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Original Article

Regional Distribution of Ataxia-Telangiectasia Cases in Iran

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Abstract

Background: Ataxia-telangiectasia (AT) is a rare, autosomal recessive neurodegenerative disease characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, immunodeficiency, recurrent infections, radiosensitivity, and an increased risk of malignancies. This study aimed to evaluate the distribution of A-T patients, parenteral consanguinity status, and diagnostic delays in different provinces of Iran.

Methods: A retrospective observational and analytical study in which all A-T patients with a recorded place of birth or residency were included. A questionnaire was designed and filled out for each patient to extract data including date of birth, gender, parental consanguinity status, family history, age of disease onset, and age of disease diagnosis.

Results: A total of 203 A-T patients (104 males and 99 females) were included in the study. Out of a total of 31 provinces, A-T patients were diagnosed and reported in 25 different provinces, while six provinces had no registered A-T patients. Tehran province, the most densely populated province in Iran, reported the predominant number and frequency of cases (52 patients or 25.6%), followed by Khouzestan (16 cases, 7.9%), Alborz (12 cases, 5.9%) and Isfahan (12 cases, 5.9%) provinces. No statistically significant relationship was found regarding family history status. Hamedan followed by Sistan and Baluchestan, and Yazd provinces had the highest delay in diagnosis.

Conclusion: Our study showed that A-T is distributed in most provinces of Iran. We found a considerably high diagnostic delay among A-T patients in Iran, especially in resource-limited provinces, including Hamedan followed by Sistan and Baluchestan, and Yazd.

Keywords: Ataxia Telangiectasia; Epidemiology; Immunodeficiency; Consanguinity

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Introduction

Ataxia telangiectasia (A-T) is an autosomal recessive disorder identified by mutations in *ataxia-telangiectasia* mutated (*ATM*) gene encoding a serine/threonine protein kinase. ATM has a central role in the double-strand break repair pathway, cell cycle arrest, and apoptosis (1), therefore defects in ATM contribute to the development of immune dysfunction, lymphoma predisposition, and sterility (2). Clinically, these patients are identified by progressive cerebellar ataxia, cutaneous and mucosal telangiectasia, variable immunodeficiency, respiratory complications, radiosensitivity, and cancer predisposition (3). Inborn errors of immunity (IEI) is found in about 70% of patients with A-T, resulting from defects in antigen receptor recombination and class switch recombination (CSR) mechanisms (2). Among patients with IEI who have monogenic defects, a history of cancer was most frequently observed in those with *ATM* mutations (4), highlighting that A-T patients require further consideration within the IEI population.

Suspecting individuals with IEI is typically based on clinical features and laboratory data; however, a definitive diagnosis should be confirmed through genetic testing. Patients with A-T generally demonstrate a poor prognosis owing to delays in diagnosis or misdiagnosis (5). Delays in diagnosis or misdiagnosis can be linked to several factors, including a wide range of clinical variability, insufficient awareness among physicians, and confusion with conditions such as ataxia-telangiectasia-like disorder 2 (ATLD2), ataxia oculomotor apraxia type 1 (AOA1), ataxia oculomotor apraxia type 2 (AOA2), spinocerebellar ataxia with axonal neuropathy (SCAN1), Nijmegen breakage syndrome (NBS, with birds like face and microcephaly), and RIDDLE syndrome (caused by RNF168 deficiency)(2). Additionally, some patients with A-T can be misdiagnosed with hyper-IgM syndrome due to defects in the CSR mechanism (6). Early diagnosis is crucial for genetic counseling and avoidance of unnecessary tests in patients with AT, as well as for prompt treatment that decreases morbidity and mortality rates in these patients (7)

A-T has an estimated prevalence of 1:40,000 to 1:300,000 people worldwide, depending on the geographic or ethnic region (8-10). There is no estimation of the prevalence of A-T in Iran. In the last registry report of the Iranian National Registry of IEI patients in 2018, 38 A-T patients with confirmed mutations were reported, and *ATM* mutations were among the most frequently recorded defects in this national report (11). The relative incidence of A-T is high in Iran, possibly owing to a high frequency of consanguineous marriage (12). Understanding the distribution of diagnosed A-T patients across different centers in Iran helps physicians focus more on the early diagnosis of these patients. Given that there are no reports on the distribution of A-T patients across the provinces of Iran, we present a report on the geographical distribution of registered A-T patients in various cities of Iran.

