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Ataxia-Telangiectasia in Iran: Clinical and Laboratory Features of 104 Patients

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Ataxia-telangiectasia is a multisystem disorder characterized by progressive neurologic impairment, variable immunodeficiency, impaired organ maturation, x-ray hypersensitivity, oculocutaneous telangiectasia, and a predisposition to malignancy. To evaluate clinical and immunologic features of Iranian patients with ataxia-telangiectasia, the records of 104 patients with ataxia-telangiectasia (54 male, 50 female) with the age range of 1.6-23.5 years were reviewed. The Iranian Primary Immunodeficiency Registry was used as the data source. Progressive ataxia was seen in all the patients. Other symptoms were eye movement disorders (n = 84), slurred speech (n = 70), mental retardation (n = 10), and ocular (n = 87) and cutaneous (n = 73) telangiectasia. Three patients developed leukemia and lymphoma, and 17 patients had family history of malignancy. Positive correlation was seen between clinical immunologic symptoms and immunoglobulin deficiencies (P = 0.004). The predominant infections were sinopulmonary and acute and recurrent infections (78 cases). Infections included pneumonia (56 patients), otitis media (34 patients), and sinusitis (50 patients). Average serum α-fetoprotein level was 149 ± 137 ng/dL. The incidence of ataxia-telangiectasia in Iran is high, possibly due to familial marriages. Treatment should be focused on supportive management to prolong survival.

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Introduction

Ataxia-telangiectasia is an autosomal recessive, multisystem disorder characterized by progressive neurologic impairment, cerebellar ataxia, variable immunodeficiency with increased susceptibility to sinopulmonary infections, impaired organ maturation, x-ray hypersensitivity, ocular and cutaneous telangiectasia, and a predisposition to malignancy [1]. Ataxia-telangiectasia is reported in all regions of the world. The incidence of ataxia-telangiectasia is about 1 case in 100,000 births [2]. The frequency of ataxia-telangiectasia mutant alleles heterozygosity was reported to be 1.4-2% of the general population [2]. Ataxia-telangiectasia occurs equally among males and females [3].

Ataxia-telangiectasia cells have abnormal sensitivity to x-rays and certain radiomimetic chemicals (but not to ultraviolet irradiation), which leads to chromosome and chromatid breaks [4]. Breakpoints are randomly distributed, but nonrandom chromosome rearrangements selectively affect chromosomes 7 and 14 at sites that are associated with T-cell receptors and heavy-chain immunoglobulin coding and with the development of hematologic malignancies. Such disturbances could account for the frequency of infections and neoplasias.

No characteristic features are detectable during very early childhood. Ataxia is usually a first diagnostic hallmark, having its onset in the first years of life. Beyond the age of 5 years, the progression of the ataxia becomes increasingly apparent and the child requires a wheelchair

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by age 10 or 11 years [5]. Oculocutaneous telangiectasia, the second diagnostic hallmark of ataxia-telangiectasia, usually has a later onset than the ataxia, typically at age 3-6 years [3]. The progression of the disease is apparent in subsequent years.

The clinical diagnosis becomes most apparent after age 10 years, when clinical characteristics are fully expressed. In very young infants, the diagnosis can be elusive and easily confused with other diseases, such as mild cerebral palsy, acute infectious or episodic ataxia, and ataxia with oculomotor apraxia (AOA). A clinical diagnosis can now be confirmed by radiosensitivity testing (colony survival assay), immunoblotting, and mutation detection [6].

Little progress has been made in treating the progressive ataxia, and the only therapeutic options are medical management of the patient's problems such as immunodeficiency, sinopulmonary infections, neurologic dysfunction, and malignancy and rehabilitation for physical and social disabilities [6].

Death typically occurs early, usually from bronchopulmonary infection, less frequently from malignancy, or from a combination of both. The median age at death is reported to be approximately 20 years [7].

Previous studies showed that in Iran ataxia-telangiectasia is more prevalent among primary immunodeficiency disorders than in most of countries. Among 440 patients in the Iranian Primary Immunodeficiency Registry, ataxia-telangiectasia was registered in 50 patients (11.4%) [8].

