ORIGINAL CONTRIBUTION

Cerebellar Ataxia With Spasmodic Cough

A New Form of Dominant Ataxia

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Background: Although mentioned in most series, "pure" autosomal dominant cerebellar ataxias, except spinocerebellar ataxia type 6, are difficult to differentiate on clinical grounds.

Objective: To describe Portuguese families with a peculiar pure form of dominant ataxia that, to our knowledge, has never been documented before and in which cerebellar signs are preceded by spasmodic cough.

Patients: Through a population-based survey of hereditary ataxias in Portugal, we identified 19 patients in 6 families with this particular disorder.

Results: The majority of patients had a pure late-onset ataxia with a benign evolution. In all of the families, attacks of spasmodic coughing preceded ataxia for 1 to 3 decades and were a reliable marker of the disease. In Portugal, this form of ataxia accounts for 2.7% of all of the dominant ataxias.

Conclusions: The families that we describe shared some relevant clinical and imagiological features with spinocerebellar ataxia type 5 and the recently described spinocerebellar ataxia type 20, allelic to spinocerebellar ataxia type 5. Spinocerebellar ataxia types 5 and 20 could be different phenotypic expressions of the same molecular disorder. The association of a dominant ataxia with spasmodic cough is rare but probably underdiagnosed.

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AUTOSOMAL DOMINANT CEREBELLAR ataxias have considerable variation and overlapping phenotypes. Cerebellar ataxia is obviously the core feature of the disease, and in some "pure" forms, it is its only manifestation. In a few families, paroxistic manifestations precede the cerebellar syndrome, as in the case of hemiplegic migraine in spinocerebellar ataxia (SCA) type 6. In recent years, we have been progressively aware of the association of dominant ataxia with spasmodic cough in a few kindreds. We describe the clinical presentation of 6 Portuguese families with this particular form and discuss possible links with SCA5 and the recently described SCA20 (allelic to SCA5).

METHODS

Between 1993 and 2004, we conducted a population-based survey of hereditary ataxias intended to cover the entire population (more than 10 million inhabitants) in Portugal.[1] Spasmodic coughing was present in 6 families with autosomal dominant ataxia. We obtained information about 19 patients, 17 of whom were examined by us. Cranial magnetic resonance imaging was performed in 10 of the 17 patients. In each family, patients with Machado-Joseph disease, dentatorubropallidoluysian atrophy, and SCA1, SCA2, SCA6, SCA7, SCA8, SCA10, SCA12, SCA14, and SCA17 mutations were excluded.

RESULTS

Pure cerebellar forms were present in 27 (12.5%) of the 216 families with autosomal dominant ataxias ascertained through the survey. Of these 27 families, only 5 had a molecular diagnosis (1 family with SCA14 and 4 families with SCA6). Six of the remaining kindreds had spasmodic cough antedating ataxia from 5 to 38 years (mean±SD interval, 17.3±10.8 years).

The age at onset ranged from 25 to 55 years for paroxistic cough attacks (mean±SD age at onset, 35.3±8.7 years) and from 40 to 65 years for cerebellar ataxia (mean±SD age at onset, 53.1±7.7 years). The age at examination varied from 45 to 77 years (**Table**).

The coughing comes in bursts without any recognizable precipitating factor (besides changes in temperature, particular smells, water steam, or candies in 1 pa-

Table. Summary of Clinical and Imagiological Features in 19 Patients With Dominant Ataxia With Spasmodic Cough

Family, No.	Patient No./ Sex	Age at Onset, y		Cough-Ataxia Interval, y	Age at Examination, y	Disease Duration, y	Frequency of Cough Episodes	Brisk DTR	Downbeat Nystagmus	Eyelid Retraction	MRI Result
		Cough	Ataxia								
1	1/M	55	60	5	74*	19	ND	+, Babinski	–	–	Dentate calcification, CA
	2/F	42	50	8	64	22	3-4/y	+	+	–	CA
	3/M	30	40	10	77	40	2-3/wk		+	–	–
2	4/M†	40	50	10	60‡	25	2/wk	ND	ND	ND	ND
	5/M	40	50	10	64	24	2/mo	–	+	+	CA
	6/M	30	60	30	76	46	1/wk	NP	+	+	CA
	7/F	30	56	26	77	47	1/wk	NP	+	+	CA
	8/F	31	40	9	45	14	Many/d	–	–	+	Normal
	9/M	30	40	10	45	15	Many/d	–	–	+	Normal
3	10/M	30	45	15	73	43	1/d	NP	+	–	–
	11/M	50	62	12	68	18	1/wk	–	–	–	–
	12/M†	42	55	13	§	35	2-3/d	ND	ND	ND	ND
4	13/F	37	53	16	69	32	ND	–	+	–	–
	14/F	25	58	33	65	40	1/wk	+	+	–	CA
	15/F	46	53	7	59	13	1/wk	+	–	–	–
	16/M	30	52	12	56	26	1-2/mo	+	–	–	–
	17/F	27	57	30	58	31	1-2/wk	–	–	–	–
5	18/M	30	65	35	68	38	1/d	–	–	–	CA
6	19/F	25	63	38	66	41	Many/d	+	–	–	Normal

Abbreviations: CA, cerebellar atrophy; DTR, deep tendon reflex; F, female; M, male; MRI, magnetic resonance imaging; ND, not determined; NP, neuropathy; +, presence of symptom; –, absence of symptom.
*Patient died at age 78 years.
†Known by history.
‡Patient died at age 65 years.
§Patient died at age 77 years.

tient), and it never occurs during sleep. It is occasionally so severe that patients become cyanosed and collapse or have urine incontinence without loss of conscience. The duration is short (ie, minutes), and drinking cold water can abort episodes. This occurs throughout life without progression in frequency, duration, or severity. In fact, the coughing episodes tend to attenuate after the onset of the ataxia (from daily to 1 episode every 2 months). The 2 youngest patients (patients 8 and 9) described 2 types of bursts that they could predict from the beginning: short, mild bursts that we could assist them with during the consultations and that repeated several times per day, and strong bursts with sneezes, lasting for several minutes and appearing every week. Another patient described having a high-pitched voice before the episode. No other voice disturbances were noted. Cough and dysphagia are not related. They progress inversely, coughing being the inaugural manifestation and tending to subside, but dysphagia being a late manifestation of the disease when ataxia is already disabling. There was no evidence of respiratory diseases, allergies, or gastric complaints.

