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ARTICLE

Non-progressive cerebellar ataxia and previous undetermined acute cerebellar injury: a mysterious clinical condition

Ataxias cerebelares não-progressivas e lesão cerebelar aguda prévia indeterminada: uma condição clínica misteriosa

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ABSTRACT

Cerebellar ataxias represent a wide group of neurological diseases secondary to dysfunctions of cerebellum or its associated pathways, rarely coursing with acute-onset acquired etiologies and chronic non-progressive presentation. We evaluated patients with acquired non-progressive cerebellar ataxia that presented previous acute or subacute onset. Clinical and neuroimaging characterization of adult patients with acquired non-progressive ataxia were performed. Five patients were identified with the phenotype of acquired non-progressive ataxia. Most patients presented with a juvenile to adult-onset acute to subacute appendicular and truncal cerebellar ataxia with mild to moderate cerebellar or olivopontocerebellar atrophy. Establishing the etiology of the acute triggering events of such ataxias is complex. Non-progressive ataxia in adults must be distinguished from hereditary ataxias.

Keywords: cerebellar ataxia, cerebellum, non-progressive ataxia.

RESUMO

Ataxias cerebelares representam um grupo amplo de doenças neurológicas secundárias a disfunções cerebelares ou das vias associadas, raramente cursando com etiologias adquiridas de início agudo e com evolução crônica não-progressiva. Nós avaliamos pacientes com ataxia cerebelar adquirida não-progressiva com apresentação prévia aguda ou subaguda. Foi realizada caracterização clínica e de neuroimagem de pacientes adultos com ataxia adquirida não-progressiva. Cinco pacientes foram identificados com o fenótipo clínico de ataxia adquirida não-progressiva. A maior parte dos pacientes apresentou início juvenil ou no adulto, de forma aguda ou subaguda, de ataxia cerebelar appendicular e de tronco com atrofia cerebelar ou olivopontocerebelar leve a moderada. Estabelecer a etiologia dos eventos agudos desencadeantes de tais ataxias é complexo. Ataxia não-progressiva em adultos deve ser diferenciada das ataxias hereditárias.

Palavras-chave: ataxia cerebelar, cerebelo, ataxia não-progressiva.

Ataxic syndromes are conditions that result from the involvement of cerebellar structures or from a combination of cerebellar and extra-cerebellar lesions affecting the brainstem, thalamus, spinal cord (spinocerebellar and posterior cord tracts), vestibulocerebellar system and frontal lobes. Cerebellar ataxias are a heterogeneous group of diseases comprising genetic and acquired etiologies[1], giving rise to lack of motor coordination, especially in fine coordinated voluntary movements. Speech disorders, movement decomposition, intention tremor, disbasia, nystagmus and other complex oculomotor disturbances, hypotonia with pendular reflexes, delayed motor milestones and the so-called cognitive-affective cerebellar syndrome may also arise as a consequence of different cerebellar disorders[2,3].

Cerebellar ataxias can be subdivided into two major categories taking into account inheritance and etiological factors: hereditary ataxias, including autosomal dominant spinocerebellar ataxias (SCA) and episodic ataxias, autosomal recessive ataxias, non-progressive congenital ataxias, mitochondrial ataxias, X-linked cerebellar ataxias; and sporadic or acquired cerebellar ataxias (including non-hereditary degenerative ataxias). From a clinical point of view, cerebellar ataxias can be divided in intermittent or episodic, non-progressive or stable (including the congenital cerebellar ataxias) and progressive[4,5,6].

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Non-progressive cerebellar ataxias result from different etiologies with chronic clinical course and insidious onset[7,8,9], but may rarely manifest as non-progressive axial and appendicular ataxias linked to a prior acute or subacute neurological insult often of unknown etiology. The vast majority of cases relate to a pure cerebellar ataxia phenotype of acute onset and early onset in the first three decades of life, usually after a parainfectious event and involving autoimmune mechanisms, associated in its clinical course with cerebellar or olivopontocerebellar atrophy. No family history of neurodegenerative disorders are described in these cases. However, there are few descriptions in the literature regarding the clinical and neuroimaging aspects and the expected natural history for such patients[9].

Given the lack of data in the current medical literature, we describe here five adult patients that presented to our Ataxia Unit with non-progressive cerebellar ataxia, related to a previous undetermined acute or subacute cerebellar injury. We provide a detailed clinical and neuroimaging features for this interesting condition, that may be frequently confused with degenerative or genetic disturbances.

