DOI: 10.1590/0004-282X20130036

ARTICLE

Clinical spectrum of early onset cerebellar ataxia with retained tendon reflexes: an autosomal recessive ataxia not to be missed

Espectro clínico da ataxia cerebelar de início precoce com reflexos mantidos: uma ataxia autossômica recessiva para não ser esquecida

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ABSTRACT

Autosomal recessive cerebellar ataxias are a heterogeneous group of neurological disorders. In 1981, a neurological entity comprised by early onset progressive cerebellar ataxia, dysarthria, pyramidal weakness of the limbs and retained or increased upper limb reflexes and knee jerks was described. This disorder is known as early onset cerebellar ataxia with retained tendon reflexes. In this article, we aimed to call attention for the diagnosis of early onset cerebellar ataxia with retained tendon reflexes as the second most common cause of autosomal recessive cerebellar ataxias, after Friedreich ataxia, and also to perform a clinical spectrum study of this syndrome. In this data, 12 patients from different families met all clinical features for early onset cerebellar ataxia with retained tendon reflexes. Dysarthria and cerebellar atrophy were the most common features in our sample. It is uncertain, however, whether early onset cerebellar ataxia with retained tendon reflexes is a homogeneous disease or a group of phenotypically similar syndromes represented by different genetic entities. Further molecular studies are required to provide definitive answers to the questions that remain regarding early onset cerebellar ataxia with retained tendon reflexes.

Key words: ataxias, autosomal recessive cerebellar ataxias, early onset cerebellar ataxia with retained tendon reflexes, EOCA.

RESUMO

As ataxias cerebelares autossômicas recessivas são um grupo heterogêneo de doenças neurológicas. Em 1981, foi descrita uma entidade neurológica incluindo ataxia cerebelar progressiva de início precoce, disartria, liberação piramidal e manutenção ou aumento dos reflexos tendíneos nos membros superiores e inferiores. Essa síndrome é conhecida como ataxia cerebelar de início precoce com reflexos mantidos. Neste artigo, o objetivo foi chamar a atenção para o diagnóstico de ataxia cerebelar de início precoce com reflexos mantidos como a segunda causa mais comum de ataxia cerebelar autossômica recessiva, após a ataxia de Friedreich, e também realizar um estudo do espectro clínico da síndrome. Doze pacientes de diferentes famílias preencheram os critérios clínicos para ataxia cerebelar de início precoce com reflexos mantidos. Disartria e atrofia cerebelar foram as características mais frequentes. No entanto, não há consenso se a ataxia cerebelar de início precoce com reflexos mantidos é uma doença homogênea ou um grupo de síndromes com fenótipos semelhantes representadas por diferentes entidades genéticas. Estudos moleculares futuros são necessários para fornecer respostas definitivas para as questões pendentes em relação à ataxia cerebelar de início precoce com reflexos mantidos.

Palavras-Chave: ataxias, ataxia cerebelar autossômica recessiva, ataxia cerebelar de início precoce com reflexos mantidos, EOCA.

Autosomal recessive cerebellar ataxias (ARCA) are a heterogeneous group of neurological disorders characterized by degeneration or abnormal development of cerebellum and spinal cord, autosomal recessive inheritance and early onset beginning before the age of 20 years. This group encompasses a large number of unusual diseases and may be considered a diagnostic challenge[1]. The most frequent ARCA is Friedreich ataxia (FA), but other diseases include ataxia with vitamin E deficiency, ataxia telangiectasia, ataxia with ocular apraxia type 1 and type 2, autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS), cerebrotendineous xanthomatosis, abetalipoproteinemia, Refsum disease and Marinesco-Sjögren syndrome. In most cases, diagnosis may be performed based on clinical and genetic evaluation[1].

In 1981, Anita Harding described the clinical and genetic features of 20 families in which affected individuals had a

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Conflict of interest: There is no conflict of interest to declare.