The objective of the present study was to evaluate clinical and immunologic features of Iranian patients with ataxia-telangiectasia.

Patients and Methods

Patients

The charts of 104 patients with ataxia-telangiectasia who had been diagnosed and treated in Children's Medical Center during a 20-year period (1985-2005) were reviewed. Patients older than 1 year were diagnosed with ataxia-telangiectasia if they had ataxia or significant motor incoordination with an increased α-fetoprotein level more than twice the upper limit of normal range (<40 ng/dL) [9]. Three of the following four characteristic clinical features were also required: (1) incoordination of head and eyes in lateral gaze deflection oculomotor apraxia [10], (2) ocular telangiectasia, (3) gait ataxia associated with an inappropriately narrow base, and (4) immunoglobulin deficiencies. In case of less than three of these characteristics, diagnosis was confirmed by studying radiation-induced chromosomal breaks in lymphocytes [11].

For family history, persons were considered as relatives if there was a first- or second-degree familial relation.

Laboratory Testing

Blood samples of the patients were tested for the immunoglobulin levels measurement on the first visit using nephelometry methods and the results were compared with the normal range of quantitative immunoglobulin levels. Before 1993, B-cell and T-cell subsets were measured with the Rosette formation technique, so in patients who were diagnosed before 1993 the B-cell and T-cell subset measurements were repeated, using flow cytometry.

For study of lymphocyte radiosensitivity, heparinized blood samples were cultured in supplemented RPMI 1640 medium. After incubation period lymphocyte cultures were exposed to 0.5 and 1 Gy gamma irradiation. Metaphases were examined for each culture after harvesting for chromatid breaks, chromosome breaks, acentric fragment, chromatid exchange, dicentric chromosome, translocation, ring chromosome, and gaps. Total numbers of aberrations per cell were studied among persons.

For those who had died, the cause of death was determined by review of the death certificate.

Statistical Methods

Data analysis was done using SPSS statistical software (version 11.0; SPSS, Chicago, IL). Initial testing results were used for the evaluation of immunologic values and CD markers. Linear regression was used to determine the association between year of disease onset and delay in diagnosis.

Results

Patient Characteristics

The study population comprised 104 patients (54 male and 50 female) who had been diagnosed with ataxia-telangiectasia. The median age of patients at the time of study was 9 years 4 months (range, 1.66-23.5 years) for males and 8 years 6 months (range, 2.17-18.33 years) for females. The median age at the time of symptom onset was 1 year (range, 0.5-9) for males and 1 year and 4 months (range, 0.33-8) for females and at the time of diagnosis was 7 years 4 months (range, 1.67-17.33) for males and 7 years 1 month (range, 2.08-15.08) for females. On average, the median diagnostic delay in our patient's group was 58 months (range, 0-208 months).

The total follow-up period was 157.75 patient-years (mean follow-up, 24.91 months; range, 0-152 months). By the year 2005, 4 patients had died (average age at death, 12 years 5 months) and 48 patients could not be located.

Statistical analysis of these data was complicated by two factors, that the diagnosis was made at increasingly earlier ages and that delay in diagnosis has significantly decreased in recent years ($r = -0.48$, $F = 27.24$, $P < 0.001$). An inverse association was observed between year of disease onset and delay in diagnosis (Fig. 1).

Serum Immunoglobulin Levels and Lymphocyte Studies

At the time of diagnosis, mean serum IgG level was 1,008 mg/dL (range, 126-3,060 mg/dL) and that of other serum immunoglobulin was 83 mg/dL for IgA (range, 0-725 mg/dL) and 240 mg/dL for IgM (range, 4-720 mg/dL). The level of IgA was under 10 mg/dL in 75.4%. Serum IgM was <25 mg/dL for 67.7%. Serum level of IgG2 was 17 mg/dL—although it was not checked in all patients. Serum IgG level was more than 2 standard deviations below normal for sex and age in 13 patients.

