finger, and finger-nose-finger were slow with severe tremor. Brain computed tomography (CT) and magnetic resonance (MR) imaging revealed no abnormalities.

On laboratory examination (Table 1), AFP was elevated to 471.20 ng/mL (normal range, <10 ng/mL). The IgG_2 level (48 mg/dL) was decreased, and the IgE concentration (1 IU/mL) was low, however, the IgA concentration (195 mg/dL) was within normal limits. The percentages of CD3-, CD4- and CD8- positive T cells were moderately reduced. Multitest CMI (cell mediated immunity) delayed type hypersensitivity skin test was negative.

On hospitalization, A-T was diagnosed. Symptomatic treatment was only given because the patient did not have recurrent serious infections.

Case 2

An 8-year-old girl came to our hospital in 1991,

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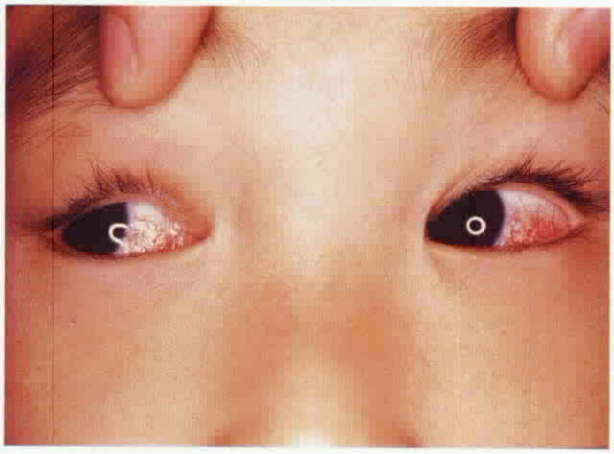

Fig. 1. Characteristic conjunctival telangiectasia observed in case 1.

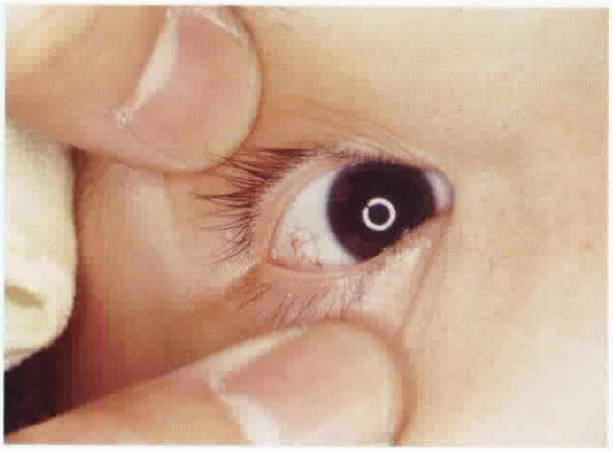

Fig. 2. Characteristic conjunctival telangiectasia observed in case 2.

complaining of progressive ataxia since she began to walk. Frequent febrile episodes were noted before she was 5 years old, and she had a prolonged, severe course of pneumonia 2 years later. No other family members suffered from recurrent episodes of respiratory tract infection.

Physical examination showed her head tilted to the right side. Telangiectasia over the bilateral bulbar conjunctivae was found (Fig. 2). An ataxic unsteady gait was observed. Intention tremor was found on a coordination test. Brain MR imaging disclosed atrophy of the cerebellum.

On laboratory examination (Table 1), lymphopenia was found (white cell count: 9570/mm^3; lymphocyte: 6%). AFP was elevated at 196.07 ng/mL, and low serum levels of IgA at 1 mg/dL, IgG_2 at 0 mg/dL and IgG_3 at 2 mg/dL were found. The IgE level was also low at 1 IU/mL. The percentages of CD3-, CD4- and CD8-positive T cells were moderately reduced in comparison to normal levels. Multitest CMI delayed type hypersensitivity skin test was negative.

A-T was diagnosed. She received prophylactic antibiotics for infection control and monthly intravenous immune globulin (IVIG) replacement therapy because of IgG subclass deficiency and frequent infection.

She was readmitted to our hospital in December 1992 due to severe cough for 1 week. Chest X-ray revealed pneumonia with pleural effusion on the right

Table 1. Immunological laboratory findings in two patients with A-T

Laboratory parameter	Case 1[a]	Case 2[b]	Reference range
IgA (mg/dL)	195	1	33 - 236
IgM (mg/dL)	182	119	100 - 198
IgE (IU/mL)	1	1	0 - 230
Total IgG (mg/dL)	861	651	608 - 1572
IgG_1 (mg/dL)[c]	877	720	400 - 989
IgG_2 (mg/dL)	48	0	123 - 534
IgG_3 (mg/dL)	57	2	21 - 129
IgG_4 (mg/dL)	16	5	1 - 151
CD3 (%)	38.8	40	67 - 81
CD4 (%)	19.1	25	41 - 55
CD8 (%)	15.2	13	30 - 40
CD19 (%)	11	40	8 - 32
CH50	34.5	41.7	23.5 - 34.5
Multitest CMI	All negative	All negative	≥ two positive

[a]A 7-year-old boy.