Received 26 October 2012; Received in final form 14 November 2012; Accepted 21 November 2012.

progressive cerebellar ataxia developing within the first two decades, associated with dysarthria, pyramidal weakness of the limbs and retained or increased upper limb reflexes and knee jerks. This disorder is known as early onset cerebellar ataxia with retained tendon reflexes (EOCA) or Harding ataxia, and other case series were reported later[2]. EOCA is clinically distinct from FA, with significant differences between those neurological conditions[2]. Several reviews have pointed out that, although FA is the most common recessive ataxia worldwide, the diagnosis of this condition may be viewed with caution when brisk tendon reflexes are present. This is because FA presents with loss of tendon reflexes in 62 to 86% of patients[3,4].

Frequently, EOCA has been excluded from ARCA list, since clinical features and genetic definition are not very well understood. In this article, we aimed to call attention for the diagnosis of EOCA as the second most common cause of ARCA, and also to perform a clinical spectrum study of this syndrome.

METHODS

A retrospective review from 486 medical records of patients attending at the Ataxia Unit, in the Universidade Federal de São Paulo, from February 2008 to September 2012, was performed. During this period, patients with different subtypes of cerebellar ataxias were followed-up in order to determine clinical and genetic diagnosis. Patients were divided into five categories based on age at onset, familial history, progression and laboratorial and genetic tests: autosomal dominant spinocerebellar ataxia (SCA), ARCA, sporadic ataxias, congenital ataxias and mithocondrial ataxias.

Patients with early onset symptoms were investigated for ARCA. Twelve patients from different families met all clinical features for EOCA. All patients had an early onset of ataxia symptoms (before 25 years old) with normal or brisk reflexes, and underwent biochemical analysis including albumin, alphafetoprotein and vitamin E, genetic test for FA, and brain imaging, in order to rule out other ARCA.

Information on age, age at onset, disease duration, consanguinity, ataxia severity (International Cooperative Ataxia Rating Scale (ICARS) and Scale for the Assessment and Rating of Ataxia (SARA)), reflexes, Babinski sign, spasticity, neuropathy (electroneuromyography), nystagmus, dysarthria and cerebellar atrophy were evaluated from medical records from all patients with suspected EOCA. All clinical details, including neurological examination and ataxia scales, were evaluated by the same researcher (JLP).

RESULTS

Table shows clinical and demographic features of the 12 patients with EOCA. Among patients with suspected EOCA, there was a slight male predominance (58.33%). The mean age was 32.67±9.41, mean age at onset was 17.25±3.86, and mean disease duration, 15.42±6.66 years. Regarding clinical features, the mean score on ICARS was 31.09±17.50 and on SARA was 12.82±5.38. Genetic test for FA was negative in all patients. No correlation was found between ataxia severity (SARA and ICARS) and disease duration. Dysarthria and cerebellar atrophy were the most common features and were present in 10 of 12 patients (Fig 1).

FA was diagnosed in 37 patients and was the most common ARCA in our Ataxia Unit. EOCA was the second

Table. Clinical features found in early onset ataxia with retained reflexes.

Patient	Gender	Age	AO	DD	Consanguinity	ICARS	SARA	ULR	KR	AR	BS	Spasticity	Neuropathy	Nystagmus	Dysarthria	Cerebellar atrophy
1	M	19	14	5	Yes	27	9	+++	+++	+++	A	A	A	P	P	P
2	M	39	22	17	No	54	20	++++	++++	+++	P	P	P	P	A	A
3	F	22	16	6	No	23	12	++++	+++	++	A	A	A	A	P	P
4	M	37	17	20	No	33	14	++	++	+++	A	A	-	P	P	P
5	M	52	25	27	Yes	15	10	+++	+++	+++	A	A	-	A	P	P
6	M	28	13	15	Yes	17	11	++	++	+++	A	A	-	P	P	P
7	F	36	21	15	No	54	18	++++	++++	++++	A	A	-	P	P	P
8	F	21	12	9	No	38	15	++++	++++	++++	P	A	P	P	P	A
9	F	36	17	19	Yes	19	7	++	++	++	A	A	A	A	P	P
10	M	40	16	24	Yes	58	22	+++	+++	+++	A	A	A	P	P	P
11	F	32	19	13	Yes	14	9	+++	+++	+++	A	A	A	A	P	P
12	M	30	15	15	No	13	6	+++	+++	+++	A	A	A	A	A	P

M: Male; F: Female; AO: Age at onset; DD: Disease duration; ICARS: International Cooperative Ataxia Rating Scale; SARA: Scale for the Assessment and Rating of Ataxia; ULR: Upper limbs reflexes; KR: Knee reflexes; AR: Achilles reflexes; BS: Babinski sign; P: Present; A: Absent.

