Journal of the Neurological Sciences 397 (2019) 138–140

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Clinical short communication

Facial grimacing and clinical correlates in spinocerebellar ataxia type 3

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ARTICLE INFO

Key-Words:
Spinocerebellar ataxia type 3
Machado-Joseph disease
Oromandibular dystonia
Facial grimacing

ABSTRACT

Introduction: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is the most common spinocerebellar ataxia (SCA) worldwide. SCA3 presents with cerebellar ataxia in association with pyramidal signs, peripheral amyotrophy, nystagmus, ophthalmoparesis, fasciculations of the face and tongue, dystonia and parkinsonism. Oromandibular dystonia (OMD) with facial grimacing (FG) in SCA3 has seldom been reported in the literature and in series of SCA3 patients.
Methods: We evaluated 104 patients with SCA (59 patients with SCA3, 20 with SCA2, 20 with SCA7 and 5 with SCA6) and assessed dystonia frequency and types.
Results: Thirteen cases of SCA3, one of SCA2 and two of SCA7 had dystonia. OMD in the form of FG was present in seven SCA3 patients (11.9%). Patients with FG were significantly younger, had earlier disease onset and a significantly higher CAG repetition length when compared to the SCA3 sample. Parkinsonism, dysphagia and pyramidal signs were significantly more frequent in the FG group than the non-FG group of the SCA3 sample.
Conclusion: Patients with SCA3 presenting with FG are younger, with earlier disease onset and higher CAG repetition length. They present with parkinsonism, dysphagia and pyramidal signs more frequently than SCA3 patients without FG.

1. Introduction

Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease is the most common spinocerebellar ataxia (SCA) worldwide and is caused by a CAG repeat expansion at exon 10 of the *ATXN3* gene, located on chromosome 14q32.1. SCA3 presents with cerebellar ataxia in association with pyramidal signs, peripheral amyotrophy, extrapyramidal signs and ophthalmoparesis. Extra-cerebellar and non-motor symptoms are now widely recognized in this condition [1–3].

Oromandibular dystonia (OMD) is the second most frequent cranial dystonia with involvement of the lips, jaws and tongue, causing involuntary mouth closure or opening, deviation of the jaw and tongue movements. When the OMD predominantly affects muscles around the mouth, a pattern of facial grimacing (FG) may occur. There are many possible etiologies for OMD, including secondary processes such as drug-induced, post-anoxic, vascular and head injury-related [4,5].

In this paper, we report the frequency of OMD with FG in a large series of SCA patients, videotaped the phenomena in six individuals with SCA3, and compared the clinical correlates of SCA3 patients with FG to those without this pattern of OMD.

2. Methods

One hundred and four patients with clinically and genetically confirmed SCAs (59 with SCA3, 20 with SCA2, 20 with SCA7 and five with SCA6) were prospectively evaluated at the Federal University of Sao Paulo from 2015 to 2017. Age at onset and disease duration was documented and ataxia severity was quantified using the Scale for Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS). OMD was defined as a cranial segmental dystonia of the lips, jaw and tongue, causing involuntary mouth closure or opening, deviation of the jaw, tongue movements or any combination of these due to repetitive or sustained spasms of masticatory, facial or lingual muscles. FG was diagnosed when OMD predominantly involved the risorius, orbicularis oris and levator anguli oris. We compared clinical data and CAG repetition length in SCA3

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https://doi.org/10.1016/j.jns.2019.01.001
Received 3 December 2018; Received in revised form 27 December 2018; Accepted 1 January 2019
Available online 02 January 2019
0022-510X/

individuals with and without FG.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 18. Differences were considered significant when $p < .05$. We employed Mann-Whitney test for continuous variables and Fisher test for categorical variables. Local ethics committee approved this study.

