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Chapter

Ataxia Telangiectasia

Barbara Pietrucha

Abstract

Ataxia telangiectasia (AT) is an autosomal recessive disorder characterized by cerebellar degeneration, telangiectasias, immunodeficiency, recurrent sinopulmonary infections, cancer susceptibility, and radiation sensitivity. AT is a complex disorder, whose neurological symptoms most often first appear in early childhood when children begin to sit or walk. They have immunological abnormalities: immuno-globulin and antibody deficiencies and lymphopenia. AT patients have an increased predisposition for cancers, particularly of lymphoid origin. AT is caused by mutations in the *ataxia telangiectasia mutated* (*ATM*) gene, and the role of the ATM protein is the coordination of cellular signaling pathways in response to DNA double-strand breaks, oxidative stress, and other genotoxic stresses. The diagnosis of AT is usually supported by the combination of neurological clinical features and specific laboratory abnor-malities (immunoglobulin A (IgA) deficiency, lymphopenia, and increased alpha-fetoprotein (AFP) levels). There are several other neurological and rare disorders that physicians must consider when diagnosing AT. Treatment of neurological symptoms in patients with AT is only symptomatic and supportive, as there are no known treat-ments that can slow or stop neurodegeneration. However, other symptoms of AT, such as antibody deficiency, lung disease, developmental disorders, diabetes, or cancer, can be effectively treated. Some hope is associated with the treatment of dexamethasone in the patient's own blood cells, which relieves neurological symptoms.

Keywords: ataxia telangiectasia, immunodeficiency, radiation sensitivity, DNA double-strand breaks, ATM protein

1. Introduction

The first description of patients with ataxia telangiectasia (AT) was published in 1926 [1], but it was not until 1958 that the term "ataxia telangiectasia" was first coined. AT was given its commonly used name by Elena Boder and Robert P. Sedgwick, who described a familial syndrome of progressive cerebellar ataxia, oculo-cutaneous telangiectasia, and frequent pulmonary infection [2]. Ataxia telangiectasia, or AT, is also referred to as the Louis-Bar syndrome (OMIM #208900). Orphanet Orpha Number: ORPHA100.

Ataxia telangiectasia is an autosomal recessive cerebellar ataxia [3]. It is also included in inborn errors of immunity (IEI) with chromosomal instability, DNA repair disorders, and less commonly known as neurocutaneous syndrome [4]. The disease is caused by a mutation in the *ataxia telangiectasia mutated* (*ATM*) gene encoding the serine-threonine protein kinase [5, 6]. ATM is a large protein

(~350 kDa) with a critical role in DNA double-strand break (DSB) repair, genome stability, cell cycle regulation, and cell survival [7]. The ATM protein is involved in natural physiological processes during DNA replication, meiosis, mitosis, V (variable), D (diversity), or J (joining) recombination or immunoglobulin class switching (CSR, class switch recombination). In addition, other targets of the ATM protein are those involved in oxidative stress metabolism [8]. ATM is mainly a nuclear protein, but it is also found in the cytoplasm and regulates the function of mitochondria and peroxisomes, and through this it affects angiogenesis and glucose metabolism. Lack of ATM protein function is associated with the development of certain disorders in AT patients, such as progressive neurodegeneration, immune deficiencies, pulmonary, metabolic, dermatological, and vascular complications [9–11].

Ataxia telangiectasia is characterized by progressive cerebellar degeneration, oculocutaneous telangiectasias, immunodeficiency, recurrent sinopulmonary infections, radiation sensitivity, premature aging, and susceptibility to cancer development, especially of lymphoid origin. Other abnormalities, such as growth failure, poor pubertal development, gonadal atrophy, insulin-resistant diabetes, lung diseases, cutaneous abnormality, and cardiovascular disease, have also been reported in AT patients [12–14].

The prevalence of AT is estimated to be <1–9/100,000. However, the incidence of AT may be higher 1/40,000 in consanguineous population or those populations with founder effect [15]. AT patients have poor prognosis; the median survival is 25 years with a wide range. The two most common causes of death in these patients are chronic pulmonary diseases and malignancy [14, 16]. AT patients show remarkable clinical and laboratory differences that reflect the presence of genotype/phenotype correlations in these patients or other genetic/environmental disease-modifying factors. The majority of ATM mutations lead to a truncated protein, while some missense and splicing site variations cause milder phenotype [17].