Coughing episodes segregated with cerebellar ataxia in all of the families. Benign but progressive cerebellar ataxia developed later, usually beginning with gait imbalance followed by dysarthria and finally by hand incoordination and dysphagia. A downbeat nystagmus was observed in 10 patients with long-standing ataxia and was absent in initial forms. Diplopia was frequently found, although it was never spontaneously mentioned by the patients. In 1 family, all of the patients had eyelid retraction. Deep tendon reflexes were occasionally brisk, although 3 patients had evidence of a mild peripheral neuropathy (absent ankle jerks and distal loss of vibration sense). Neither palatal tremor nor other relevant neurological signs were found.

Cranial magnetic resonance imaging was performed in 10 patients, revealing moderate cerebellar atrophy with normal brainstem (namely, normal bulbar volume and normal bulbar olives) in 7 of the patients. One patient had bilateral calcifications of the dentate nuclei. Images were normal in 3 patients with short duration of ataxia.

COMMENT

CLINICAL DEFINITION

We have described 6 Portuguese families affected by a particular disorder characterized by a late-onset, mostly pure cerebellar ataxia that is preceded by episodes of spasmodic coughing beginning 1 to 3 decades earlier. In all of the families, coughing bursts segregate with cerebellar ataxia and are a reliable marker of the family's disease. Besides cerebellar ataxia, downbeat nystagmus is frequent.

FREQUENCY

In Portugal, cerebellar ataxia with spasmodic cough accounts for 2.7% of the phenotypic spectrum of all of the families with autosomal dominant cerebellar ataxia. It is

therefore a rare form, but certainly not so rare as to explain the fact that there are no previous descriptions of similar kindreds. It is possible that it is currently underdiagnosed.

COUGH AND THE CEREBELLUM

Cough is a complex respiratory act triggered by both reflex and voluntary mechanisms. Neurons in the ventrolateral medulla that generate both cough and respiratory patterns are known to interact with neural networks in the cerebellum-rostral interposed nucleus, rostral fastigial nucleus, and infracerebellar nucleus.[2] Electrical stimulation of the cervical vagus afferents produces evoked potentials on both the cerebellar cortex and its deep structures, and deep cerebellar nuclei appear to be involved in neural activities essential for breathing and coughing.[3,4] Furthermore, in cats, the primary alteration in cough responsiveness following cerebellectomy, or lesion of the interposed nucleus, was found to be a dramatic reduction in the cough frequency.[2,5]

The question is how a neurodegenerative disease model, like that which was found in the families we describe here, can have cough episodes as its first manifestation. We may hypothesize that the neurodegenerative process becomes noticed through disproportionate central facilitation of cough reflex. Another interesting feature is the reduction of the frequency of coughing episodes after the onset of the cerebellar ataxia together with evidence of cerebellar atrophy. To our knowledge, this is the first time in humans that a disease associated with progressive cerebellar dysfunction is temporally correlated with strong attenuation of cough reflex in a manner similar to that which happens in animals after cerebellar lesions.

PROXIMITY TO OTHER DOMINANT ATAXIAS

We did not find any articles describing the association of dominant ataxia with spasmodic cough. There are rare cases of spasmodic dysphonia with tremor or late-onset cerebellar ataxia.[6,7] Recently, a large family with a dominant ataxia with spasmodic dysphonia was described.[8] The dysphonia was always present (in 1 patient antedating ataxia) and had been stable for years in contrast with the progression of ataxia. Another particular feature was a palatal tremor in 2 patients. Besides cerebellar atrophy, the magnetic resonance image showed calcification of the dentate nuclei. There was also an increased inferior olivary T2 signal in the patients with palatal tremor. The family's disease mapped to the pericentromeric region of chromosome 11, and its candidate region overlapped that of SCA5. For this family, there is a provisional assignment of SCA20 to be confirmed after a definite exclusion of SCA5.

Spinocerebellar ataxia type 5 was first reported in 1994 when Ranum et al[9] described a large kindred descending from President Lincoln with a "generally non–life-threatening cerebellar ataxia" that had a wide range of age at onset and mapped to the centromeric region of chromosome 11. Two other families with a similar clinical presentation and disease that was assigned to the same locus were subsequently described.[10,11] No reference was made to the presence of spasmodic cough.

The Portuguese families we have described shared some relevant features with these families with disease linked or allelic to the SCA5 locus; they had pure, benign dominant ataxias coursing with cerebellar atrophy but sparing the brainstem. In 1 patient, there were dentate calcifications, as with SCA20. On the other hand, spasmodic cough is not far from this last kindred's most characteristic feature, spasmodic dysphonia. Both represent some kind of laryngeal hyperreactivity and vagal dysfunction. Interestingly enough, SCA20 maps in the same region as SCA5. Could these 2 entities, together with autosomal dominant ataxia with spasmodic cough, correspond to different mutations of the same gene in the SCA5 locus?

In any case, the association of spasmodic coughing with dominant ataxia defines a new syndrome. Looking for previous cough episodes should thus be an obligatory step when interviewing patients with dominant ataxias.

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