3. Results

The demographic and molecular data from all subgroups of the sample is shown on Table 1. Dystonia was present in one case of SCA2 (5%), thirteen individuals with SCA3 (22%), and two with SCA7 (10%). Patients with SCA6 did not have any form of dystonia. The patient with SCA2 had severe cervical dystonia, while the two patients with SCA7 had generalized dystonia affecting cervical, truncal and appendicular muscles. Among those with SCA3, 12 had multifocal involvement (five with bilateral lower limb dystonia, three with OMD and bilateral lower limb dystonia, two with OMD and all four limbs dystonia and one with OMD, cervical dystonia and bilateral upper limbs dystonia) and one had focal dystonia (OMD). In total, seven patients with SCA3 (11.9%) had OMD presenting with FG (Supplementary Video 1). Table 2 summarizes clinical and demographic evaluation according to the presence or absence of FG. Patients with FG were significantly younger, had earlier disease onset and a significantly higher CAG repetition length than patients without FG. Parkinsonism, dysphagia and pyramidal signs were significantly more frequent in the FG group. Two patients were treated with botulinum toxin. Despite improvement in the dystonia, they subsequently developed prominent dysphagia. One of them ultimately had to undergo percutaneous gastrostomy, which was removed after three months.

Table 2
Comparison between the groups of patients with and without facial grimacing.

	No facial grimacing ($N = 52$)	Facial grimacing ($N = 7$)	p
Age (mean ± SD)	48.19 ± 11.18	31.86 ± 7.34	< 0.001[a,*]
Age of onset (mean ± SD)	37.69 ± 10.16	25.57 ± 4.46	0.001[a,*]
Disease duration (mean ± SD)	10.50 ± 6.49	8.14 ± 4.88	0.293[a]
Alelle 1 (mean ± SD)	20.64 ± 4.15	23.80 ± 1.30	0.122[a]
Alelle 2 (mean ± SD)	71.17 ± 4.48	74.60 ± 1.67	0.018[a,*]
ICARS (mean ± SD)	36.02 ± 15.93	42.86 ± 16.64	0.301[a]
SARA (mean ± SD)	11.74 ± 6.04	14.36 ± 7.75	0.512[a]
Gender (M/F);% Female	22/30; 57.70%	4/3; 42.85%	0.69[b]
Ophthalmoparesis N (%)	42 (84%)	5 (71.43%)	0.59[b]
Collier sign N (%)	14 (29.17%)	4 (57.15%)	0.20[b]
Amyotrophy N (%)	10 (19.2%)	4 (57.1%)	0.062[b]
Neuropathy N (%)	41 (85.41%)	6 (85.71%)	1.00[b]
Parkinsonism N (%)	12 (25%)	7 (100%)	< 0.001[b,*]
Pyramidal signs N (%)	14 (29.17%)	6 (85.71%)	< 0.001[b,*]
Dysphagia N (%)	12 (26.67%)	5 (71.43%)	0.031[b,*]

M: Male; F: Female; ICARS: International Cooperative Rating Scale; SARA: Scale for the Assessment and Rating of Ataxia; SD: standard deviation. Collier sign: bilateral or unilateral eyelid retraction; Neuropathy was defined by the presence of decreased vibration sense and reduced deep tendon reflexes in the lower limbs with or without distal amyotrophy; Parkinsonism was defined by the presence of bradykinesia combined with rigidity; Pyramidal signs were characterized by spasticity and/or hyperreflexia and/or Babinski sign.

[*] Statically significant.

[a] Mann-Whitney test.

[b] Fisher test.

4. Discussion

In this series, dystonia was more frequent in patients with SCA3 than in those with SCA2, SCA6 and SCA7. FG only occurred in SCA3, and was associated with younger age, earlier disease onset, higher number of CAG repetitions, parkinsonism, dysphagia and pyramidal signs.

Previous studies have shown that dystonia is frequent in SCA3 patients [6] and associated with earlier age of disease onset and higher CAG expansions [7,8]. In the largest Brazilian sample with SCA3 patients published to date [7], involving 381 patients, dystonia occurred in 14 patients (3.2%). Three of them had OMD. In another sample of 75 patients with SCA3 [8], dystonia was present in 21 (28%) and associated with earlier age of onset and larger CAG expansion. Two out of these 75 patients had FG, but blepharospasm and foot inversion were the most common dystonic phenotypes. In a cohort of 85 patients with SCAs 1, 2 and 3, extrapyramidal features occurred in 41 individuals (48.2%), of which 17 had SCA2 (60.7%), nine had SCA3 (52.9%) and 15 had SCA1 patients (37.5%) [9]. Dystonia was present in 13 out of the 85 cases (15.2%); more often in SCA2 (17.9%) and SCA3 (17.6%) than in SCA1 (12.5%). One patient with SCA2 and two with SCA1 had FG, but none of the SCA3 individuals displayed this feature. The authors did not find significant differences in the number of CAG repeats of the abnormal allele between those with and without extrapyramidal features [9].