METHOD

A retrospective review from 725 medical records of patients attending at the Ataxia Unit, in Federal University of São Paulo (UNIFESP), from February 2008 to December 2014, was performed. Our study was approved by our institutional Ethics Committee. All patients were followed-up for at least 1 year and underwent clinical, neuroimaging and genetic tests. Patients were properly evaluated for mutations of the most common forms of hereditary cerebellar ataxias (Friedreich ataxia, Spinocerebellar ataxia types 1, 2, 3, 6 and 7)[10,11]; analysis of serum vitamin E, vitamin B12, albumin, cholesterol and alpha-fetoprotein levels; spine and brain magnetic resonance imaging (MRI) studies; and, if necessary, cerebrospinal fluid (CSF) analysis and electrodiagnostic studies (electroneuromyography and electroencephalography)[12]. An extensive evaluation for infectious conditions and other causes of acute cerebellar ataxia (Table 1) were also performed including serum and CSF basic serological studies for syphilis, CMV (cytomegalovirus), HSV (herpes simplex virus) and toxoplasmosis.

In order to define progressive or non-progressive ataxia, all patients were evaluated for ataxia severity by using specific scales in at least two moments, separated for at least one year. The scales were performed by the same researcher (JLP): Scale for the Assessment and Rating of Ataxia (SARA) and International Cooperative Ataxia Rating Scale (ICARS)[13]. Also, the patients were questioned about worsening of the ataxia with time.

The inclusion criteria for acquired non-progressive ataxia was: (i) chronic non-progressive cerebellar ataxia with previous acute or subacute-onset; (ii) normal evaluation in subsidiary exams; and (iii) absence of exclusion criteria. Exclusion criteria included: (i) cerebellar ataxia associated with other neurological manifestations, including epilepsy, myoclonus, spastic paraparesis, neuropathy and movement disorders; (ii) cerebellar ataxia in the setting of a established systemic disorder, including neurocutaneous syndromes, autoimmune rheumatologic and granulomatous diseases, hereditary autoinflammatory syndromes, hematological disorders, infectious diseases and neoplastic and paraneoplastic conditions; (iii) positive family history for hereditary cerebellar ataxia (including spinocerebellar ataxias and autosomal recessive cerebellar ataxias); (iv) cerebellar ataxias with definitive diagnosis of a genetic or acquired chronic etiology; (v) neuroimaging features highly suggestive of an alternative diagnosis (i.e. leukodystrophies); (vi) specific laboratorial examination findings (serum and cerebrospinal fluid analysis), including specific inherited neurometabolic disorders; (vi) sensory ataxia; and (vii) episodic, intermittent, recurrent or remitting-relapsing clinical course.

Table 1. Main differential diagnosis of acute cerebellar ataxia[7,8,9,14,15,16,17,18,19,20,21,22].

Differential diagnosis of acute cerebellar ataxia
I. Inflammatory postinfectious disorders
II. Inherited neurometabolic disorders (frequently intermittent or recurrent)
Maple syrup urine disease, Hartnup disease, *SLC19A3* gene mutation, GLUT1 deficiency, partial biotinidase deficiency, pyruvate-dehydrogenase deficiency, NARP syndrome, Leigh's syndrome, pyruvate carboxylase deficiency type C, organic acidemias/acidurias (urocanic, isovaleric, propionic and methylmalonic), urea cycle disorders (carbamoylphosphate-synthetase deficiency, ornithine-transcarbamoilase deficiency, arginase deficiency, argininosuccinate synthethase deficiency), carnitine acethyltransferase deficiency, other aminoacidopathies
III. Infectious disorders
Acute infectious cerebellitis and rhombencephalitis (e.g. Chickenpox virus, Epstein-Barr virus)
IV. Cerebrovascular disorders
Stroke (cerebellar infarction or hemorrhage), dural sinus thrombosis
V. Ion channel disorders
Episodic ataxias
VI. Miscellaneous
Drug-induced, demyelinating disorders (multiple sclerosis, acute disseminated encephalomyelitis), Paraneoplastic (rare)

RESULTS

Five patients met clinical criteria for adult non-progressive cerebellar ataxia related to previous acute or subacute onset. Table 2 discloses clinical and neuroimaging features observed in our five patients. They presented during their second to third decade of life (mean value: 20,8 years) with acute presentation varied from abrupt (around seconds to few minutes) up to 1 month (mean value: 10 days). All five patients presented to our clinic after five to 30 years from the symptoms onset (mean value: 18 years), wherein two of them with previous history of gastrointestinal infectious disease in the last month. Gait instability was present in all patients and 40% had head tremor and slurred speech (n = 2). All patients had global and appendicular ataxia associated with dysarthria. Headache, diplopia, Achilles clonus with brisk tendon reflexes in the lower limbs and lower limbs hypoesthesia have also been described as complementary findings in each isolated case (n = 1). Regarding ataxia severity scores, SARA scores varied from 8 to 10 and ICARS scores varied from 31 to 40. All patients remained with the same score in SARA and ICARS scales after one year of follow-up. All patients presented with abnormal neuroimaging findings, 3 patients had cerebellar atrophy and 2 had olivopontocerebellar atrophy (Figure).