Methods

Patients

A total number of 203 patients diagnosed as A-T across centers in Iran and registered in Iranian primary immunodeficiency registry (IPIDR) database were included in the present study. The patients were diagnosed according to the European Society for Immunodeficiency (ESID) guideline (13), which include ataxia and at least two of the following: oculocutaneous telangiectasia, elevated Alpha-fetoprotein (AFP), cerebellar hypoplasia on magnetic resonance imaging (MRI), and lymphocyte A-T karyotype with translocation chromosome 7:14.

Data Collection

A questionnaire was designed and filled out for each patient to extract data including date of birth, gender, parental consanguinity status, family history, age of disease onset, and age of disease diagnosis. The Province or city of each patient was defined based on their place of birth or residency. The delay of diagnosis, defined as the difference between the age of disease onset and the age of disease diagnosis, was assessed for each patient. Patients with incomplete data were excluded.

Statistical Analysis

Data analysis was performed using SPSS statistical software (version 26.0; SPSS, Chicago, IL). Categorical data were expressed as frequencies (percentages), while numerical data were pre-

sented as mean and standard deviation (SD). The chi-square test was used to compare categorical data. Numerical data were tested for normality through the Kolmogorov-Smirnov test and were compared using the Student's T-test or analysis of variances (ANOVA) test.

Results

Geographical Distribution of A-T Patients in Iran

A total of 203 A-T patients including 104 males and 99 females were included in the study. The geographical distribution of A-T patients in different provinces of Iran is illustrated in **Figure 1**. Out of a total of 31 provinces, A-T patients were diagnosed and reported in 25 different provinces, while six provinces, including Bushehr, Chaharmahal and Bakhtiari, Golestan, Ilam, North Khorasan, and Kohgiluyeh and Boyer-Ahmad, had no registered A-T patients **(Figure 1)**. Tehran province, the most densely populated province in Iran, reported the predominant number and frequency of cases (52 patients or 25.6%), followed by Khouzestan (16 cases, 7.9%), Alborz (12 cases, 5.9%) and Isfahan (12 cases, 5.9%) provinces.

Parenteral Consanguinity Status of A-T Patients

Of 186 (80.9%) patients with a reported parental consanguinity status, 157 (84.4%) patients had consanguineous parents. The relationship between parenteral consanguinity status and the provinces was investigated to determine which part of the country has the highest parental consanguinity. The highest proportions of parenteral consanguinity among patients were found in the following provinces: Fars, Mazandaran, Hamedan, Markazi, Razavi Khorasan, Sistan and Baluchestan, Hormozgan, Semnan, Kermanshah, Gilan, Zanjan, Yazd, and Qom (each with a 100% rates), while the lowest rates were reported in Ardabil, followed by Kurdistan and Kerman (0%, 33.3% and 50%, respectively)**(Table 1).**

Family History Status of A-T Patients

A positive family history of IEI and/or A-T was detected in 74 (36.5%) patients **(Table 2)**. No statistically significant relationship was found between family history status and the province of birth based on the chi-square test results (p = 0.261). The family history status of patients in different birth provinces is illustrated in **Table 3.**

Diagnostic Delay of A-T Patients in Different Regions of Iran

A delay in diagnosis was present in 154 patients and ranged between 0 and 159.0 months, with an average of 54.68 months (SD = 35.5). There were no statistically significant differences between means of delay of diagnosis in different provinces