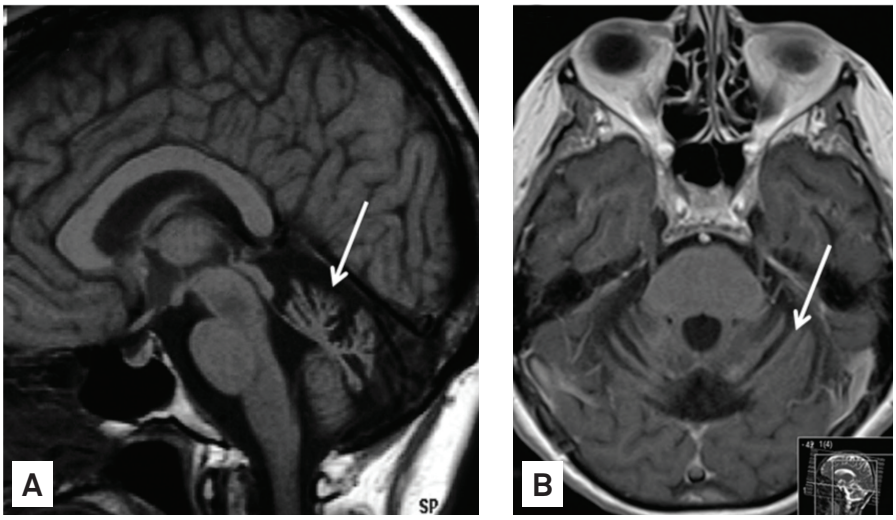

Fig 1. (A) Sagittal T1-weighted and (B) axial T1-weighted brain MRI disclosing marked global cerebellar atrophy in a patient with early onset ataxia with retained reflexes.

most common cause of ARCA (12 patients), followed by ataxia with oculomotor apraxia type 2 (7 patients), ataxia telangiectasia (4 patients), ARSACS (4 patients), ataxia with vitamin E deficiency (3 patients) and cerebrotendineous xanthomatosis (1 patient). There are several patients under investigation for ataxia with oculomotor apraxia type 1 (3 patients), coenzyme Q10 deficiency (2 patients), mithocondrial ataxia (3 patients) and Marinesco-Sjögren syndrome (1 patient). No patients with Refsun disease and abetalipoproteinemia were confirmed. Congenital ataxias were not included in this list.

DISCUSSION

Our study highlights how relevant is to consider EOCA in the differential diagnosis of ARCA, since it might correspond to its second most common cause. An autosomal recessive inherited disorder is suggested, as half of the patients had consanguineous parents. Additionally, dysarthria was presented in almost all patients and might be considered a frequent neurological finding. We also observed that almost all patients presented with cerebellar atrophy on brain magnetic resonance imaging (MRI) studies, in opposite to FA patients. Conversely, spasticity was an unusual clinical feature. No correlation was found between ataxia severity and disease duration, which express that EOCA has a heterogeneous progression.

Although the phenotype of FA has classical findings, such as loss of tendon reflexes, sensory loss, scoliosis, foot deformity, diabetes mellitus and cardiac abnormalities, there are variations in the clinical presentation. These include the late onset Friedreich ataxia (LOFA) and also Friedreich ataxia with retained reflexes (FARR)[5,6]. Thus, the presence of retained reflexes does not exclude the diagnosis of FA, and a genetic test is recommended despite an atypical ARCA presentation[7]. No patient with FARR phenotype was identified in our study. A normal brain magnetic resonance imaging (MRI) without cerebellar atrophy is also a remarkable finding in FA patients (Fig 2)[8,9].