Ataxia telangiectasia patients have much milder clinical progress as a result of retained expression of either normal [18, 19] or mutant ATM protein with residual activity [20–22]. These patients often retain the ability to walk into adulthood and consequently might be diagnosed when adults [19, 23]. The terms "classic" and "mild" are used to distinguish two different but widely recognized clinical presentations of AT. People with mild AT have less severe, later onset of symptoms associated with longer survival. Ataxia telangiectasia-like disorder (ATLD) [24–26], ataxia oculomotor apraxia type 1 (AOA1) [27, 28], and ataxia oculomotor apraxia type 2 (AOA2) [29–32] have neurological features similar to those of AT.

2. Clinical picture and management

In the classic presentation of AT, ataxia is often the first diagnostic sign that appears during the toddler years, usually manifest between 6 and 18 months of age. Children also have difficulty standing or sitting still and may sway slowly side-to-side or backwards. Because most of the children with classic AT have stable neurological symptoms for the first 4–5 years of life, they can initially be diagnosed as having "ataxic cerebral palsy" [33]. Beyond the age of 10, the movement problems typically cause a child to be confined to a wheelchair [34]. Eye movement abnormalities emerge in early school years. Dysarthria, which is the consequence of impaired coordination of respiratory, phonatory, and bulbar functions, can occur at any time and may or may not progress [35, 36]. Drooling may persist beyond expected ages. Swallowing

difficulties typically worsen in early teen years. Most of these neurological problems stop progressing after the age of about 12–15 years. AT patients manifest hallmarks of cerebellar dysfunction such as truncal swaying, gait ataxia, dyssynergia, muscle hypotonia, and sudden falls [33], and may have abnormal involuntary movements, including chorea, dystonia, dysphagia, athetosis, myoclonic jerks, or various tremors [37, 38]. Other extrapyramidal symptoms may include body hypokinesia or brady-kinesia and facial hypomimia [34, 35]. Distal-to-proximal advancing loss of tendon reflexes is also characteristic of AT [39], reflecting a progressive sensory and motor neuropathy [35, 40].

Cerebellar degeneration in AT originates from atrophy of cerebellar vermis and hemispheres involving the dendrites and axons of Purkinje cells (PCs) and granule neurons [2]. However, microcephaly does not usually occur in AT patients because it is caused by the progressive accelerated aging process. For the majority of AT patients, neuroimaging studies in the toddler years and early childhood years are normal. As the disease progresses, MRI studies support the pathological finding of progressive and diffuse cerebellar atrophy [34, 41]. Due to the radiation exposure inherent in computed tomography (CT), MRI is the preferred method of visualizing the central nervous system (CNS) in patients with AT. Intellectual disability is not a common sign in AT; however, it occasionally occurs [8]. The correlation of neurodegenerative phenotype and ATM deficiency remains unclear, but the hypothesis suggested that ATM is the main player in maintaining cellular homeostasis and preventing disease in the nervous system. The prevailing dogma in the field is that specific neuronal cells within the cerebellum (primarily Purkinje and granule cells) are particularly sensitive to the loss of ATM. Normal ATM protein may allow neurons to repair damage DNA or initiate apoptotic pathway [42, 43]. On the other hand, neurodegeneration may be attributable to deficient-reactive oxygen species (ROS) homeostasis following dysfunction of ATM in neurons [34].

The second major symptom of AT ocular telangiectasias often occurs after the onset of neurological symptoms, usually by the age of 5–8 years, sometimes later or never. The absence of telangiectasias does not exclude the diagnosis, but is a common cause of delayed diagnosis [44, 45]. Telangiectasias may also appear on sun-exposed areas of skin in some patients and in other locations such as the pharyngeal wall, and have been seen deep inside the brain of older people with AT. The ocular telangiectasia do not bleed or itch, though they are sometimes misdiagnosed due to chronic conjunctivitis or allergy [20, 46].