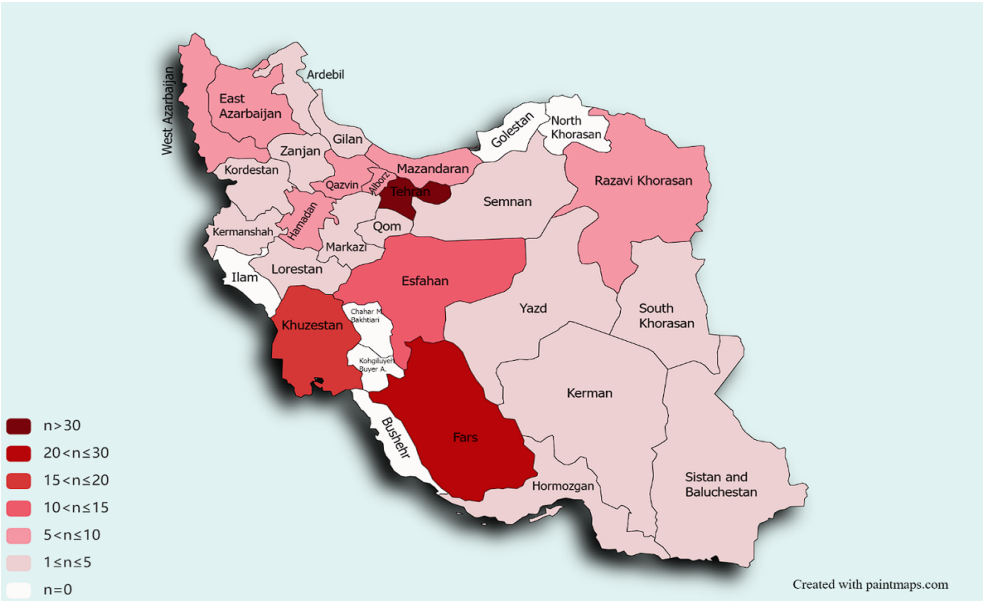

Figure 1. Distribution by different Iran provinces of ataxia telangiectasia patients.

Table 1. Parenteral consanguinity status of reported ataxia telangiectasia patients in different provinces of Iran

Province	Non-consanguineous	Consanguineous
Khouzestan (N=14)	7.1%	92.9%
Tehran (N=50)	20%	80%
Alborz (N=12)	8.3%	91.7%
Lorestan (N=4)	25%	75%
Markazi (N=5)	0%	100%
Isfahan (N=11)	9.1%	90.9%
Mazandaran (N=10)	0%	100%
Fars (N=5)	0%	100%
Qazvin (N=6)	33.3%	66.7%
Hamedan (N=6)	0%	100%
Razavi Khorasan (N=5)	0%	100%
Semnan (N=2)	0%	100%
East Azerbaijani (N=8)	25%	75%
West Azerbaijan (N=7)	42.9%	57.1%
Zanjan (N=1)	0%	100%
Qom (N=1)	0%	100%
Yazd (N=1)	0%	100%
Hormozgan (N=2)	0%	100%
Sistan and Baluchestan (N=2)	0%	100%
Kerman (N=2)	50%	50%
Kermanshah (N=1)	0%	100%
Kurdistan (N=3)	66.7%	33.3%
Ardabil (N=1)	100%	0%
Gilan (N=1)	0%	100%

Table 2. Demographic data of ataxia telangiectasia patients

Variables		Frequency
Gender Number (%)	Male	104 (51.2)
	Female	99 (48.8)
Parental consanguinity Number (%)	Consanguineous	157 (77.3)
	Non-consanguineous	29 (14.3)
	Unknown	17 (8.4)
Family history of inborn errors of immunity Number (%)	Positive	74 (36.4)
	Negative	109 (53.7)
	Unknown	20 (9.8)

as determined by one-way ANOVA (p =0.395). Hamedan followed by Sistan and Baluchestan and Yazd provinces had the highest delay in diagnosis (mean: 88, 84 and 84 months, respectively); however, the lowest diagnostic delay belonged to Gilan province (mean: 12 months). The delay in diagnosis of A-T patients in different provinces of Iran is illustrated in **Figure 2.**

Discussion

A-T has been reported across all global regions (1), and there is some data on the prevalence of A-T in some countries, such as the USA (about 1 in 88,000) (14). However, no report on the prevalence of A-T in Iran compares with data from other countries. Researching the disease's prevalence in a large population would require more time and resources. Here, we present only the data on reported A-T cases from different regions of the country. This study revealed a widespread distribution of A-T patients across Iran, as most provinces reported cases. The highest number of cases was recorded in Tehran, which serves as a referral center for IEIs in Iran. The high number of reported A-T cases from Tehran could be attributed to: (1) the large population residing in provincial capitals, with Tehran being the most populous province in Iran, and (2) Tehran serving as a referral center for IEIs in the country. Regarding other provinces, as expected, the capital cities had the highest number of A-T patients, probably infrastructure and access to specialized care.