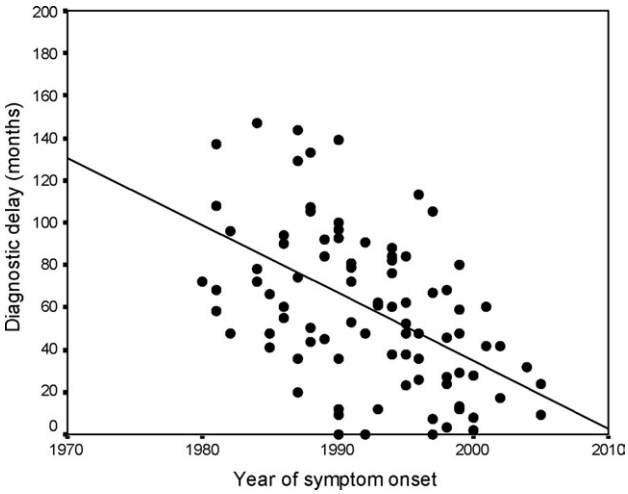

Figure 1. Diagnostic delay in comparison with year of onset of symptoms in ataxia-telangiectasia patients.

Patients with lower IgG level had higher incidence of recurrent respiratory infections (85% vs. 72%), although this difference was not statistically significant. Median serum IgE level was 9 mg/dL. There was a reverse correlation between infectious episodes and immunoglobulin levels (Pearson correlation coefficient $r = 1$; $P = 0.004$).

In 75.8% of subjects, a relative lack of CD4+ T-cells (<400 cell/mm3) and in 44.4% of patients severe lack of CD4+ T-cells (<200 cell/mm^3) was found. T-cell subset analysis, by immunologic flow cytometry, showed a reversed CD4/CD8 ratio in 46.5% of patients. Mean CD19 level was 14.25% (2-73). Serum α-fetoprotein level was 149 ± 137 ng/dL (Fig. 2). Immunologic findings are summarized in Table 1.

Radiosensitivity

Exposure of lymphocytes of ataxia-telangiectasia patients to either 0.50 or 1.00 Gy X-rays at the G2 phase of the cell cycle will disclose a large chromosomal radiosensitivity in these patients, which can be measured within 72 hours of receipt of the blood sample [12]. Analysis of irradiated metaphases of our patients showed a mean level of 6.33 chromatid gaps, breaks, and interchanges (triradials and quadriradials) per cell (range, 3.8-13) for 0.5 Gy and 15.03 (3.75-30) for 1 Gy irradiation in specimens from each patient, compared with a mean of 1.67 (range, 1-2.8) for 0.5 Gy and 2.96 (range, 1.5-4.17) for 1 Gy in lymphocytes from normal individuals (Fig. 3). This difference is statistically significant for both irradiation doses ($P = 0.009$ for 0.5 Gy; $P = 0.008$ for 1 Gy).

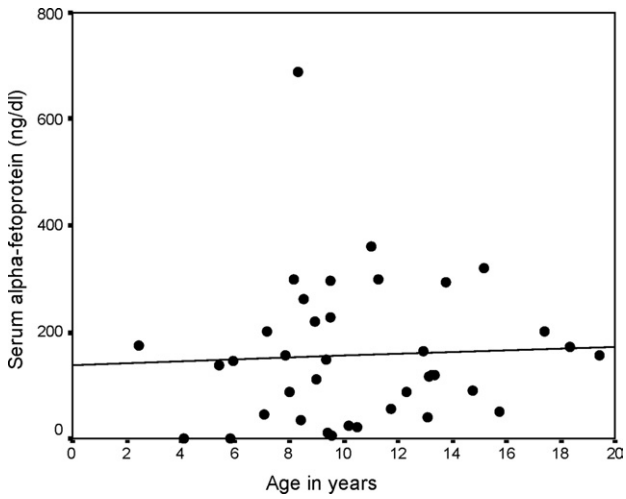

Figure 2. Serum α-fetoprotein levels in individuals with ataxia-telangiectasia by age.

