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Review article

Ataxia-telangiectasia — A historical review and a proposal for a new designation: ATM syndrome

Hélio A.G. Teive [a,*], Adriana Moro [a], Mariana Moscovich [a], Walter O. Arruda [a], Renato P. Munhoz [b], Salmo Raskin [c], Tetsuo Ashizawa [d]

[a] Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba, PR, Brazil
[b] Movement Disorders Centre, Toronto Western Hospital, Toronto University, Toronto, ON, Canada
[c] Genetika Laboratory, Curitiba, PR, Brazil
[d] Neurology Department and McKnight Brain Institute, University of Florida, Gainesville, FL, USA

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ABSTRACT

The authors review ataxia telangiectasia, emphasizing historical aspects, genetic discoveries, and the clinical presentations of the classical and atypical forms. In fact, ataxia telangiectasia represents a multisystem entity with pleomorphic neurological and systemic manifestations. ATM syndrome is proposed as a more adequate designation for this entity.

Contents

1. Introduction

Ataxia telangiectasia (A-T) is a rare autosomal recessive neurodegenerative disease caused by mutations in the A-T gene characterized by progressive neurological dysfunction in association with multisystem abnormalities and cancer predisposition [1–3]. It occurs in 1 out of 88,000 live births in the USA (1 in 300,000 and 1 in 40,000 live-births) with onset of symptoms in infancy, particularly between the ages of two and five years [1,3]. Classical neurological signs include progressive cerebellar ataxia, oculomotor abnormalities — particularly ocular apraxia, movement disorders — such as chorea, and cognitive dysfunction. The condition presents with multisystem involvement, which includes immunodeficiency, sinopulmonary infections, radiosensitivity, cancer predisposition, oculocutaneous telangiectasia and elevated

* Corresponding author at: Rua General Carneiro 1103/102, Centro, Curitiba, PR 80060-150, Brazil.
E-mail address: hagteive@mps.com.br (H.A.G. Teive).

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serum alpha-fetoprotein levels [1–6]. The gene responsible for this disorder, ATM (ataxia telangiectasia mutated), codes for the protein kinase ATM, which plays an important role in DNA damage repair [1–3,5,7]. After the genotype was defined, it became evident that there is a wide spectrum of phenotypic manifestations, including the classical phenotype with mild and severe forms and childhood and adult onset, as well as atypical clinical presentations without oculocutaneous telangiectasia [8–13]. Our aim is to present a historical review and discuss a new proposal for defining this entity.

2. Methods

The electronic database PubMed was searched from 1958 until 2014 using the following terms to find relevant articles: ataxia-telangiectasia AND clinical review OR atypical AND ataxia-telangiectasia OR ataxia-without-telangiectasia. No language restrictions were applied. Total number of found papers was 291. Forty two out of these were selected based on the relevance to the subject of the paper. We included clinical reviews and case series; experimental studies were excluded. Furthermore, additional chapters of textbooks were included in the review due to their importance.

