neurogenetics (2019) 20:161–164
https://doi.org/10.1007/s10048-019-00580-7

SHORT COMMUNICATION

Spasmodic dysphonia as a presenting symptom of spinocerebellar ataxia type 12

Jessica Rossi[1,2] · Francesco Cavallieri[3,4] · Giada Giovannini[2] · Carla Budriesi[1,2] · Annalisa Gessani[2] · Miryam Carecchio[5] · Daniela Di Bella[6] · Elisa Sarto[6] · Jessica Mandrioli[2] · Sara Contardi[2] · Stefano Meletti[1,2]

Received: 18 April 2019 / Accepted: 25 May 2019 / Published online: 13 June 2019

Abstract

Autosomal dominant spinocerebellar ataxia (SCA) type 12 is a rare SCA characterized by a heterogeneous phenotype. Action tremor of the upper limbs is the most common presenting sign and cerebellar signs can appear subsequently. In many cases, minor signs, like dystonia, can be predominant even at onset. Laryngeal dystonia (spasmodic dysphonia) has been observed only in one case of SCA12 and never reported at disease onset. We present a 61-year-old female who developed spasmodic dysphonia followed by dystonic tremor and subsequent ataxia diagnosed with SCA12. Thus, spasmodic dysphonia can be a presenting symptom of SCA12.

Keywords Acoustic analysis · Ataxia · Dystonic tremor · Neurodegenerative · SCA12 · Spasmodic dysphonia

Introduction

Autosomal dominant spinocerebellar ataxia (SCA) type 12 is a rare SCA due to a CAG expansion (> 51 CAG) in the non-coding 5′ region of the PPP2R2B gene [1], which encodes a brain-specific regulatory subunit of the heterotrimeric serine/threonine phosphatase PP2A, implicated in the regulation of many cellular processes that involve protein phosphorylation: cell growth and differentiation, DNA replication, cellular morphogenesis and cytokinesis, regulation of kinase cascades, ion

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10048-019-00580-7) contains supplementary material, which is available to authorized users.

✉ Jessica Rossi
jessicarossi.mail@gmail.com

Francesco Cavallieri
francesco.cavallieri@unimore.it

Giada Giovannini
giovannini.giada@gmail.com

Carla Budriesi
carla.budriesi@unimore.it

Annalisa Gessani
annalisa.gessani@hotmail.it

Miryam Carecchio
mcarecchio@gmail.com

Daniela Di Bella
daniela.DiBella@istituto-besta.it

Elisa Sarto
elisa.sarto@istituto-besta.it

Jessica Mandrioli
mandrioli.jessica@aou.mo.it

Sara Contardi
scontardi@gmail.com

Stefano Meletti
stefano.meletti@unimore.it

[1] Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

[2] Unit of Neurology, AOU Modena, Modena, Italy

[3] Neuromotor & Rehabilitation Department, Neurology Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy

[4] Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

[5] Department of Neuroscience, University of Padua, Padua, Italy

[6] Medical Genetics and Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico “C. Besta”, Milan, Italy

channel function, neurotransmitter release, microtubule assembly, and apoptosis [2]. SCA12 has been firstly described in an American family of German descent and subsequently in a cluster of families from Northern India [1]. In 2010, Brussino et al. reported cases of SCA12 from two families coming from the city of Ferrara, in northeast of Italy [3]. Action tremor can be the presenting and most common sign at disease onset in SCA12, as opposed to other types of SCAs, in which ataxia often predominates at the beginning [4]. The age of onset ranges between 8 and 55 years but seems to cluster primarily between the third and fifth decades of life. During the disease course, mild cerebellar dysfunction, hyperreflexia, parkinsonian features, dystonia, psychiatric symptoms, and dementia can appear [5]. Spasmodic dysphonia has been observed only in one case of SCA12 [6] but not reported at disease onset. Here, we present a 61-year-old female who developed spasmodic dysphonia followed by dystonic tremor and subsequent ataxia in which a pathogenic CAG repeat length in the SCA12 gene was found.