Table 1. Immunologic findings of 104 ataxia-telangiectasia patients

	Female, Median (range)	Male, Median (range)
Immunoglobulins, mg/dL		
IgG	980 (220-2,200)	800 (125-3,060)
IgG2	1.4 (0.3-155)	1.25 (0.47-100)
IgA	58 (0-345)	41.5 (0-725)
IgM	184 (53-720)	270 (4-564)
IgE	10 (1-800)	8 (0-640)
Lymphocyte markers, %		
CD3	45.45 (20.00-76.30)	50.00 (13.90-89.00)
CD4	20.85 (8.95-44.00)	23.00 (1.81-78.72)
CD8	22.00 (10.00-46.67)	25.50 (1.40-76.03)
CD19	11.34 (2.26-28.10)	11.60 (2.00-73.02)

Clinical Manifestations

The main categories of associated diseases reported up to the time of study were gait problems, oculocutaneous telangiectasia, infection, and cancer.

Although some subjects are no longer available, they were not excluded from the total group, so the frequency of these conditions is likely to be an underestimate. It must also be noted that the true incidence of some conditions

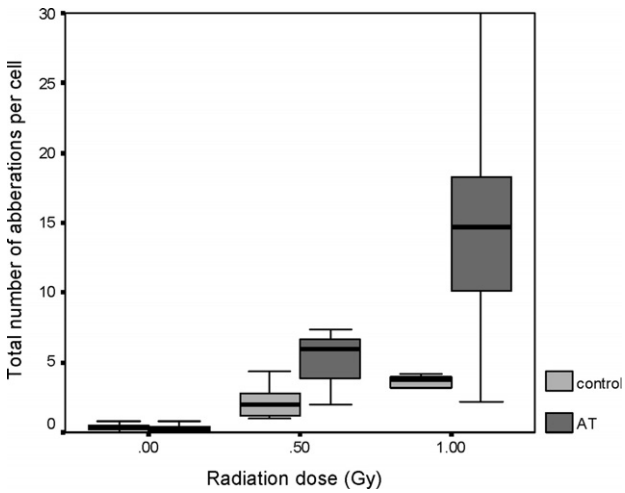

Figure 3. Chromosome damage in lymphocytes induced by different doses of gamma radiation: 0, 0.5, and 1 Gy. Levels of chromatid type damage in two groups, patients and controls. Error bars indicate 1 standard deviation.

Table 2. Clinical symptoms of 104 ataxia-telangiectasia patients

Symptom	Patients Affected, No.	Age of Onset, Years, Median (range)
Ataxia	104	3 (1-7)
Speech disorder	22	10 (8-18)
Eye movement disability	75/93*	8 (7-18)
Choreoathetotic movement	81/93*	6 (4-8)
Seizure	9	†
Mental retardation	10	†
Growth retardation	39	†

* Data were lacking for this symptom in 11 patients.
† Age of onset for this symptom could not be determined.

would be particularly difficult to determine, given that many patients had never had biopsies.

Neurologic Deficits Progressive gait and truncal ataxia were seen in all of our patients with onset between 1 and 7 years of age. There was a loss of muscle strength in older patients, which was more marked distally and in the lower limbs; muscular fasciculations were not seen. A majority of patients (80.6%) demonstrated apraxia of horizontal and vertical saccadic eye movements, manifested as a pause before being able to move the eyes to a new area of interest. This was most obvious on horizontal gaze. Rapid head movements and blinks were used to assist in eye movements. Speech was dysarthric in nearly all of patients, and 70 patients always had slurred speech. Nonetheless, although patience might be required, speech was always understandable. No formal intelligence tests were performed, but some comments can be made. All individuals could cooperate with a neurologic examination. Mild mental retardation was present in 10 patients (9.6%). Nine patients (8.7%) had epilepsy (Table 2).

Telangiectasia Conjunctivocutaneous telangiectasia the second hallmark of ataxia-telangiectasia patients was began at the median age of 6 years (cutaneous, 3-12 years; conjunctival, 2-10 years) (Fig. 4). Conjunctival telangiectasia was seen in 87 of 104 patients (83.8%), and cutaneous telangiectasia (especially prominent blood vessels on the ear helix) was seen in 73 of 104 patients (70.2%).