3. Results

3.1. Historical review

The term ataxia-telangiectasia (A-T) was initially proposed by Boder and Sedgwick in 1957 [6,14,15], however, this clinical entity received other designations that include Louis-Bar syndrome, suggested by Centerwall and Miller in 1958, and Boder–Sedgwick syndrome, suggested by Sagarra (1959), Jablonsky (1969) and François (1972) [6]. The first eponym relates to Madame Louis-Bar, a Belgian neurologist who published a case report in 1941 describing a nine-year-old boy with progressive cerebellar ataxia and extensive cutaneous telangiectasia, including this new disease in the group of phakomatoses [6,16]. For the next couple of decades, A-T was referred to worldwide as Louis-Bar syndrome, until 1964, when Martin [17] published the manuscript *Aspect choréoathétosique du syndrome d'ataxie-télangiectasie*, stating that there was a previous description of A-T in the literature, published in French by Syllaba and Henner (1926), fifteen years before the classical description by Louis-Bar [17]. In fact, Syllaba and Henner described three adolescent Czech siblings with progressive chorea and dystonia in association with ocular telangiectasia [18]. Subsequently, in 1968, Henner confirmed that the disease described previously was in fact A-T [6]. Two other important studies were published in 1957, one by Boder and Sedgwick [14] and another by Biemond [19]. Boder and Sedgwick described eight patients with classical A-T, suggesting the name "ataxia-telangiectasia" [6,15]. They also reported the absence of the thymus and ovaries in their cases [15]. Biemond published another case series with neuropathological findings in which he described the familial nature of this disorder and the presence of extrapyramidal manifestations [19]. Later, several groups published case series of A-T patients, including Wells and Shy (1957), Centerwall and Miller (1958), Boder and Sedgwick (1958, 1960, 1963) and Dunn et al. (1964) [4,6,14,15]. The 1963 publication of Boder and Sedgwick evaluated the clinical features of 101 cases of A-T and found cerebellar ataxia (100% of cases), oculocutaneous telangiectasia (100% of cases), characteristic facies (98%), choreoathetosis (91%), progeric changes of the skin and hair (88%), eye movement apraxia (84%), sinopulmonary infections (83%), familial occurrence (45%) and mental retardation (33%) [20]. In 1964, Dunn et al. published a case report of two Canadian patients with A-T in which they described neuropathological findings and atrophy of the thymus, adrenals, spleen and lymphoid tissues, as well as bronchiectasis and the presence of bilateral ovarian dysgerminoma [4]. In 1972, Waldmann and McIntire described the presence of high levels of serum alpha-fetoprotein in patients with A-T [21]. In 1984, Byrne et al. described a sibship of three ataxic patients, associated with dystonia, chorea, dementia, peripheral neuropathy, with IgE deficiency, chromosomal abnormalities, but, without telangiectasias or alpha-fetoprotein elevation [22]. The authors proposed that A-T should be defined as a syndrome of "multiple neurological system degeneration, immunological attrition, chromosomal instability and predisposition to malignancy" [22]. In 1993, Friedman and Weitberg published a case report about a 17-year old boy with cerebellar ataxia associated with dystonia, myoclonus, pyramidal signs, seizures, recurrent sinopulmonary infections, persistent lymphopenia, immunoglobulin deficiency, and elevated alpha-fetoprotein, but without telangiectasia [13]. The authors proposed a new definition for this entity, as "ataxia with immune deficiency" [13].

3.2. A-T — Genetic discoveries

In 1988, Gatti et al. mapped the A-T gene to chromosome 11q22–23 [23]. In 1995, Savitsky et al. (an international consortium led by Shiloh and Collins) identified the defective gene responsible for A-T (ATM) [24]. Subsequently, in 1996 and 1997, multiple cell cycle checkpoints and the product of the ATM gene, the protein kinase ATM, were described. Since then, several mutations have been found in the ATM gene, including truncating mutations, which result in the total absence of ATM kinase activity, and one missense or splice site mutation, leading to decreased kinase activity [7,12,25,26]. In general, mothers of A-T children who are heterozygous for the ATM mutation and are therefore carriers have a high risk of developing breast cancer [27]. In 2001, Stewart et al. studied ATM kinase activity levels in cells from A-T patients and suggested that this activity correlates with the degree of neurological symptoms in these patients (residual A-T mutated protein function is related to a less severe phenotype) [25]. In a seminal study in 2012, Verhagen et al. showed that the presence of ATM protein and residual kinase activity correlates with the phenotype in A-T patients in a genotype–phenotype study [7]. Patients without ATM kinase activity showed the classical phenotype of A-T while the presence of residual ATM kinase activity correlated with a milder and atypical phenotype, including the absence of telangiectasia, normal endocrine and pulmonary function, normal immunoglobulins, significantly lower X-ray hypersensitivity in lymphocytes and extended lifespan [7]. Verhagen et al. also showed that cancer occurs later in life in these patients [7].