Case description

A 61-year-old woman born in Ferrara province developed at the age of 50 years alteration of voice followed by head dystonic tremor. Few years later, she developed gait instability and ataxia. Later on, cognitive deterioration and depression appeared. Her paternal aunt died from an unspecified neurodegenerative disorder and two first-degree cousins developed a similar condition in their fifties. Genetic analyses for SCA1, SCA2, SCA3, and SCA6 were negative. The proband's neurological examination showed irregular dystonic tremor of the head and postural and intentional tremor of the upper limbs, mild left dysmetria during finger-to-nose testing and diffuse hyperreflexia. Stance and gait were characterized by instability, wide-based stance, and impossibility to perform tandem gait (Video). A brain MRI revealed generalized cortical and milder subcortical atrophy, particularly evident in the cerebellum and anterior-posterior diameter of the midbrain (Fig. 1a–c). Neuropsychological assessment showed executive and attentive function impairment, with deficit of learning skills for verbal and spatial material, attention, and logic processing.

Speech evaluation

Speech evaluation based on analysis of sustained phonation, diadochokinesis with repetition of alternated syllables (pa-ta-ka), spontaneous speech, reading, and count 1 to 20 was performed. Perceptual and acoustic analysis was acquired by means of the open-source Praat software® [7]. Evaluations were made at a silent voice conversation intensity (< 50 dB of background noise) and each evaluation was recorded using a microphone maintained at 20 cm from the patient's lips.

Genetic analysis

Given the clinical presentation, the family history suggesting an autosomal dominant familiarity, the provenience of the patient, and the peculiar finding of spasmodic dysphonia, CAG repeat length in the PPP2R2B gene was tested.

Results

Speech analysis

Perceptual analysis of spontaneous speech showed intermittent voice breaks, strained voice, and dysfluent effortful speech with word break or difficult to start. Involuntary disruption of phonation resulted from an instability of activity in adductor muscles [8]. The perceptual analysis of sustained phonation was comparable and revealed a reduction on phonatory duration with blockages, hard glottal attacks, strain-strangled voice quality, and breathiness. The patient could not produce sustained phonemic vowel-like sounds or voluntary change voice fundamental frequency (Fig. 1d, e). We analyzed the main acoustic parameters correlated with spasmodic dysphonia, including standard deviation of the fundamental frequency (F0SD), jitter, shimmer, fraction of locally unvoiced frames (the fraction of pitch frames that are analyzed as unvoiced), number of voice breaks, degree of voice breaks, and the total duration of the breaks between the voiced parts of the signal, divided by the total duration of the analyzed part of the signal [9–11]. Furthermore, the maximum time phonation and harmonic-to-noise ratio [12] were analyzed. Acoustic analysis showed some of the known acoustic parameters associated with spasmodic dysphonia, such as high values of F0SD, high level of jitter and shimmer, and low HNR with increased noise energy and deterioration of harmonic structure [13]. The present findings were in agreement with previous studies in that phonatory breaks, high value of F0SD reflecting laryngeal instability, and aperiodicity are major aberrant acoustic events related to the overadduction of the vocal folds in adductor spasmodic dysphonia [9, 10].

Genetic results

Genetic analysis was performed and revealed heterozygosity for an expanded allele with 61 CAG repeats confirming the diagnosis of SCA12.