DISCUSSION

Chronic non-progressive cerebellar ataxias in adults represent an uncommon group of cerebellar diseases, especially in cases apparently associated to postinfectious states as frequently described in pediatric acute cerebellitis. Despite most common non-progressive cerebellar ataxias are congenital, clinical presentation in such cases of non-progressive ataxia has a similar profile to the observed in our sample, highlighting gait ataxia with nearly pure cerebellar presentations associated with nonspecific neuroimaging findings, such as mild cerebellar vermis or global cerebellar atrophy[4,8].

There is a wide group of differential diagnosis for adult or juvenile-onset non-progressive cerebellar ataxias (Table 3)[7,8,9,14,15,16,17,18,19,20,21]. Most cases, when properly investigated, may disclose a definite diagnosis regardless

Table 2. Clinical profile of adult patients with non-progressive cerebellar ataxia.

Patients	1	2	3	4	5
Age at evaluation	38 years	13 years	38 years	48 years	52 years
Gender	F	M	F	F	F
Age of onset	14 years	13 years	22 years	11 years	44 years
First complaint	GI	GI (intermittent)	GI, head tremor, slurred speech	GI, head tremor, slurred speech	GI
Duration of first complaints	Minutes	1 month	5 days	5 days	10 days
Type of cerebellar ataxia	Axial, appendicular	Appendicular	Appendicular	Axial, appendicular	Appendicular
Other neurological findings	Mild dysarthria	Mild dysarthria, headache, diplopia, Achilles clonus	Moderate dysarthria, headache	Mild dysarthria, left VI cranial nerve palsy (congenital)	Mild dysarthria, distal lower limbs hypoesthesia
Medical history	Constipation	Scoliosis	No	No	Constipation
Neurological family history	Brother with cerebral palsy	Brother with seizures since 13-year-old	No	No	No
Abnormal neuroimaging findings	Moderate OPCA	Mild CA	Mild CA	Mild to moderate CA	Mild OPCA
SARA score	10	10	8	8	10
ICARS score	33	33	31	40	65

M: male; F: female; GI: gait imbalance; OPCA: olivopontocerebellar atrophy; CA: cerebellar atrophy; SARA: scale for the assessment and rating of ataxia; ICARS: international cooperative ataxia rating scale.

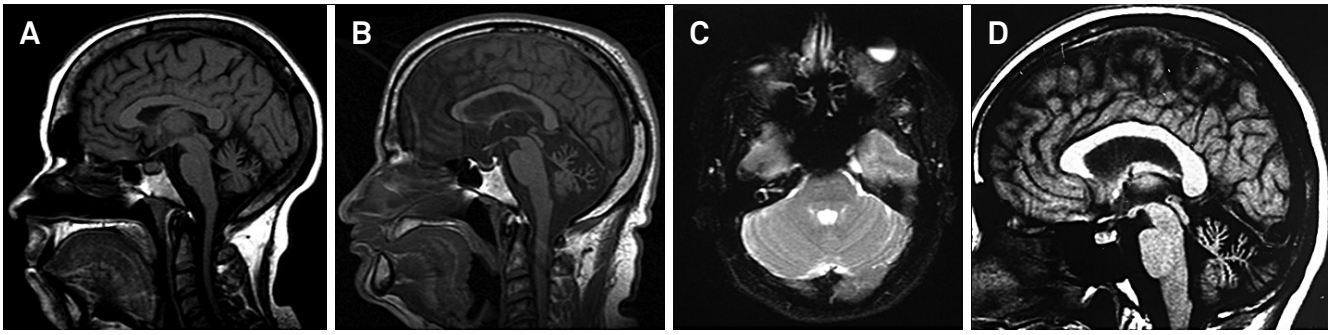

Figure. Neuroimaging findings from patients 1, 2, 3 and 5, with variable degrees of pure cerebellar atrophy (Patient 2, 1B; Patient 3, 1C; Patient 5, 1D) and olivopontocerebellar atrophy (Patient 1, 1A).

Table 3. Main differential diagnosis of non-progressive cerebellar ataxia[7,8,9,14,15,16,17,18,19,20,21,22].