[b]An 8-year-old girl.

[c]The IgG subclass levels were determined by nephelometric methods using human IgG subclass Beckman array kits from the Binding Site Limited (Birmingham, UK).

side. Abdominal echography showed a para-aortic solid mass with cystic formation over the left lower retroperitoneal area. Abdominal CT showed a low-density mass over the para-aortic area and lower abdominal area. Laparotomy for biopsy was performed. The pathological diagnosis was diffuse large cell immunoblastic T-cell lymphoma. Work-ups revealed a stage III disease. Chemotherapy with the TPOG-LC (Taiwan Pediatric Oncology Group-large cell) protocol was started in January 1993. She died in November 1993 due to severe interstitial pneumonitis and respiratory failure.

Discussion

Neurological symptoms are one of the earliest features of A-T, most often in the form of cerebellar ataxia, which is the clinical hallmark of A-T and present in all patients [7]. The ataxia typically becomes evident shortly after the child begins to walk (at about 12 to 14 months of age) and the movement disorders progress to the stage of enforcing a wheelchair existence by the age of 10 or 11 years as independent walking becomes impossible [7]. The ataxia is predominantly truncal. Our cases were both found with truncal ataxia at 1 year of age. Other cerebellar signs, such as dysmetria or intention tremor, present somewhat later. A large proportion of A-T patients develop progressive spinal muscular atrophy (mostly hands and feet) and dystonia in their third or forth decades. Choreoathetosis is the most prominent extrapyramidal feature in A-T patients and it occurs to some degree in about 90% of the patients [8].

Telangiectasia is an essential and pathognomonic part of the disease and is usually first observed in patients between 3 and 6 years of age [7]. It can be progressing steadily and spread in a characteristic symmetrical pattern. The telangiectases are first found in the angles of the eyes and spread horizontally to the border of the cornea. The most commonly affected area is the exposed parts of the bulbar conjunctiva [9]. Case 1 of this report was observed with telangiectasia over the bilateral bulbar conjunctiva at 2 years of age, case 2 was at 5 years of age. Eyelids, external parts of the ears, the butterfly area of the face and the creases and V-area of the neck can also be involved. The telangiectatic vessels in A-T rarely hemorrhage. Ocular motor abnormalities are also a prominent feature of A-T [10]. Deficits are observed in the eye movement systems that stabilize images on the retina. Abnormalities in the systems that maintain fixation and gaze are also impaired. The prevalence of oculomotor abnormalities observed on examination increases with advancing age and these abnormalities are more prevalent in patients with more prominent neurological manifestations of A-T [11]. Clinical oculomotor signs that are particularly useful diagnostically because they frequently precede the development of telangiectasia, such as the abnormalities in saccade latency, amplitude and head movement, can be found in 50% of A-T patients by 2 years of age [11].

Impaired immunologic status is noted in almost all A-T patients and decreased concentration or absence of serum IgA and IgE secondary to reduced synthesis or hypercatabolism, has been reported in most patients. Selective IgA deficiency is found in 50% to 80% of affected individuals. A variety of other humoral immunodeficiencies have been described, including decreased IgG_2, or total IgG or combined IgG_2/IgG_4 subclass levels. Antibody responses to viral and bacterial antigens may be impaired [7,12,13]. Case 1 of this report presented with decreased IgE and IgG_2 levels, and case 2 presented with decreased IgA, IgE and IgG_3 levels and absent IgG_2. Cellular immunity is also impaired in A-T patients. Peripheral blood counts usually reveal lymphopenia or granulocytopenia [7,14]. Case 2 had lymphopenia (lymphocyte count of case 2: 574/mm^3). T-cell immunity is abnormal in about 60% of A-T patients as evidenced by a negative delayed hypersensitivity response to skin-sensitizing antigens and a delayed homograft-rejection response [15]. Both cases of this report were noted with reduced proportions of CD3-, CD4- and CD8-positive T cells and negative results on multitest CMI. The response of peripheral lymphocytes to phytohemagglutinin (PHA) and to specific antigens is often abnormal [16]. It is also manifested by abnormally developed or absent adenoids, tonsils, lymphoid tissue, and thymus gland [10,13].