The number of trinucleotides repeats could explain the low frequency of dystonia in our cohort of SCA2 patients. Among our cases the mean CAG repeats was 40.3. Correspondingly, a study of SCA2 phenotypes indicates that a median of 40 is associated with absence of dystonia [10]. Moreover, in a series of 110 patients, the mean CAG repeats in those without and with dystonia were 40.3 and 42.9, respectively [11]. The frequency of dystonic features is poorly characterized in SCA7, but craniocervical dystonia was reported in individuals with 44–67 CAG repeats [12] and a proband with 42 repeats manifested writer's cramp [13]. SCA6 rarely presents with dystonia.

Coutinho and Andrade [14] have systemized the clinical presentation of SCA3 into 3 main types. Type 1 or Joseph type is characterized by ataxia, external ophthalmoplegia, and pyramidal and extrapyramidal signs. It has an early age at onset (mean of 24.3 years) and rapid progression. Type 2 or Thomas type displays ataxia and external ophthalmoplegia with or without pyramidal and extrapyramidal signs, peripheral neuropathy and intermediate age at onset (mean of 40.5 years). Type 3 or Machado type exhibits ataxia, external ophthalmoplegia, peripheral neuropathy with or without mild pyramidal and extrapyramidal signs and late age at onset (mean of 46.8 years). Given the earlier onset and marked extrapyramidal signs, all seven patients with SCA3 of our series who presented with FG can be

Table 1
Demographic and molecular data of all subgroups of spinocerebellar ataxia patients.

SCA type	Number of patients	Female sex (%)	Mean age at onset (range)	Mean age (range)	Mean disease duration (range)	Mean number of CAG repeats (range)
2	20	50	32.6 (15–50)	43.6 (26–65)	11.0 (1–26)	40.3 (34–46)
3	59	56	36.2 (29–47)	46.2 (34–58)	10.2 (4–16)	71.6 (67–76)
6	5	100	57.2 (50–70)	71.8 (58–90)	14.6 (2–25)	22.0 (18–24)
7	20	60	28.5 (10–51)	33.0 (13–56)	5.4 (1–15)	50.3 (41–67)

classified as type 1. We noted a very high prevalence of parkinsonism (100%) and pyramidal signs (85.7%) in SCA3 patients with FG as compared to the SCA3 patients without FG (25% and 29.1%, respectively).

The presence of movement disorders in patients with SCA is a presumed sign of degeneration of other brain areas in addition to the cerebellum [15]. In a volumetric magnetic resonance imaging study, Nunes et al. [8] identified atrophy in the pre- and paracentral cortices and disproportionally atrophic thalami, cerebellar white matter and ventral diencephalon in SCA3 patients with dystonia when compared to those without it.

We conclude that FG is associated with younger age, lower age at disease onset, higher CAG repeats and other neurological manifestations, namely dysphagia, parkinsonism and pyramidal signs. SCA3 should be included among the other etiologies of neurodegenerative diseases presenting OMD with FG, such as progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, Wilson's disease, neuroacanthocytosis, neuroferritinopathy, neurodegeneration with brain iron accumulation, Lesch-Nyhan syndrome, GM3 gangliosidosis, Niemann-Pick disease Type C and hypermanganesemia with dystonia, polycythemia and cirrhosis. Other authors possibly did not use FG when describing lower face dystonia in SCA, which would explain a lower incidence of this feature in previous series of SCA3 patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.01.001.

Authors' roles

1. Case report project: A. Conception, B. Organization, C. Execution;
2. Genetic testing: A. Conception, B. Execution;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Vale, TC: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).
Pedroso, JL: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).
Rezende Filho, FM: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).
Braga-Neto, P: 1B, 1C, 3B.
Barsottini, OG: 1A, 1B, 1C, 3A, 3B (Nothing to disclose).

Conflict of interest

We have no conflict of interest relevant to this work.

Financial disclosure

No specific funding was received for this work.

