Journal of the Neurological Sciences 355 (2015) 3–6

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

ARTICLE INFO

Article history:
Received 9 December 2014
Received in revised form 15 May 2015
Accepted 18 May 2015
Available online 29 May 2015

Keywords:
Ataxia-telangiectasia
Cerebellar ataxia
Immunodeficiency
Malignancies
Oculocutaneous telangiectasia
Alpha-fetoprotein

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).

http://dx.doi.org/10.1016/j.jns.2015.05.022
0022-510X/

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