Appearance and Build The majority of patients appeared thin, some strikingly so. In 39 patients, apparent failure to thrive was present. This was often correlated with reduced immune function or neurologic severity, but not age, sex, or food intake.

Infections in the Course of Disease In 26 patients, there was no suggestion of immune deficiency; 65 patients had probable immune deficiency, suffering from more infections than expected, but with no more than one admission to hospital; 13 patients had severe immune deficiency, with suppurative lung disease or severe infections requiring repeated inpatient treatment. In the present series, immune dysfunction was variable between individuals and a positive correlation was seen between clinical immunologic symptoms and immunoglobulin deficiencies ($P = 0.004$).

The predominant infections seen were sinopulmonary. Acute and recurrent infections were found in 78 of the 104 (75%) patients; 31 patients were admitted to hospital because of infections. The overall average number of admissions was 0.63 ± 1.4 per person.

Of the 104 patients, 56 (53.9%) had pneumonia, 2 of whom developed bronchiectasis, and 67 patients (64.4%) had a history of recurrent upper respiratory infections; these infections included otitis media in 34 patients, sinusitis in 50 patients, and pharyngitis in 7 patients. Recurrent diarrhea was seen in 22 patients (21.2%). Recurrent urinary tract infections, candidiasis, hepatosplenomegaly, were seen in 7 (6.7%), 8 (7.7%), and 7 (6.7%) patients, respectively.

The most common organisms responsible for infections were *Pneumococcus* species and *Escherichia coli*. For many patients, however, no culture tests were performed, so we cannot estimate the true incidence of each microorganism.

No episodes of meningitis or of bone or joint infections were reported, and no adverse reactions following immunizations.

Other Symptoms Rickets was seen in 5 of the 104 patients; however, this may be due to poor nutritional state rather than the ataxia-telangiectasia as such.

Consanguinity and Family History

Parental consanguinity was reported in 79 families among our patients. Families of 17 patients had history of malignancy: 10 gastrointestinal malignancies, 7 breast cancer, 3 lymphoma, 1 leukemia, 1 skin malignancy, and 1 prostate cancer.

Eleven patients had a positive family history of recurrent infections, and 35 patients had a positive family history of immunodeficiency (mostly ataxia-telangiecta-

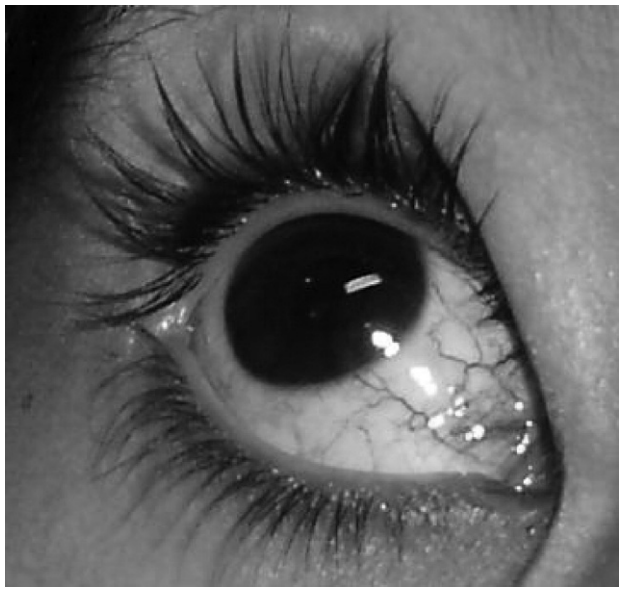

Figure 4. Bulbar telangiectasia in a 7-year-old boy with ataxia-telangiectasia.

sia). Eighteen sibling pairs with ataxia-telangiectasia were studied. In one of the families, out of four children the three male siblings had ataxia-telangiectasia and the girl was normal. Premature death with unknown reason was present in 9 families.

Mortality and Cancer

Four of our patients are known to have died. The exact cause of death is unknown, but in one case chronic pulmonary disease due to tuberculosis contributed (in this case, the age at death was 7 years).

Three patients developed leukemia and lymphoma, which was confirmed by node biopsy report of pathology: one was ALL-L2; one was Hodgkin lymphoma, mixed cellularity type; and one was non-Hodgkin lymphoma.