Other ocular symptoms include: abnormal eye movement and visual disturbances caused by degeneration of the cerebellar cortex manifesting in AT including oculomotor apraxia, periodic alternating nystagmus (PAN), gaze-evoked nystagmus, strabismus, and vestibulo-ocular (VOR) abnormalities [47–49]. Patients with AT have prominent defects in the eye movement systems that stabilize images on the retina and in the systems that shift direction of gaze.

The next clinical manifestation of AT are recurrent respiratory infections. Chronic lung disease develops in more than 25% of people with AT, mostly progressing with the increasing age and neurological deterioration. Respiratory complications are the leading cause of morbidity and mortality among AT patients, as 50% of patients die in adolescence from respiratory failure [13, 16, 50]. Generally, there are three major types of lung diseases in AT patients, including recurrent sinopulmonary infections and bronchiectasis, interstitial lung disease (ILD)/pulmonary fibrosis, and neuro-muscular disorders affecting respiratory function [13, 51, 52]. The pathogenesis of lung disease in AT patients is multifactorial, related to immune deficiency, abnormal

DNA damage repair, signs of premature aging, chronic inflammation, and oxidative stress [53]. Patients with respiratory infections are most often found to have reduced or absent serum immunoglobulin G2 (IgG2) and a defect in class switch recombination (CSR) [54, 55]. These mechanisms are associated with disease progression due to recurrent infections, emphysema, ineffective cough and airway clearance disorders, and oropharyngeal dysphagia [51, 52, 56].

People with AT have a decrease in their measured forced vital capacity (FVC). This may result in a functionally restrictive lung phenotype, similar to that with neuromuscular weakness associated with reduced lung reserve. A weak or ineffective cough leading to impaired mucociliary clearance (MCC) can also contribute to reduced respiratory capacity. Reduced FVC and MCC can cause recurrent respiratory infections. In addition, the situation is exacerbated by the presence of immunodeficiencies, aspiration, increased chromosomal breakage, cell senescence, inflammation, and impaired DNA damage repair due to ATM deficiency [56–58]. Shortened telomeres and sensitivity to ionizing radiation are also characteristic of AT and can increase the risk of complications such as pulmonary fibrosis when treating malignancies [59, 60].

Interstitial lung disease has been described in individuals with AT, although the exact incidence is unknown. In patients with AT who died from chronic respiratory disease, ILD was present in about 25% [61]. Symptoms of ILD include a nonproductive cough lasting >1 month, shortness of breath, and fever. There are abnormal auscultatory changes over the lungs, and interstitial changes on chest radiography. ILD can occur even in the absence of immunodeficiency. Antibiotic therapy does not result in improvement [62]. Diagnosis of ILD on the basis of clinical examination is often difficult because symptoms are nonspecific. Restrictive lung disease on pulmonary function testing may suggest the presence of an interstitial process. In AT patients with pulmonary symptoms that do not completely resolve after intensive treatment of the infection, chest radiography is helpful, but due to increased radiosensitivity, MRI may become the technique of choice. A lung biopsy is required to confirm the diagnosis of ILD. However, the diagnostic benefits of a procedure such as a lung biopsy should always be weighed against the risks associated with anesthesia and surgery [62]. It should be considered that in patients with AT, secondary pulmonary lymphoma may clinically and radiographically mimic ILD [63]. The increased risk of developing pulmonary fibrosis in patients with AT may be a result of chemotherapy for malignancies [60]. In patients with AT, progressive neuromuscular decline can worsen pulmonary function, e.g., bulbar muscle dysfunction can result in swallowing dysfunction and chronic aspiration [13, 57].

Chronic lung disease is the leading cause of death in AT (about 30%), and early intervention is key to preventing or slowing its progression. Pulmonary function tests should be performed in all children with AT starting at the age of 6 and continued annually [56, 64], and performed prior to any surgical procedure requiring anesthesia.

Chest computed tomography (CT), considered to be the "gold standard," is the best tool for assessing changes in chronic lung disease (CLD) [65]. Due to hypersensitivity to radiation, exposure to ionizing radiation should be avoided in patients with AT [66, 67]. MRI of the chest becomes such a method, which is a useful nonradiation tool in several lung diseases, because it is highly compatible with computed tomography of the chest [68–70].