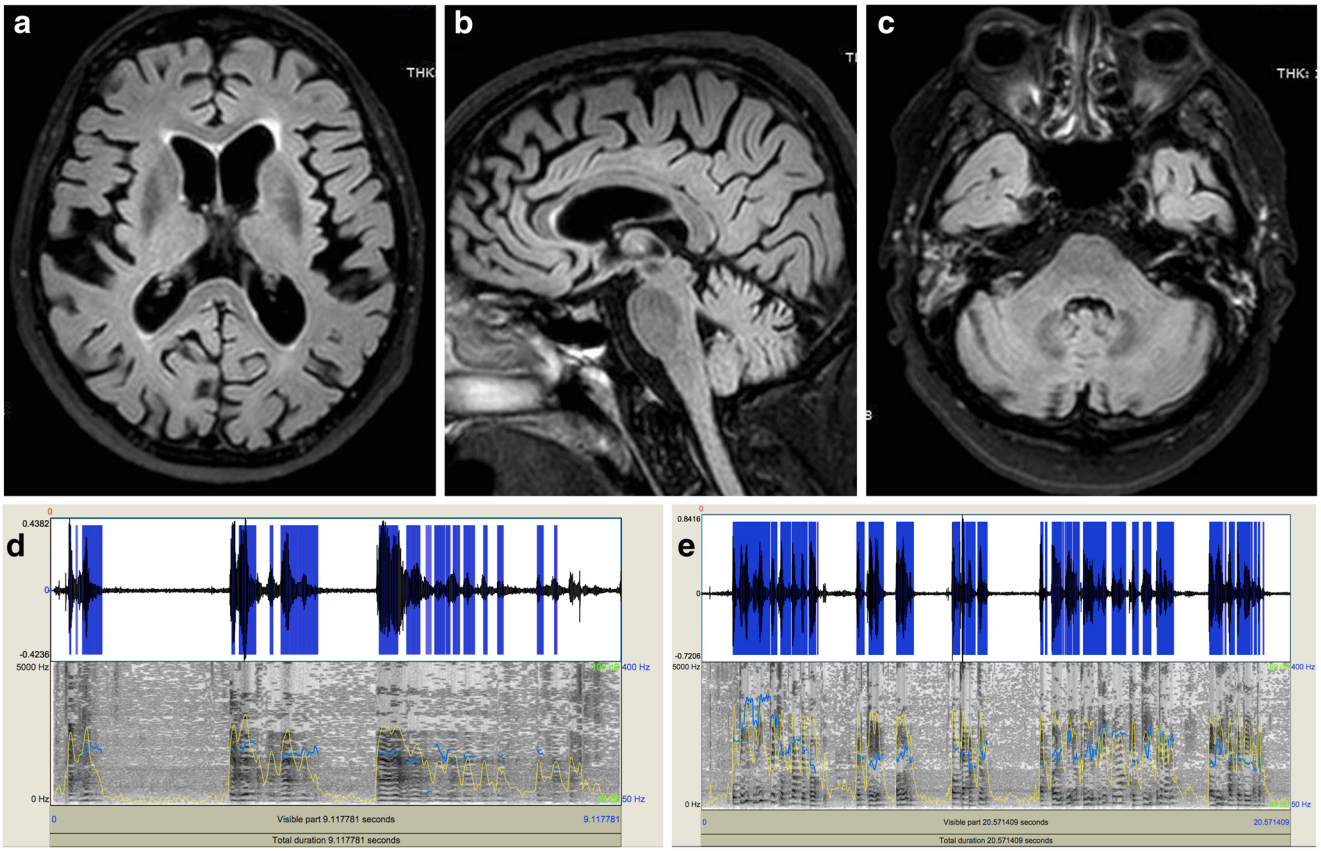

Fig. 1 **a**–**c** 3-T brain MRI shows evidence of supra- (**a**, **b**) and infratentorial (**b**, **c**) volume loss. **d**, **e** Acoustic analysis of spontaneous speech (**e**) and sustained phonation (**d**), performed with Praat software®. The upper window represents the waveform diagram; the horizontal scale represents time, while vertical scale represents sound pressure. The lower window represents the signal spectrogram; the vertical direction represents frequency, while the horizontal direction represents time. Yellow line shows the variation of signal intensity; blue line indicates pitch variations. The analysis revealed frequent voice breaks, strained and dysfluent effortful speech production consistent with spasmodic adductor dysphonia

Clinical data

Treatment with trihexyphenidyl (4 mg/day) was started and determined partial amelioration of head and upper limb tremor and spasmodic dysphonia. To date, after 12-month follow-up, the patient's conditions were unchanged with a persistent symptomatic effect of trihexyphenidyl on dystonic tremor and speech alterations.

Discussion

Compared with other SCAs, SCA12 is characterized by phenotypic variability. A low-frequency (3 Hz) postural and kinetic tremor of the upper limbs is usually the first manifestation and can be more evident during activities requiring fine motor coordination, such as writing or object manipulations [5]. The tremor is slowly progressive and tends to increase in amplitude and distribution, involving the head and neck over the course of a decade. Cerebellar dysfunction tends to be limited to upper limb dysmetria, oculomotor abnormalities, broad-based stance, and difficulty to perform tandem gait [5]. During disease progression, SCA12 patients can also manifest hyperreflexia with reappearance of primitive reflexes, dementia, and psychiatric symptoms like anxiety or depression [1]. A significant phenotypic heterogeneity has been observed in patients from different ethnic backgrounds [5]. Signs of parkinsonism are more frequent in the American court, while facial myokymia, axial dystonia, and a subclinical sensory or sensory and motor neuropathy have been described specifically in Indian courts [1]. In many cases, uncommon signs, like dystonia, can be predominant even at onset, making the diagnosis challenging. Dystonia can affect upper limbs, neck, face, and larynx, causing spasmodic dysphonia [14]. Among genetically determined dystonias characterized by laryngeal involvement, differential diagnosis includes DYT-ANO3 (DYT24), KMT2B, DYT-GNAL (DYT25), DYT-TUBB4A (DYT4), and DYT-THAP1 (DYT6) with striking laryngeal involvement [14]. Among the SCAs, spasmodic dysphonia has been described in SCA20 [15] and in SCA2 [16]. Spasmodic dysphonia in SCA12 has been described only in one patient by Ganos et al. [6] as a sign that developed late during the disease progression. In our case, spasmodic dysphonia was the presenting symptom and we were able to better