Discussion

Syllaba and Henner [13] first published descriptions of patients with ataxia-telangiectasia in 1926. They observed progressive choreoathetosis and ocular telangiectasia in three members of a single family. Some 15 years passed before the next report; in 1941, Louis-Bar [14] described progressive cerebellar ataxia and cutaneous telangiectasia in a Belgian child. The syndrome subsequently received the name of Louis-Bar. Ataxia-telangiectasia was not described as a distinct clinical entity for another 16 years, until Biemond in 1957 [15] and Boder and Sedgwick in 1960 [16] with the aid of autopsies, reported organ developmental abnormalities; neurologic manifestations; and a third major feature of the disease, recurrent sinopulmonary infection.

ATM (ataxia-telangiectasia mutated) is the only gene known to be associated with ataxia-telangiectasia. The normal gene has 3,056 amino acids containing 66 exons (62 of them coding) and 13-kb cDNA. More than 500 unique mutations are known. No hot spots have been identified. Fewer than 1% of nonconsanguineous affected individuals in North America share a common mutation, and are compound heterozygotes [1,17]. Most mutations are the null type, resulting in no protein product. Founder-effect mutations have been described for the following populations: Amish (100%), Costa Rican (96%), Sardinian (>95%), English (73%), Norwegian (55%), Japanese (>50%), Italian (35%), and Polish (>30%), Spanish (65%), Brazilian (65%), and Hispanic-American (37%) [17].

The present article reports the clinical and laboratory features of 104 ataxia-telangiectasia patients aged 2-20 years. In Iran, a registry (the Iranian Primary Immunodeficiency Registry, or IPIDR) has been active since 1997, and 440 cases with a variety of primary immunodeficiency diseases had been registered by the end of 2001 [8]. Compared with the pattern in other registries, ataxia-telangiectasia was relatively more prevalent in IPIDR. This may be due to the high consanguinity seen in majority of our patients.

Consanguineous marriages may increase the risk of autosomal recessive disorders and multifactorial diseases [18], and inheritance of ataxia-telangiectasia is thought to be autosomal recessive [19]. Consanguineous marriages have been a long-standing social habit among Iranians (the overall rate of consanguineous marriage is 38.6%), and early records of consanguinity are found in Iranian mythology [20]. In a study of Iranian primary immunodeficient patients consanguinity, was present in 81.1% (60 of 74) of ataxia-telangiectasia patients [21]. It is important to inform the general population about the dangers of consanguinity, which is very common in some areas such as Iran. Premarital examination including a thorough history and family history to avoid genetic diseases could be suggested, especially in a community where the rate of consanguineous marriage is high.

The present clinical findings are similar to those previously reported by Boder and Sedgwick [22] for 101 cases and Woods and Taylor [23] for 70 cases. Table 3 summarizes the clinical findings of the three studies.

Table 3. Clinical features of ataxia-telangiectasia across three studies

Clinical Feature	Present Study	Woods and Taylor [23]	Boder and Sedgwick [22]	Combined, %
Progressive cerebellar ataxia	104/104	70/70	101/101	100
Dysarthria	104/104	70/70	70/70	100
Characteristic face and postures	104/104	70/70	60/61	99.6
Flexor or equivocal plantars	†	47/70	60/61	81.7
Intact sensation	†	69/70	51/52	98.4
Ocular telangiectasia	87/104	65/70	100/100	92
Choreoathetosis	81/93*	68/70	61/67	91.3
Peculiarity of eye movements	84/104	70/70	47/56	87.4
Diminished or absent reflexes	†	50/70	54/61	79.4
Frequent sinopulmonary infections	78/104	43/70	60/72	73.6
Failure to thrive	39/104	30/52	42/58	51.9
Mental retardation	9/104	0‡/70	22/66	12.9

* Data were lacking for this symptom in 11 patients.
† Not all patients could be assessed.
‡ Intelligence was not formally assessed.