Table 3. IEI family history status of ataxia telangiectasia patients in different provinces of Iran.

Province	Negative	Positive
Khouzestan (N=13)	38.5%	61.5%
Tehran (N=48)	58.3%	41.7%
Alborz (N=12)	50%	50%
Lorestan (N=4)	100%	0%
Markazi (N=5)	60%	40%
Isfahan (N=10)	80%	20%
Mazandaran (N=10)	30%	70%
Fars (N=6)	66.7%	33.3%
Qazvin (N=7)	28.6%	71.4%
Hamedan (N=6)	66.7%	33.3%
Razavi Khorasan (N=4)	50%	50%
Semnan (N=2)	100%	0%
East Azerbaijani (N=8)	75%	25%
West Azerbaijan (N=7)	85.7%	14.3%
Zanjan (N=1)	100%	0%
Qom (N=1)	100%	0%
Yazd (N=1)	100%	0%
Hormozgan (N=2)	50%	50%
Sistan and Baluchestan (N=2)	100%	0%
Kerman (N=2)	100%	0%
Kermanshah (N=1)	100%	0%
Kurdistan (N=3)	66.7%	33.3%
Ardabil (N=1)	0%	100%
Gilan (N=1)	0%	100%

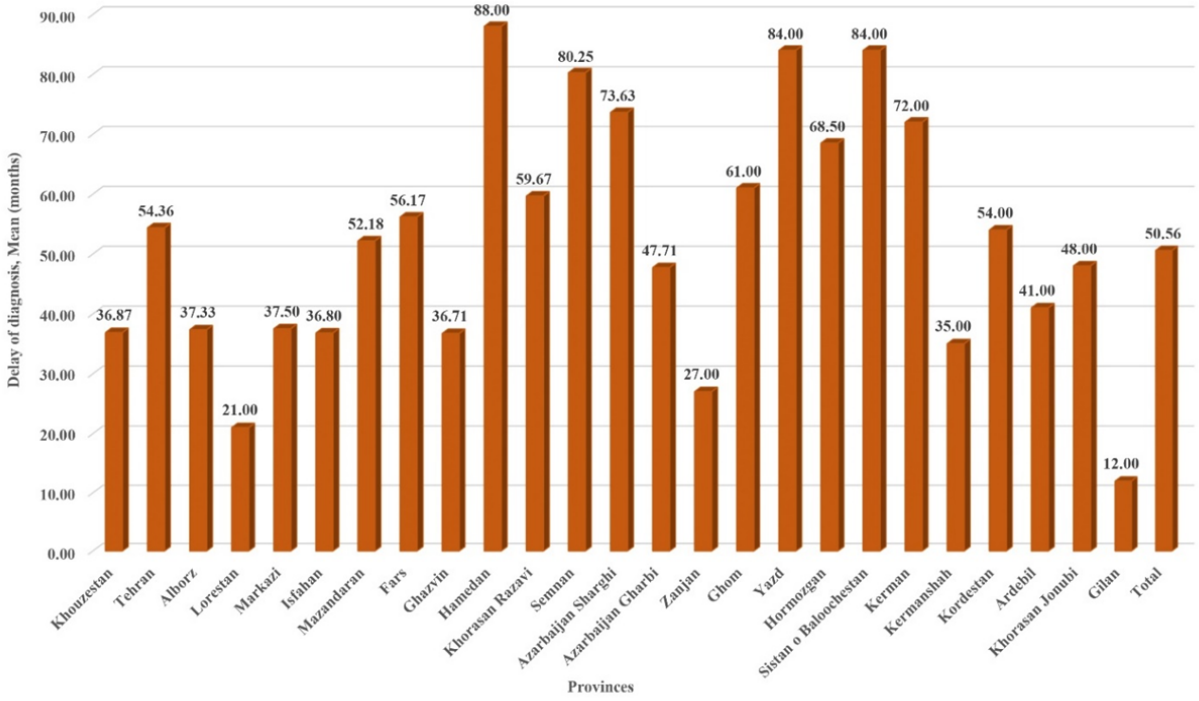

Figure 2. Delay of diagnosis of ataxia telangiectasia patients in different provinces of Iran