characterize it thanks to the perceptive and acoustic speech analysis. This clinical-instrumental approach allowed us to gain a better understanding of the patient's clinical phenotype and to target more accurately the genetic analysis. In conclusion, spasmodic dysphonia can be a presenting symptom of SCA12. Therefore, if laryngeal dystonia is the onset of a progressive clinical picture that includes other additional features, such as cerebellar dysfunction, hyperreflexia, parkinsonism, psychiatric symptoms, or dementia, it is indicated to think about spinocerebellar ataxia and adopt a multidisciplinary approach, in order to better define it and guide further investigations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all individual participants for whom identifying information is included in this article.

References

1. O'Hearn E, Holmes SE, Margolis RL (2012) Spinocerebellar ataxia type 12. Handb Clin Neurol 103:535–547
2. Holmes SE, Hearn EO, Ross CA, Margolis RL (2001) SCA12: an unusual mutation leads to an unusual spinocerebellar ataxia. Brain Res Bull 56:397–403
3. Brussino A, Graziano C, Giobbe D et al (2010) Spinocerebellar ataxia type 12 identified in two italian families may mimic sporadic ataxia. Mov Disord 25:1269–1291
4. Holmes SE, O'Hearn E, Margolis RL (2003) Why is SCA12 different from other SCAs? Cytogenet Genome Res 100:189–197
5. Gazulla J (2012) Spinocerebellar ataxia. 7:139–154
6. Ganos C, Saifee TA, Kassavetis P, Erro R, Batla A, Cordivari C, Bhatia KP (2014) Dystonic tremor and spasmodic dysphonia in spinocerebellar ataxia type 12. Mov Disord Clin Pract 1:79–81
7. Boersma P, Weenink D (2013) Praat: doing phonetics by computer [computer program]. Version 5.3.51, retrieved 2 June 2013 from http://www.praat.org/
8. Zwirner P, Murry T, Woodson GE (1993) A comparison of bilateral and unilateral botulinum toxin treatments for spasmodic dysphonia. Eur Arch Otorhinolaryngol 250:271–276
9. Chen Z, Li J, Ren Q, Ge P (2018) Acoustic and perceptual analyses of adductor spasmodic dysphonia in Mandarin-speaking Chinese. J Voice S0892-1997(17):30435–30436. https://doi.org/10.1016/j.jvoice.2017.12.007
10. Zwirer P, Murry T, Woodson GE (1993) Perceptual-acoustic relationship in spasmodic dysphonia. J Voice 2:165–171
11. Adams SG, Hunt EJ, Charles DA et al (1993) Unilateral versus bilateral botulinum toxin injections in spasmodic dysphonia: acoustic and perceptual results. J Otolaryngol 22:171–175
12. Esposito M, Dubbioso R, Apisa P et al (2015) Spasmodic dysphonia follow-up with videolaryngoscopy and voice spectrography during treatment with botulinum toxin. Neurol Sci 36:1679–1682
13. Cannito MP, Doiuchi M, Murry T, Woodson GE (2012) Perceptual structure of adductor spasmodic dysphonia and its acoustic correlates. J Voice 26:818.e5–818.13
14. Albanese A, Di Giovanni M, Lalli S (2019) Dystonia: diagnosis and management. Eur J Neurol 26(1):5–17
15. Mundwiler A, Shakkottai VG (2018) Autosomal-dominant cerebellar ataxias. Handb Clin Neurol 147:173–185
16. Infante J, Berciano J, Volpini V, Corral J, Polo JM, Pascual J, Combarros O (2004) Spinocerebellar ataxia type 2 with levodopa-responsive parkinsonism culminating in motor neuron disease. Mov Disord 19(7):848–852