3.3. The A-T phenotype after the genotype was defined

In previous studies of A-T published before the discovery of the ATM gene, the frequency of cerebellar ataxia and ocular and cutaneous telangiectasias was very high (around 100% of cases) [4,14,15,20,28]. However, after the A-T gene was identified several studies emphasized the presence in genetically proved cases of A-T of atypical clinical pictures that did not include cerebellar ataxia or ocular and cutaneous telangiectasias [8,11,22,29–33]. Trimis et al. published a case report of a six-year-old girl with genetically proved A-T but an unusual absence of neurologic symptoms [10]. Alterman et al. studied two siblings with A-T and severe cellular phenotype but mild neurological clinical presentation [12]. Moin et al. evaluated clinical and laboratory features of 104 patients with A-T and found that cerebellar ataxia was present in all of the patients. However, ocular and cutaneous telangiectasias were present in 87 and 73 of the cases, respectively [34]. In a Brazilian case series of 10 patients with A-T, half of the cases did not have ocular or cutaneous telangiectasia (Teive et al., unpublished data). This series of cases involved patients from eight families, aged 2 to 18 years, with genetically confirmed A-T. The ten patients had cerebellar ataxia, cerebellar atrophy on MRI, and elevated alpha-fetoprotein. Three cases had leukemia or lymphoma and four had immunoglobulin deficit.

The most relevant case series of A-T with atypical clinical manifestations are shown in Table 1. This table summarized 50 patients with atypical A-T, demonstrating the presence of movement disorders and motor disturbances in 86% of cases, cerebellar ataxia in 78% of cases

Table 1
Atypical cases/variants of A-T.

Author	No/mild Neurol Manif	Breast cancer only	No cerebellar ataxia	No oculocutaneous telangiectasia	Ocular abnor.[a]	Peripheral neuropathy	Spinal atrophy
Ying et al. (1981)				✓			
Byrne et al. (1984)				✓			
Taylor et al. (1987)				✓			
Maserati et al. (1988)				✓			
Stell et al. (1989)				✓	✓[b]		
Churchyard et al. (1991)			✓	✓			
Lanzi et al. (1992)				✓			
Willems et al. (1993)						✓	✓
Friedman & Weitberg (1993)				✓			
de Graaf et al. (1995)				✓			
Klein et al. (1996)				✓			
Trimis et al. (2004)	✓						
Alterman et al. (2007)	✓						
Moin et al. (2007)				✓Ocular = 17/104 ✓Cutaneous = 31/104			
Carrillo et al. (2009)			✓	✓Only on the posterior pharyngeal wall			
Paglia et al. (2010)		✓					
Saunders-Pullman et al. (2012)			✓	✓			
Charlesworth et al. (2013)			✓	✓			
Grabli et al. (2014)			✓	✓	✓		
Méneret et al. (2014)			✓ 7%	✓ 64%	✓		

Neurol Manif = neurological manifestations.
[a] Ocular abnormalities other than ocular apraxia.
[b] Abnormalities of saccades, absence of smooth pursuit and optokinetic nystagmus, periodic alternating nystagmus.

and oculo-cutaneous telangiectasia in only 16% of cases. Different movement disorders have been described in patients with A-T, including dystonia, myoclonus, chorea, parkinsonism and postural, rest, and kinetic tremor [35–43]. The most common movement disorders described in A-T patients are shown in Table 2. Verhagen et al. studied a clinical spectrum of A-T in adulthood and founded 13 patients with variant A-T [44]. The most common neurologic features were cerebellar ataxia (92.3%), dystonia (72.7%), choreo-athetosis (69.2%), resting tremor (66.6%), polyneuropathy (20%), and neuronopathy of anterior horn cells (87.5%) [44]. Ménerer et al. evaluated 14 adult patients with A-T, with a focus on movement disorders. Ataxia was present in 93% of patients, dystonia and myoclonus in 86%, and chorea was not found in this series of patients with A-T [45].