Consanguineous marriages raise the incidence of autosomal recessive disorders, including A-T (15). Over 20% of the human population worldwide lives in communities with a preference for consanguineous marriages, and it is estimated that over 8.5% of all children have consanguineous parents (16). Consanguinity is prevalent in most Middle Eastern countries (such as Iran), ranging from 20% to 70% (16, 17). In a study involving 306,343 couples from 12 different ethnic/religious populations in Iran, the overall rate of consanguineous marriage was 38.6% (18), suggesting a potentially higher prevalence of A-T in Iran and highlighting the need for conducting epidemiological studies in this country. consanguineous marriage is correlated with various socio-demographic factors, including age, educational level, income, and place of residence. It has been demonstrated that consanguineous unions occur more frequently in rural settings (19). Previous studies revealed significant differences in the prevalence of consanguinity among different Iranian ethnic groups in southeast Iran, with rates ranging from 31.1% in the Lur ethnic group to 47.2% in the Balouch and 49.8% among the Sistani population (18, 19). In our study, the southern, central, and eastern regions of Iran had high rates of consanguinity, which is nearly consistent with these findings. In comparison to other countries with high consanguinity, such as India (60%)(20), Iran has a higher consanguinity rate (84%). Regarding a positive family history of immunodeficiency or A-T, our study indicated a high rate, with 38.2% of the cases having a positive family history. Therefore, it seems to be necessary to educate society about the potential threats of consanguineous marriage to reduce the incidence of fatal genetic diseases, including A-T, especially considering the high rate of positive family histories of immunodeficiency and A-T in the population.

Diagnosis of A-T is considered challenging because of its rarity and diversity of clinical presentations. In resource-limited settings, the diagnosis is more challenging due to a lack of healthcare professionals and knowledge of A-T (21). Diagnostic delays for IEIs, including A-T, have significantly decreased over time, although variations persist across different countries (22). Most of our A-T patients showed a considerable delay in diagnosis. We showed that Hamedan, Yazd, and Sistan and Baluchestan provinces, the most resource-limited province in Iran, had the highest delay in diagnosis. Consistent with a previous report of Iranian A-T patients, the mean diagnostic delay was 54.79 months(23), which is much higher than in developed countries such as the United Kingdom (8 months)(24). The significant diagnostic delays in Iran, especially in some cities of the country, can be related to a lack of appropriate infrastructure, and limited awareness regarding the diagnosis of A-T. Increasing awareness of A-T, combined with rapid, and accurate diagnostic tests, contributes to further decreasing diagnostic delay.

Conclusion

Our study, for the first time, depicted the geographical distribution of A-T in Iran. Knowing the prevalence or the number of diagnosed A-T patients in different cities of Iran can provide a better understanding of the burden of the disease, help recognize gaps in diagnosis and treatment, and inform public health strategies to improve patient care and support of these patients across the country.

Conflict of Interests

There is no conflict of interest

References

1. Amirifar P, Ranjouri MR, Lavin M, Abolhassani H, Yazdani R, Aghamohammadi A. Ataxia-telangiectasia: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Expert Rev Clin Immunol. 2020;16(9):859-71.
2. Amirifar P, Ranjouri MR, Yazdani R, Abolhassani H, Aghamohammadi A. Ataxia-telangiectasia: A review of clinical features and molecular pathology. Pediatr Allergy Immunol. 2019;30(3):277-88.
3. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016;11:1-21.
4. Fekrvand S, Abolhassani H, Esfahani ZH, Fard NNG, Amiri M, Salehi H, et al. Cancer trends in inborn errors of immunity: A systematic review and meta-analysis. J Clin Immunol. 2024;45(1):34.
5. Devaney R, Pasalodos S, Suri M, Bush A, Bhatt JM. Ataxia telangiectasia: presentation and diagnostic delay. Arch Dis Child. 2017;102(4):328-30.