The manifestation of immunodeficiency in AT is usually sinopulmonary infections that are often manifested early in life [13, 51]. Abnormalities of the immune system are observed in approximately two-thirds of patients with AT due to impaired antigen receptor recombination and class switch recombination (CSR). Generally, selective

immunoglobulin A (IgA) deficiency, hypogammaglobulinemia, immunoglobulin G (IgG) subclasses' deficiency, gammopathy, and failure to make specific antibodies in responses to vaccines or infections are frequent findings in AT patients [71, 72]. A small percentage of patients with AT may also have hyper-immunoglobulin M (hyper-IgM). Since some existing symptoms of AT, such as atactic gait and dysarthria, might not be present in infancy, the diagnosis of these patients may be confused with the diagnosis of hyper-IgM syndrome [73–75]. The most common deficiencies of cellular immunity are lymphopenia with decreased B- and T cells, reduced number and faulty functioning of CD4+ T lymphocytes [71, 76]. The progressive reduction of the cellular compartment during life may reduce life expectancy of people with AT [77]. Another problem in AT patients is an increased risk of developing autoimmune and/or chronic inflammatory diseases that are associated with immune dysregulation [78, 79]. About a quarter of patients with AT may have autoimmune disorder, the most frequent organ involved being the skin with vitiligo and psoriasis. Diseases, such as Hashimoto's thyroiditis (HT), juvenile idiopathic arthritis (JIA), immune thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia (AIHA), have also been reported [80–82].

All patients with AT should have at least one comprehensive immunological evaluation to assess the number and type of B- and T cells, the levels of serum immunoglobulins (IgG, IgM, and IgA) and antibody responses to T cell-dependent (e.g., tetanus, *Hemophilus influenzae* b) and T cell-independent (pneumococcal polysaccharide) vaccines [51, 83].

There are no general recommendations as to how often immunological tests should be repeated, certainly they should be performed when problems with infections occur or worsen [56, 84, 85].

Immunization of people with AT may be less effective, and these individuals often have a suboptimal response to pneumococcal vaccine, as well as to other vaccines [86]. If antibody function is normal, all routine childhood immunizations should be given, except the measles, mumps and rubella (MMR) vaccine [56]. Among other reasons, because chronic cutaneous granulomas can be associated with AT [87, 88] and they have been linked to replication of the incompetent rubella virus vaccine strain detected by PCR [89–91].

There are also skin lesions. Common skin abnormalities associated with AT include oculocutaneous telangiectasias, skin atrophy, café-au-lait spots, vitiligo, seborrheic dermatitis, and premature graying [92–94]. These patients may also have an increased incidence of vitiligo and warts, which may be due to immunodeficiency, making treatment of these complications difficult [51]. Other skin changes are cutaneous granulomas with unknown pathogenesis that occur uncommonly in various inborn errors of immunity (IEI) and manifest in almost 10% of AT patients [95]. These lesions have not been associated with an identifiable pathogen, but sometimes can be associated with painful ulceration, bleeding, or might erode down to muscle or bone [87, 96].

It has been proposed that cutaneous granulomas can be considered as a manifestation of dysregulation in innate immunity, wound healing, and tissue repair explained by the immune defects in these primary immunodeficiency disorders (PIDs) [87]. Recent data suggest that more than 40% of AT patients with cutaneous granulomas present a hyper-IgM phenotype. AT patients with granulomas had an equal distribution of all lymphocyte subsets, except for a significant reduction in B cells, naive CD4+ cells and naive CD8+ T cells, in the presence of normal total natural killer (NK) and T cells [11, 87]. B cells, CD19+, appear to play a fundamental role in wound healing; it was observed that mouse CD19 deficiency stopped skin wound healing [97].

Recently, an association has been found between the administration of live rubella vaccines and the formation of cutaneous and visceral rubella-positive granulomatous in people with AT, as well as in other immunodeficiencies with impaired DNA repair [98, 99].