3.4. A proposal for a new designation of A-T

It is now known that various diseases associated with DNA damage response (DDR) manifest with neurological symptoms and immunodeficiency [1–3,7,12,46,47]. These can simulate A-T phenotypically and include diseases such as A-T-like disorder (ATLD — Mre11 deficiency) and Nijmegen breakage syndrome (NBS, or nibrin/Nbs1 deficiency), with microcephaly and mental retardation, without ataxia, apraxia or telangiectasia, and A-T (Fresno), a mixture phenotype (A-T and NBS) with mutations in the ATM gene [1–3,47]. In 2007, Gatti et al. proposed a disease category called XCIND syndrome, an acronym for X-ray irradiation sensitivity, cancer susceptibility, immunodeficiency, neurological abnormality and double-strand DNA breakage [48]. Furthermore, it is important to mention another possible diagnosis that might be considered: ataxia with oculomotor apraxia types 1 and 2, spinocerebellar ataxia with axonal neuropathy (SCAN) and autosomal recessive cerebellar ataxia with SYNE1 mutation [1].

Now that the ATM gene has been identified, the genotype–phenotype correlation of A-T confirms that the clinical picture of this condition is very broad, with non-classical presentations with and without neurological abnormalities, with movement disorders (chorea, dystonia), without cerebellar ataxia and without ocular and cutaneous telangiectasias. These cases are described as atypical cases of A-T, or A-T variants. However, in our opinion, it is time to replace the name A-T by ATM syndrome. In summary, ATM syndrome represents a neurodegenerative disorder with multisystem involvement due to the absence or reduced levels of ATM protein and kinase activity. The syndrome is characterized by the presence of movement disorders, such as cerebellar ataxia, dystonia, chorea and myoclonus, in association with systemic abnormalities such as immunodeficiency, malignancies, oculocutaneous

Table 2
Movement disorders described in patients with genetically proved A-T.

Reference/Mov Disord	Chorea	Dystonia	Myoclonus	Parkinsonism	Tremor	Other
Huang et al. [35]	Absent	Torticollis	Absent	Absent	Absent	
Churchyard et al. [9]	Absent	Generalized	Absent	Absent	Absent	
Woods et al. [43]	Generalized	Generalized	Absent	Absent	Absent	
de Graaf et al. [36]	Absent	Absent	Generalized	Absent	Absent	
Klein et al. [37]	Generalized	Absent	Absent	Absent	Absent	
Yanofsky et al. (2009)	Absent	Generalized	Absent	Absent	Absent	Dyskinesia
Carrilo et al. [38]	Absent	Oromandibular	Absent	Absent	Absent	
Saunders-Pullman et al. [39]	Absent	Cranio-cervical and brachial	Generalized	Absent	Absent	
Shaikh et al. [42]	Absent	Upper limb Segmental	Generalized	Absent	Upper limbs Postural/rest	
Charlesworth et al. [41]	Absent	Cervical dystonia and DRD	Absent	Absent	Absent	
Nissenkorn et al. [40]	Generalized	Absent	Generalized	Present	Absent	
Grabli et al. [33]	Absent	Generalized	Generalized	Absent	Upper limbs	
Ménerer et al. [45]	Absent	Focal/segmental	Segmental/multifocal	Mild parkinsonism	Rest/action tremor	

Mov Disord = movement disorders; DRD = dopamine responsive dystonia.

telangiectasias and an increase in alpha-fetoprotein levels [1–3,7,12,27,34,44,46,48–51]. In our opinion, the most important first step in the evaluation of patients with autosomal recessive neurodegenerative disease is the alpha-fetoprotein testing, which could aid in the diagnosis of these atypical cases.

4. Conclusion

Although the eponym Louis-Bar syndrome and the name A-T are well known around the world, they are inappropriate for this disease. Madam Louis-Bar was not the first to describe this disorder. The syndrome can present with other movement disorders in addition to ataxia and a significant number of cases do not present with telangiectasia at all. Thus, we propose naming this important disease ATM syndrome.

Conflict of interest

Dr. Teive, Dr. Moro, Dr. Moscovich and Dr. Raskin have no conflict of interest to disclose. Dr. Munhoz received travel support for scientific meetings from Abbvie Pharmaceuticals; no conflict of interest. Dr. Ashizawa: this work was partly supported by the NIH Grant NS083564.

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