Due to the variable degree of immunodeficiency in A-T patients, some patients are troubled with recurrent severe infections, whereas others suffer from only mild infections and have undetectable immunodeficiency. Recurrent sinopulmonary infections (nasal sinuses, middle ear, lungs) are common, and usually result in chronic bronchitis, bronchiectasis, or both [10]. These infections occur in roughly 80% of the A-T patients. They may begin early in life, or patients may remain relatively symptom-free for 10 years or more [12,14]. Case 2 of this report was found with frequent episodes of respiratory tract infection, including a severe course of pneumonia. Case 1 did not complain of recurrent serious infection till now, however, his T-cell immunity was impaired. Recurrent episodes of respiratory tract infection usually occur when the initial diagnosis of A-

T is delayed.

Hypersensitivity to ionizing radiation and various chemical agents, and predisposition to cancer are the hallmarks of classical A-T. It has been reported that a radiation dose to sterilize 90% of homozygote A-T cells was on the average only about 32% of the dose to sterilize 90% of the normal cells, and the dose in heterozygote cells was 75% [17]. Hypersensitivity to ionizing radiation has been linked to chromosomal instability, abnormalities in genetic recombination, and defective signaling to programmed cell death and several cell cycle checkpoints activated by DNA damage [18].

More than one-third of A-T patients develop malignancy [7]. The incidence of lymphomas and acute lymphocytic leukemias is markedly elevated, with as many as from 10% to 15% developing tumors [19]. Case 2 of this report was found with lymphoma at 9 years of age. Epidemiological studies have described a 3 to 5 fold increased risk of cancer (particularly breast cancer in women) associated with the heterozygous mutation [20]. This increased risk may be because ATM acts as a tumor suppressor. ATM can be detected by DNA fiber hybridization, LOH (loss of heterozygosity) analysis and immunoblotting for ATM [21].

If a child presents with the two diagnostic hallmarks of A-T, early-onset cerebellar ataxia and oculocutaneous telangiectasia, a clinical diagnosis of A-T can be made. But these two typical clinical pictures are not present in all A-T patients in early life, especially oculocutaneous telangiectasia. However, the diagnosis can be made earlier, before the appearance of telangiectasia, if appropriate confirmatory laboratory tests are obtained. Elevated serum AFP and identification of ATM can help us to do it. Other symptoms including the characteristic oculomotor apraxia, recurrent sinopulmonary infections or a typical A-T family history can also help in making an early diagnosis of A-T. Although there is no specific therapy for A-T patients at present, early diagnosis is important for genetic counseling, appropriate medical care, and the avoidance of unnecessary and costly diagnostic tests [22].

The most common misdiagnosis in A-T patients is cerebral palsy [22]. A-T in the later stages can also be confused with Friedreich ataxia, particularly if the pathognomonic oculocutaneous telangiectasia is minimal and there is peripheral neuropathy or signs of posterior column disease. However, none of the laboratory markers of A-T, such as elevated serum AFP or variable immunodeficiency, is found in Friedreich ataxia or cerebral palsy.

Individuals with A-T heterozygotes (A-T carriers) have no clinical expressions of the disease and seem to be healthy [23]. The incidence of this condition is as high as 1% in the general population and particularly high in female breast cancer patients [24]. A-T carriers have an increased hypersensitivity to radiation and a strong predisposition to develop malignant tumors [23]. However, if the radiosensitive and cancer susceptible subpopulation can be identified, treatment for A-T patients with cancer can be adjusted to provide a more effective radiation dose to obtain an optimal outcome. The normal tolerance dose for radiation therapy should be reduced from 15% to 20% in these patients [25].

No satisfactory definitive treatment to halt the progression of A-T has been found. All treatments are based on symptoms and are highly individualized due to the variable multisystemic manifestations. Vigorous supportive therapy, including aggressive physical therapy, antibiotics, supplemental immunoglobulin treatment as needed, and surveillance by a variety of specialists, is essential to avoid permanent complications and maintain the quality of life for A-T patients [26]. Because A-T patients are hypersensitive to radiation and chemotherapy, they should be treated with a lower fraction of the usually therapeutic dosage if they suffer from a malignancy and treatment with radiomimetic chemotherapeutic agents must be avoided [25].

The clinical variability of A-T makes it difficult to state an overall prognosis. There may be early death with malignancy, sinopulmonary infection, or progressive neurologic disease or there may be prolonged survival [27]. In a review of 58 published autopsies by Boder, pulmonary disease alone accounted for 46% of deaths, malignancy alone accounted for 23% and the two conditions were seen together in another 28% of deaths [28]. Today, A-T patients can survive into the fourth and fifth decades, and even to the sixth [29].

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