Poor growth is a common feature in classic AT [100–102]. Various factors may influence growth failure in AT. They include chronic infections, insulin-like growth factor 1 (IGF-1) hormone deficiency, and reduced nutrient intake due to fatigue and swallowing problems [84, 102–104]. On the other hand, growth retardation is common in patients with AT and may be a primary feature of the disease, directly related to the ATM mutation. The study, in an Israeli cohort of patients with AT, demonstrated that impaired growth was more prominent in females than males, and that this difference is apparent at an age before gonadotropins begin to affect growth rates. Delayed pubertal development is often described as an aspect of AT. Gonadal atrophy or dysgenesis resulting in delayed pubertal development and early menopause has been reported [105–107]. We know of pregnancies in people with mild AT, but not in anyone with the classic form of the disease [108 and own observations].

Vitamin D deficiency has been commonly found in patients with AT, given the implications for bone health and possibly for susceptibility to malignancies [12].

People with AT have been found to have cholesterol profiles associated with a higher risk for cardiovascular disease [109], diabetes with insulin resistance [110], and steatohepatitis [111, 112]. These findings suggest that ATM dysregulation is associated with the development of metabolic syndrome, demonstrating a significant role of functional protein in glucose and insulin metabolism [113, 114]. People with AT should undergo screening for these conditions during adolescence and early adult life so that timely treatments can be initiated.

People with AT have an increased predisposition to malignancy, ranging from 10 to 25% [73, 115]. The most common types of malignancies in patients with AT are lymphoid tumor. Leukemias and lymphomas (T-cell acute lymphoblastic leukemias [ALLs] and T-cell lymphocytic leukemias [T-PLL]) tend to occur in younger patients under the age of 20. These two types of cancers account for 85% of all malignancies in children [116]. B-cell non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) have also been frequently described in patients with AT [117, 118]. Adult patients with AT are susceptible to both lymphoid malignancies and solid tumors, such as cancers of the breast, stomach, liver, parotid gland, and esophagus [84, 119].

Another factor that may predispose to the development of lymphomas (such as HL and B-cell NHL) is the Epstein-Barr virus (EBV). Individuals with AT present an impaired immune response to EBV infection, which is associated with cellular immune deficiencies and DNA repair defects [11, 120].

Adults with AT may benefit from annual whole-body MRIs to screen for malignancies. Patients diagnosed with malignancy should be treated in specialist centers and treatment modifications and dose reductions are usually needed to minimize side effects and optimize outcomes [121, 122].

Heterozygous carriers of the ATM mutation have an increased risk of developing breast cancer, with an estimated risk of 5.1 over that in the whole population, whereas there is no evidence for an increased risk of lymphoid malignancies [119, 123]. A 2016 meta-analysis found the cumulative risk of breast cancer in carriers to amount to approximately 6% by age 50 and 30% by age 80 [124]. While there is insufficient evidence that ATM heterozygotes may increase the risk of other cancers, there are studies suggesting an increased risk of gastric and colorectal cancers [125]. Cancer

screening guidelines are being developed for ATM mutation carriers. Standard breast cancer surveillance, including monthly breast self-exam, yearly breast MRI and mammogram and, additionally for both male and female ATM mutation carriers, colon cancer screenings with a colonoscopy (every 3–5 years compared to every 10 years for the whole of the population), should be performed [126].

Another complication observed in older people with AT pertains to orthopedic complications: these include an acquired clubfoot deformity and, less commonly, scoliosis. Sometimes finger contractures develop, most often due to inflammatory connective tissue disease, but sometimes due to neuropathy [127 and own observation].

Some people with AT suffer from bladder and/or bowel incontinence, recurrent vomiting especially in the morning, decreased sleep efficiency, and dizziness which may connect with neurological complications [84, 128].

Feeding and swallowing (chewing) can become difficult for people with AT as they get older [52]. Involuntary movements can make it difficult to eat independently and cause a mess or extend meal times excessively. Dysphagia is common in AT and usually appears in the second decade of life due to neurological changes that impair the coordination of oropharyngeal movements. Problems involving the pharynx can cause aspiration of fluids, food, and saliva. Dysphagia with silent aspiration can cause pulmonary sequelae in AT [52].