Differential diagnosis of non-progressive cerebellar ataxia
I. Cerebellar and posterior fossa congenital malformations (including midbrain-hindbrain developmental malformations) – most with infancy-onset
Hypoplasia of the vermis and/or cerebellar hemispheres, Pontocerebellar hypoplasia, Dandy-Walker syndrome Syndromic complex congenital malformations with cerebellar or pontocerebellar hypoplasia or dysgenesis (i.e. Joubert syndrome, Gomez-Lopez-Hernandez syndrome, among others)
II. Non-progressive congenital cerebellar ataxias – infancy-onset
Cerebellar hypoplasia of the granular cell layer Dysequilibrium syndrome (*VLDLR*-associated cerebellar hypoplasia) Congenital granuloprival hypoplasia of cerebellar and hippocampal cortex Syndromic congenital non-progressive cerebellar ataxias (i.e. Gillespie syndrome, Autosomal recessive cerebellar hypoplasia and endosteal sclerosis, among others)
III. Chronic non-progressive encephalopathy – neonatal-onset
Including prenatal and perinatal aetiologies
IV. Inherited neurometabolic disorders – variable age at onset (most in infancy)
Congenital disorders of glycosylation (CDG) types Ia and Iq Succinic-semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria) Others: Mitochondrial disorders, Pyruvate dehydrogenase deficiency, GLUT1 deficiency syndrome
V. Spastic-ataxic syndromes and/or degenerative spinocerebellar ataxias
Early-onset cerebellar ataxia with retained tendon reflexes (Harding ataxia)
VI. Adult-onset sporadic cerebellar ataxias
Post-infectious and autoimmune cerebellar ataxia; toxic agents (i.e. drug abuse and addiction, drug exposure, environmental toxins)

the availability of complex clinical and research diagnostic tools. As it may be related to autoimmune or demyelinating diseases, such as postinfectious states, general laboratorial studies, including serologies and CSF analysis may explain neurological compromise in patients, especially if performed during acute phase of presentations[12]. For instance, antiganglioside antibodies are not commonly investigated and may be crucial in Miller-Fisher syndrome (anti-GQ1b, anti-GM1 and anti-GD1a antibodies) and in post-viral cerebellar cerebellitis. This fact may explain the undetermined etiology of the presented cases, since the symptoms onset occurred years ago. Also, we had no access to the previous investigation in the context of acute cerebellar symptoms of the patients related herein.

Although a basic genetic battery profile for spinocerebellar ataxias that resulted negative has been performed, sporadic ataxia and non-progressive symptoms are strongly against an autosomal dominant genetic condition. It is also recognized the high importance of a complete metabolic screening for inborn errors of metabolism linked to intermittent or acute presentations of cerebellar ataxia[19]. The lack of an expanded investigation for inborn errors of metabolism is a limitation of our study.

Of note, genetic forms of ataxia usually present with olivopontocerebellar atrophy instead of pure cerebellar atrophy. Olivopontocerebellar atrophy may be prominent in some spinocerebellar ataxias (types 1, 2, 3, 7), in congenital disorder of glycosylation type Ia, in glutamate dehydrogenase type 1 deficiency, in some mitochondrial disorders and in the genetic group of congenital olivopontocerebellar atrophies and pontocerebellar hypoplasias[12,18,22]. By contrast, other non-progressive cerebellar ataxias can exhibit highly suggestive neuroimaging findings as the "molar-tooth sign" with hypoplasia of the cerebellar vermis in Joubert syndrome, the rhombencephalosynapsis in Gomez-Lopez-Hernandez syndrome, and cystic dilatation of the fourth ventricle with hypoplasia and upward rotation of the cerebellar vermis in Dandy-Walker malformation[4,8,12]. Despite pure cerebellar atrophies occurred frequently in our sample, they can also arise in chronic non-acquired ataxias, including ataxia-oculomotor apraxias, ataxia-telangiectasia-like disorders, GM2 gangliosidosis, abetalipoproteinemia and some mitochondrial disorders[22].

It is also clear that some cases may be related to mild phenotypes (variable expressivity) of other neurogenetic disorders and to some susceptibility loci which should be noted clinically during acute infectious and metabolic decompensations. Whole-exome or multiple genes panel analysis with next-generation sequencing may improve the diagnostic work-up of cerebellar ataxias without clinical and neuroimaging remarks or cerebellar ataxias in the context of complex neurological phenotypes[5,11,23,24,25]. However, up to now there is limited evidence that such new molecular techniques would help in the diagnosis of classic presentations of acute-onset non-progressive cerebellar ataxias in the adult.

In conclusion, this article describes the clinical phenotype and neuroimaging features of an unusual syndrome characterized by non-progressive cerebellar ataxias in adults. General neurologists must be aware that non-progressive cerebellar ataxias in adults are related to a previous acute or subacute cerebellar injury, and that genetic or degenerative causes are unlikely.

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