6. Amirifar P, Mozdarani H, Yazdani R, Kiaei F, Moeini Shad T, Shahkarami S, et al. Effect of class switch recombination defect on the phenotype of ataxia-telangiectasia patients. Immunol Invest. 2021;50(2-3):201-15.
7. Cabana MD, Crawford TO, Winkelstein JA, Christensen JR, Lederman HM. Consequences of the delayed diagnosis of ataxia-telangiectasia. Pediatrics. 1998;102(1 Pt 1):98-100.
8. Hassin-Baer S, Bar-Shira A, Gilad S, Galanty Y, Khosravi R, Lossos A, et al. Absence of mutations in ATM, the gene responsible for ataxia telangiectasia in patients with cerebellar ataxia. J Neurol. 1999;246(8):716-9.
9. Woods CG, Bundey SE, Taylor AM. Unusual features in the inheritance of ataxia telangiectasia. Hum Genet. 1990;84(6):555-62.
10. Swift M, Morrell D, Cromartie E, Chamberlin AR, Skolnick MH, Bishop DT. The incidence and gene frequency of ataxia-telangiectasia in the United States. Am J Hum Genet. 1986;39(5):573-83.
11. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, et al. Fourth update on the Iranian National Registry of Primary Immunodeficiencies: integration of molecular diagnosis. J Clin Immunol. 2018;38:816-32.
12. Abolhassani H, Azizi G, Sharifi L, Yazdani R, Mohsenzadegan M, Delavari S, et al. Global systematic review of primary immunodeficiency registries. Expert Rev Clin Immunol. 2020;16(7):717-32.
13. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763-70.
14. Teive HA, Moro A, Moscovich M, Arruda WO, Munhoz RP, Raskin S, et al. Ataxia-telangiectasia - A historical review and a proposal for a new designation: ATM syndrome. J Neurol Sci. 2015;355(1-2):3-6.
15. Hadizadeh H, Salehi M, Khoramnejad S, Vosoughi K, Rezaei N. The association between parental consanguinity and primary immunodeficiency diseases: A systematic review and meta-analysis. Pediatr Allergy Immunol. 2017;28(3):280-7.
16. Shawky RM, Elsayed SM, Zaki ME, El-Din SMN, Kamal FM. Consanguinity and its relevance to clinical genetics. Egypt J Med Hum Genet. 2013;14(2).
17. Hoodfar E, Teebi AS. Genetic referrals of Middle Eastern origin in a western city: inbreeding and disease profile. J Med Genet. 1996;33(3):212-5.
18. Saadat M, Ansari-Lari M, Farhud D. Short report consanguineous marriage in Iran. Ann Hum Biol. 2004;31(2):263-9.
19. Neshan A, Tabatabaei SM, Mohammadi M, Narooie-Nejad M, Behmaneshpour F. The prevalence and patterns of consanguineous marriages and associated factors in Southeast Iran. Gene Cell Tissue. 2024;11(3).
20. Mahadevappa M, Kamble N, Kumar DS, Yadav R, Netravathi M, Pal PK. A clinical profile of 100 patients with ataxia telangiectasia seen at a tertiary care center. Ann Mov Disord. 2020;3(1):33-8.
21. van Os NJ, van Aerde KJ, van Gaalen J, Merkus PJ, Silveira-Moriyama L, Tajudin TA, et al. Diagnosis and management of ataxia-telangiectasia in resource-limited settings. J Int Child Neurol Assoc. 2020;1(1).
22. Anderson JT, Cowan J, Condino-Neto A, Levy D, Prusty S. Health-related quality of life in primary immunodeficiencies: Impact of delayed diagnosis and treatment burden. Clin Immunol. 2022;236:108931.
23. Moin M, Aghamohammadi A, Kouhi A, Tavassoli S, Rezaei N, Ghaffari S-R, et al. Ataxia-telangiectasia in Iran: clinical and laboratory features of 104 patients. Pediatr Neurol. 2007;37(1):21-8.
24. Devaney R, Pasalodos S, Suri M, Bush A, Bhatt JM. Ataxia telangiectasia: presentation and diagnostic delay. Arch Dis Child. 2017;102(4):328-30.