Dysphagia can also cause nutritional deficiencies, as the process of eating becomes slow and difficult. Some people with AT stop eating or reduce their food intake due to frustration or fatigue with the process. Inadequate caloric intake can contribute to stunted growth in children and weight maintenance in the elderly, causing a lower body mass index (BMI) compared to healthy, age-matched controls [104, 129–131]. Poor nutrition can exacerbate symptoms of neurological disability. Abnormal respiratory-swallowing coupling is associated with an increased risk of aspiration and can cause swallowing problems before the development of feeding and pulmonary sequelae in AT [132].

3. AT diagnosis

A clinical diagnosis of AT can usually be made on the basis of the presence of characteristic neurological and non-neurological clinical signs and specific laboratory findings. Laboratory studies may be helpful in diagnosing AT by finding elevated alpha-fetoprotein (AFP) levels after age 1, spontaneous and X-ray-induced chromosomal breaks and/or rearrangements in cultured lymphoblastoid cell lines, and reduced cell survival after irradiation [133]. Imaging studies show cerebellar atrophy, not always apparent on MRI in young children, which does not necessarily correlate with the clinical picture [127].

The most common immunological abnormalities found in AT are deficiency of serum IgA, IgE, and selective IgG subscales, elevated IgM levels, lymphopenia (affecting mainly T lymphocytes), and reduced diversity of the T-cell receptor (TCR) immune repertoire [51, 71]. It is important to combine the symptoms present with the results of laboratory tests. A definitive diagnosis can be confirmed by the absence or deficiency of ATM kinase activity, measured in a lymphoblastoid cell line derived from the patient's blood or in fibroblasts from a skin biopsy, and finally the detection of pathological mutations in the *ATM* gene. As elevated serum AFP levels are observed in ≥95% of patients with AT and these levels should therefore be assessed in any child >1 year of age with unexplained atactic gait [134, 135]. The cause of elevated

Disorder	Gene	Ataxia	Telangiectasia	Immunodeficiency	Radiosensitivity	Malignancy	AFP
A-T	*ATM*	+	+	+	+	+	↑
ATLD1	*MRE11*	+	—	—	+	NK	N
ATLD2	*PCNA*	+	+	—	NK	+	N
AOA1	*APTX*	+	—	—	+	—	N
AOA2	*SETX*	+	—	—	—	—	↑
NBS	*NBS1*	—	—	+	+	++	N
RIDDLE	*RNF168*	+/−	+	+	+	NK	↑

ataxia-telangiectasia (A-T), ATLD 1 – ataxia telangiectasia-like disorder 1 (ATLD1), ataxia telangiectasia-like disorder 2 (ATLD2), ataxia oculomotor apraxia type 1 (AOA1), ataxia oculomotor apraxia type 2 (AOA2), Nijmegen breakage syndrome (NBS), radiosensitivity, immunodeficiency, dysmorphic features, and learning difficulties (RIDDLE), alpha-fetoprotein (AFP).

Table 1.
Clinical and laboratory features of rare genetic disorders that can be discriminate with A-T.

serum AFP levels in most people with AT remains unknown. Assessment of AFP levels can be a helpful tool in the early diagnosis of AT [45].

As the whole exome sequencing becomes increasingly standard clinical practice for individuals with unusual and/or unexplained symptoms, it is likely that more people with mild forms of AT will be diagnosed [136]. This will necessarily change our views on the phenotypic expression of AT. Prenatal genetic diagnosis is possible when prospective parents each have confirmed pathogenetic mutations in ATM. Preimplantation genetic diagnosis (PGD) can avoid the birth of an affected child in parents who have an affected child (or children) with AT. At least two such cases have been described in the literature so far [137, 138].

Additionally, the newborn screening (NBS) test for severe combined immuno-deficiency (SCID), introduced in recent years, can identify children born with other immunodeficiencies, including AT, which involve a deficiency or absence of T and B lymphocytes [139, 140]. Despite the lack of effective treatments for AT, early diagnosis allows for genetic counseling and family education, as well as intensive supportive care. Genetic counseling can provide AT genetic testing for siblings and other family members and help interpret test results.