Ataxia is usually a first diagnostic hallmark, having its onset in the first years of life. Among our patients, median age at onset of ataxia was 3 years (range, 1-7). This is congruent with findings of other studies, that beyond the age of 5 years the progression of the ataxia becomes increasingly apparent and the child requires a wheelchair by age 10 or 11 years [3,6]. In 2004, Trimis et al. [24] reported the case of a 6-year-old girl without any neurologic symptoms.

Among the other classic early features of ataxia-telangiectasia are cerebellar atrophy, slurred speech, oculomotor apraxia, and choreoathetosis, which are seen in most of our patients. In all of them, these neurologic problems were progressive and nothing could be done except supportive care such as physiotherapy and other rehabilitative therapies.

Neuroimaging of patients was not available, and so we could not determine whether cerebral malformations were present in our population; however, clinical signs of spinocerebellar degeneration, which has been previously reported [25,26], were quite common among our patients: most of them had gait and truncal ataxia, oculomotor apraxia, choreoathetosis, and dysarthria. The short stature and thinness of many of the study patients is also seen in other DNA homeostasis disorders, such as Bloom's syndrome and Fanconi's anemia [27]. Most patients are wheelchair dependent by age 10-15 years, but mild forms are not rare [28].

Mental retardation occurred in nearly 10% of our patients. Mental retardation is not usually a common feature in ataxia-telangiectasia, but occasionally occurs [3,5]. The rate of mental retardation in the study population may be a result of a high consanguinity rate among our patients, rather than ataxia-telangiectasia.

Oculocutaneous telangiectasia, the second diagnostic hallmark of ataxia-telangiectasia, usually has a later onset than the ataxia (median age of onset in our patients was 6 years), typically at age 3-6 years. The progression of the disease is apparent in subsequent years [3,6].

An elevated serum α-fetoprotein level is a useful screening test for ataxia-telangiectasia [29]. Ataxia-telangiectasia patients with a normal serum α-fetoprotein have previously been described [30,31], and five further patients are reported here. A grossly elevated α-fetoprotein level in a patient with known ataxia-telangiectasia may indicate hepatitis, or a liver or gonadal malignancy. Although one of our patients with α-fetoprotein level of 700 ng/dL had no malignancies himself, possibly due to his age of 8 years, there was family history of multiple malignancies in his first- and second-degree family members: two breast cancers, two gastric cancers, and one lymphoma.

Immunodeficiency was characterized in 60-80% of patients, predisposing them to recurrent pulmonary and sinus infections [23]. Although recurrent respiratory tract infection was seen in 54% of our patients, only in two patients it was severe enough to develop bronchiectasia. Although it may be due to the young age of our patients, it may also reflect the fact that severe immunodeficiency is not a common feature in ataxia-telangiectasia [32].

In a retrospective study in the United States, mortality from all causes in ataxia-telangiectasia was 50-fold higher for white and 147-fold higher for black patients with ataxia-telangiectasia than expected based on overall U.S. mortality rates [33]. Boder and Sedgwick [22] reviewed 58 complete autopsy cases: 27 (46%) deaths were caused by pulmonary infection alone, 12 (21%) by malignancy alone, 16 (28%) by a combination of both, and 3 (5%) by other reasons. Although immune dysfunction was very variable between individuals, positive correlation was seen between clinical immunologic symptoms and immunoglobulin deficiencies ($P = 0.004$).

For most patients (85-90%), the differentiation between ataxia-telangiectasia and normal lymphocytes is clear cut, and increased radiosensitivity is therefore a reliable method for confirming the diagnosis. Increased radiosensitivity is present at birth and can be used to help in diagnosis. The level of induced chromosomal breakage overlaps with the normal range in 10-15% of patients. It is rare, however, for the level to be completely normal. In addition to induced chromosome damage, the level of spontaneously occurring damage in ataxia-telangiectasia is usually analyzed. Taken with the clinical features, an increase of both spontaneous and induced damage would indicate the diagnosis of ataxia-telangiectasia. The occurrence of chromosome 7 and 14 translocations in the presence of only a small increase in radiosensitivity would also tend to support a diagnosis of ataxia-telangiectasia, as would a large increase in radiosensitivity alone [31,34]. There is, therefore, good evidence for heterogeneity in the levels of induced chromosome damage in ataxia-telangiectasia.