One of the largest series of EOCA described by Chio et al. evaluated patients for 50 years. They concluded that EOCA was the third most common cause of ARCA, after FA and ataxia telangiectasia[10]. Klockgether et al. evaluated 14 patients with EOCA and compared clinical, electrophysiological and MRI observations with FA patients. Sensory disturbances, foot deformity and scoliosis were encountered less frequently in EOCA than in FA patients. Electrophysiological findings in EOCA were variable and pointed out to an axonal degeneration in peripheral nerves. Our study demonstrated that axonal neuropathy was present in only 25% of patients. Cerebellar atrophy was a frequent neuroimaging feature in all EOCA series, in opposite to FA[9]. The demonstration of cerebellar atrophy in the majority of EOCA patients supported the view that EOCA was distinct from FA[9]. Additionally, some data also has demonstrated that EOCA is characterized by a heterogeneous progression[11,12].

Although past decade has seen great advances in unraveling the biological basis of hereditary ataxias, knowledge on the genetic features of EOCA is still extremely restricted. Sporadic reports have demonstrated new mutations in recessive ataxias. For instance, SYNE1 mutation is a gene responsible for a recessive inherited pure cerebellar ataxia[13]. Concerning that genetic test is not available for the diagnosis of EOCA, we strongly recommend a biomarker investigation, including albumin, alphafetoprotein and vitamin E, and genetic test for FA, in order to exclude other potential ARCA[14].

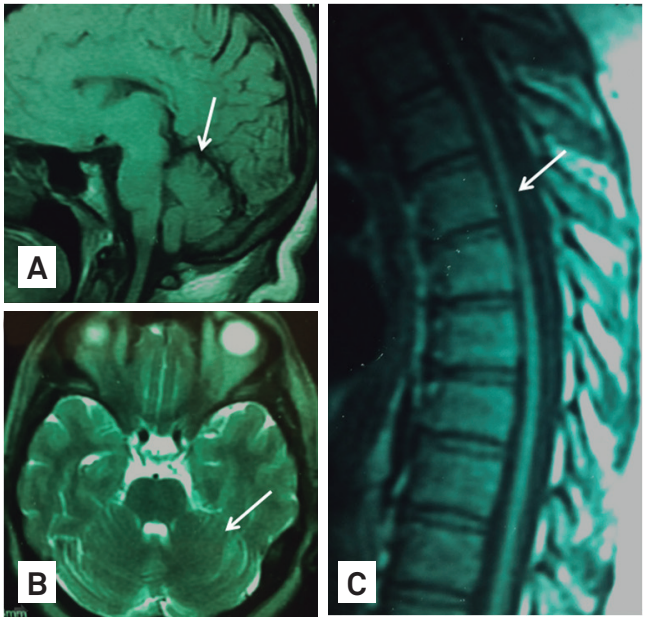

Fig 2. (A) Sagittal T1-weighted and axial T2-weighted brain MRI disclosing normal cerebellar volume, without atrophy, in a patient with Friedreich ataxia; (C) sagittal T1-weighted thoracic spine MRI of the same patient, showing atrophy of the spinal cord.

Interestingly, although patients described in our sample mostly had brisk reflexes, spasticity was present only in one patient, similarly to other series[15]. This is a crucial issue, since spasticity in a context of ARCA (also called hereditary spastic-ataxias) might suggest other rare neurological conditions, such as ARSACS, hereditary spastic paraplegia and autosomal recessive spastic ataxia[16,17]. Therefore, spasticity should be considered a neurological hallmark against the diagnosis of EOCA.

On the whole, this article highlighted the importance to consider EOCA as the second most common ARCA. The lack of a genetic marker should not be a limitation to consider this syndrome. Also, we reinforce the relevance to exclude other ARCA, by performing a biochemical investigation and genetic test for FA in order to exclude FARR. Based on this data, the clinical spectrum of EOCA might include autosomal recessive inherited cerebellar ataxia, dysarthria, retained reflexes associated or not with neuropathy and cerebellar atrophy on brain MRI. It is uncertain, however, whether EOCA is a homogeneous disease or a group of phenotypically similar syndromes represented by different genetic entities. Further molecular studies are required to provide definitive answers to the questions that remain regarding EOCA.

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