Differential diagnosis. There are some rare disorders that can be misdiagnosis with AT based on similar clinical and laboratory features. The most common disorders that are sometimes confused with AT are: cerebral palsy (CP) and Friedreich's ataxia (FA or FRDA). Each of these diseases can be distinguished from AT based on neurological examination and clinical history. CP, unlike AT, is a nonprogressive motor dysfunction resulting from early brain injury [141]. In addition, most children with CP manifest regional or diffuse spasticity in a pattern not seen in AT. Children with ataxia due to CP will not manifest laboratory abnormalities associated with AT. In FRDA, symptoms usually tend to present later between the ages of 10 and 16 and differ from AT in the absence of telangiectasias and oculomotor apraxia, the early absence of tendon reflexes, a normal AFP, the frequent presence of scoliosis, cardiomyopathy, and abnormal ECG features [84, 142].

Other disorders with childhood-onset ataxia include ataxia telangiectasia like disorder 2 (ATLD2), ataxia oculomotor apraxia type 1 (AOA1), ataxia oculomotor apraxia type 2 (AOA2), radiosensitivity, immunodeficiency, dysmorphic features, and learning difficulties (RIDDLE) syndrome (RNF168 deficiency), and spinocerebellar ataxia with axonal neuropathy (SCAN1).

Immunodeficiency is one of the common symptoms of Nijmegen breakage syndrome (NBS, with birds like face and microcephaly), ataxia telangiectasia like disorder 1 (ATLD1, due to meiotic recombination 11 homolog A (MRE11) deficiency), and RIDDLE syndrome that can be confused with AT. As in AT, elevated serum AFP levels are also present in AOA2 and RIDDLE syndrome. Therefore, knowledge of the gene mutation in a child with ataxia, immunodeficiency, telangiectasias, radiosensitivity, and elevated AFP can distinguish AT from other disorders with ataxia of childhood onset [11, 143]. A comparison of the clinical and laboratory features of these disorders is shown in **Table 1**.

4. AT treatment

Treatment of AT is symptomatic and supportive. As regards the neurological symptoms, no therapy can slow degeneration, but physical, occupational, and speech therapies as well as exercise may help maintain function. In some patients,

certain anti-Parkinson and antiepileptic drugs may partially ameliorate symptoms. Commonly prescribed drugs include trihexyphenidyl (an antimuscarinic), amantadine (an antiparkinsonian) [144], baclofen (an antispastic), and botulinum toxin injections (a paralytic). Less commonly used drugs that may also be beneficial include gabapentin and pregabalin (an anticonvulsant), and clonazepam (a tranquilizer and antiseizure medication) [34, 145]. Also, glucocorticoids (especially betamethasone) have been reported to improve neurological symptoms in AT but corticosteroid side effects were quickly observed [146]. To avoid the characteristic side effects of long-term steroid administration, a method of monthly infusions of autologous erythrocytes loaded with dexamethasone has been developed (EryDex; EryDel, Urbino, Italy). Preliminary results are promising, with demonstrated efficacy in improving neurological status, especially in young patients with AT [147, 148].

Regular screening to assess lung function can detect early deterioration of lung function and allow earlier intervention. These interventions may include chest physiotherapy, a cough support device, and assistance to improve MCC. These interventions can be used daily as maintenance therapies. In some children with AT, with bronchial hyperresponsiveness, bronchodilators may benefit [57]. Children with chronic or recurrent sinopulmonary disease should be treated with antibiotics when appropriate, chest physiotherapy and airway clearance techniques to reduce the risk of developing bronchiectasis and chronic lung disease [57].

To maintain respiratory muscle strength and minimize the progression of lung disease, it is important to have adequate nutrition and maintain a normal body mass index. All people with AT should avoid secondhand smoke exposure and have minimal exposure to other environmental pollution. If lung disease develops, appropriate management should be considered: liberal use of antibiotics, antibiotic prophylaxis, corticosteroids, and immunoglobulin supplementation in those patients with AT who are immunocompromised [57, 62].

Recurrent lung infections may involve dysfunctional swallow (dysphagia) with aspiration, but some people with AT can be taught to drink, chew, and swallow more safely reducing the risk of aspiration [56]. Because the nutritional deficit in some people with AT may be more severe than previously appreciated, early nutritional intervention and ongoing nutritional support and education for patients, families, and caregivers are crucial [101, 149].