An in vitro radiosensitivity assay named colony survival assay is being proposed for more accurate and specific diagnosis. This test determines colony formation of lymphoblastoid cells following irradiation with 1 Gy [35,36]; it takes approximately 3 months to complete. As Sun et al. [36] reported, the colony survival assay was abnormal in 103 of 104 patients (99%) carrying at least one *ATM* mutation; however, 7 of the 104 patients scored in an intermediate radiosensitivity range that overlaps with the normal range. For such patients, a dose-response curve can be obtained, using several radiation exposure doses (1.0, 1.5, and 2.0 Gy). Using just the 1 Gy exposure, the sensitivity of the colony survival assay is >99% and the specificity is >93%. The Nijmegen breakage syndrome has an identical irradiation sensitivity phenotype to ataxia-telangiectasia; the clinical features are, however, easily differentiated [37].

In patients with ataxia-telangiectasia, early death is frequently due to pulmonary disease, but malignancies are also a common cause. According to other studies, the

incidence of malignancy is 60-300 times higher than in healthy persons, and, on autopsy report, 49% of cases had malignant tumors [38]. In the present study, however, only three patients had blood malignancies. This may be due to our brief follow-up period (mean, 24 months). For type of tumor, the present results are in accord with previous data that show lymphoreticular malignancies as the most common tumors seen in ataxia-telangiectasia patients, especially non-Hodgkin lymphomas, but other kinds of tumors also occur [39,40].

Other tumors reported usually involve the liver and gonads, which are organs often reported to be dysplastic in ataxia-telangiectasia, and tumors of the stomach [41]. The lifetime risk of cancer among patients with ataxia-telangiectasia has been estimated to be 10-38% [29,42,43], which is about 100-fold more than the population rate [33]. In the absence of chronic bronchopulmonary disease and lymphoreticular malignancy, however, ataxia-telangiectasia is consistent with survival into the fifth or sixth decade. Given the increased radiosensitivity seen in ataxia-telangiectasia, treatment of tumors may be problematic. The diagnosis should be considered in any child presenting with a tumor and gait disorder [4,12].

Studies have found an excess of malignancies in parents and grandparents of patients with ataxia-telangiectasia [44], the most repeatable and pronounced observation being an increase in female breast cancer: a relative risk of 6.8 has been calculated in one study [45]. Whether this is a heterozygote manifestation of carriage of the ataxia-telangiectasia gene, a function of a common ataxia-telangiectasia haplotype, or due to some other phenomenon remains to be clarified. It is odd that the tumor spectrum seen in patients with ataxia-telangiectasia differs from that of their parents [41].

In the present study, there was a relatively high delay in diagnosis of ataxia-telangiectasia. This may be in part because complete symptoms of ataxia-telangiectasia present over time, and no characteristic features are detectable during very early childhood, but it may also be a result of low awareness of physicians about rare disorders such as ataxia-telangiectasia, just as for other immunodeficiency disorders. In one study, the median diagnostic delay was compared between 1989 and 2005 [46]; the authors showed that a reduction in diagnostic delay could be achieved by enriching the knowledge and awareness of physicians about primary immunodeficiencies [47].

The delay in diagnosis decreased markedly with time (Fig. 1). This may be due variously to better diagnostic tools or methods, increase in knowledge of our physicians about primary immunodeficiency disorders, and beginning of registry program in Iran. Similar reductions in delayed diagnosis have been described for other immunodeficiency disorders in Iran, such as X-linked agammaglobulinemia [48] and common variable immunodeficiency [49].

Conclusion

The relative incidence of ataxia-telangiectasia among patients with primary immune deficiency disorders is high in Iran, possibly due to consanguineous marriages. There is no definite cure for this disorder, but supportive treatment may prolong survival. Good patient and parental education should include tactful genetic counseling and an explanation of the multisystem nature of the disease.

Special attention should be given to the susceptibility of adult members of families with ataxia-telangiectasia to malignant neoplasms and to the importance of regular examinations for early cancer detection.

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