High-calorie foods are then recommended, and a gastrostomy tube (G-tube or feeding tube) is rarely used. A gastrostomy tube is recommended when a child cannot eat enough to grow, is not gaining weight and when dysphagia with aspiration causes breathing problems and/or when meals take too long or stressful [150].

People with IgG deficiency or impaired antibody function should receive standard immunoglobulin replacement therapy. Despite the low T-lymphocyte count found, prophylactic antibiotic use to prevent opportunistic infections is not necessary, unless individuals are treated chronically with corticosteroids, other immunosuppressive drugs, or chemotherapy [56, 84, 85]. Individuals with normal ability to produce antibody should receive an annual influenza vaccine, and additional pneumococcal vaccines at intervals to maintain high levels of antipneumococcal antibodies [85].

Cutaneous granulomas can be persistent, progressive, and very difficult to treat. To date, treatment has been attempted with topical and systemic corticosteroids, intravenous immunoglobulin, antitumor necrosis factor therapy, and antiviral therapy, with either mediocre or transient results [96, 151]. Only in immunodeficient patients with DNA repair disorders who underwent hematopoietic stem cell transplantation due to cancer observed granuloma healing [152, 153, and own observation].

In adolescent females, sex hormone replacement therapy may need to be considered to support optimal linear growth, development of secondary sex symptoms, and prevention of osteoporosis. Vitamin D levels should be monitored and treated with an appropriate dose [12].

Despite the poor prognosis of many AT cancers, they manage to be successfully treated. Cancer treatment should only take place in specialized oncology centers and only after consultation with a clinician who has specific experience in AT. Standard cancer treatment regimens should be modified to minimize or prevent cytotoxicity from radiomimetic drugs [73, 85]. Radiotherapy can only be used exceptionally and at reduced doses. The use of cyclophosphamide needs to be monitored as late onset of severe hemorrhage from bladder telangiectasia has been observed [154]. Even with modified therapy, late complications of chemotherapy are observed in some people with AT [155]. Although routine bone marrow transplantation is not currently recommended [156], it has however been performed successfully in several cases of hematopoietic malignancies in AT [157, 158].

5. Quality of life

Children with AT experience varying degrees of difficulty in functioning at school due to progressive neurodegeneration. There is an impairment of fine and gross motor coordination, resulting in reduced writing and computer skills. Dysarthria and delayed speech initiation, poor facial expressions, and delayed reaction time to visual and verbal cues, which limit the ability to communicate, are observed. Eye movement disorders with oculomotor apraxia limit reading ability. Mental and physical fatigue is commonly observed. People with AT, through the prism of motor disability, may additionally be perceived as intellectually impaired without actually having any impairment. Social awareness is usually normal. Although this disparity can lead to social isolation and depression, many people with AT do well to overcome these difficulties, especially in the presence of a supportive environment at school. As survival and quality of life improve, some people with AT manage to complete higher education and lead independent lives with support [85].

6. Final remarks

That's why a number of voluntary patient organizations and support groups have sprung up in various countries around the world, working closely with scientific and medical experts to find effective therapies to improve quality of life and provide education and support for families affected by AT. The most active internationally are the AT Children's Project from the USA and the AT Society from the UK. In October 2014, a clinical guidance document on the diagnosis and treatment of ataxia telangiectasia in children was published by the UK AT Society [128]. To quickly make data on people with AT available to researchers and doctors for analysis, the Global AT Family Data Platform was launched in July 2016 [159]. In parallel with the Platform and voluntary patient organizations, work is underway on an international registry of patients with AT. The registry will include baseline and longitudinal data provided by clinicians and clinical centers that treat people with AT. Analysis of data from growing patient registries [128, 159] will inform natural history, improve disease management, and aid therapy development.

7. Conclusion

1. There are still many unresolved questions regarding the complexity and severity of AT, such as the influence of environmental factors, disease-modifying genes, epigenetics, telomere length, and the gut microbiome on the presentation, severity, and progression of various AT manifestations, which remain unknown.

2. Researchers are investigating ways to apply recent breakthroughs in the fields of gene and mutation-targeted therapies to AT [160, 161].

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