Financial disclosure for the last 12 months

The authors declare that there are no additional disclosures to report.

Ethical statement

Full consent was obtained from the patient for the case report publication. Authors have read the Journal's Ethical Publication Guidelines.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patients have consented to the publication of the videos accompanying this manuscript. We declare no conflicts of interest and no financial support for this work.

References

[1] J. van Gaalen, P. Giunti, B.P. van de Warrenburg, Movement disorders in spinocerebellar ataxias, Mov. Disord. 26 (5) (2011) 792–800.
[2] L. Schols, S. Peters, S. Szymanski, R. Kruger, S. Lange, C. Hardt, O. Riess, H. Przuntek, Extrapyramidal motor signs in degenerative ataxias, Arch. Neurol. 57 (10) (2000) 1495–1500.
[3] J.L. Pedroso, M.C. Franca Jr., P. Braga-Neto, A. D'Abreu, M.L. Saraiva-Pereira, J.A. Saute, H.A. Teive, P. Caramelli, L.B. Jardim, I. Lopes-Cendes, O.G. Barsottini, Nonmotor and extracerebellar features in Machado-Joseph disease: a review, Mov. Disord. 28 (9) (2013) 1200–1208.
[4] H.A. Jinnah, S.A. Factor, Diagnosis and treatment of dystonia, Neurol. Clin. 33 (1) (2015) 77–100.
[5] R.O. Maciel, J.L. Pedroso, O.G. Barsottini, Facial grimacing as a clue for the diagnosis of GM1 type 3 gangliosidosis, Arq. Neuropsiquiatr. 69 (2B) (2011) 406–407.
[6] A. Moro, R.P. Munhoz, M. Moscovich, W.O. Arruda, S. Raskin, H.A. Teive, Movement disorders in spinocerebellar ataxias in a cohort of Brazilian patients, Eur. Neurol. 72 (5–6) (2014) 360–362.
[7] L.M.P. Catai, C.H.F. Camargo, A. Moro, G. Ribas, S. Raskin, H.A.G. Teive, Dystonia in patients with spinocerebellar ataxia 3 - machado-joseph disease: an underestimated diagnosis? Open Neurol. J. 12 (2018) 41–49.
[8] M.B. Nunes, A.R. Martinez, T.J. Rezende, J.H. Friedman, I. Lopes-Cendes, A. D'Abreu, M.C. Franca Jr., Dystonia in Machado-Joseph disease: clinical profile, therapy and anatomical basis, Parkinsonism Relat. Disord. 21 (12) (2015) 1441–1447.
[9] K. Jhunjhunwala, M. Netravathi, M. Purushottam, S. Jain, P.K. Pal, Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3, J. Clin. Neurosci. 21 (6) (2014) 1002–1006.
[10] T.L. Monte, F.S. Pereira, E.D.R. Reckziegel, M.C. Augustin, L.D. Locks-Coelho, A.S.P. Santos, J.L. Pedroso, O. Barsottini, F.R. Vargas, M.L. Saraiva-Pereira, L.B. Jardim, N. Rede, Neurological phenotypes in spinocerebellar ataxia type 2: Role of mitochondrial polymorphism A10398G and other risk factors, Parkinsonism Relat. Disord. 42 (2017) 54–60.
[11] G. Cancel, A. Durr, O. Didierjean, G. Imbert, K. Burk, A. Lezin, S. Belal, A. Benomar, M. Abada-Bendib, C. Vial, J. Guimaraes, H. Chneiweiss, G. Stevanin, G. Yvert, N. Abbas, F. Saudou, A.S. Lebre, M. Yahyaoui, F. Hentati, J.C. Vernant, T. Klockgether, J.L. Mandel, Y. Agid, A. Brice, Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families, Hum. Mol. Genet. 6 (5) (1997) 709–715.
[12] Y. Lin, J.Y. Zheng, Y.H. Jin, Y.C. Xie, Z.B. Jin, Trinucleotide expansions in the SCA7 gene in a large family with spinocerebellar ataxia and craniocervical dystonia, Neurosci. Lett. 434 (2) (2008) 230–233.
[13] N. Gaillard, G. Castelnovo, A. Brice, P. Labauge, Writer's cramp secondary to spinocerebellar ataxia type 7, Rev. Neurol. (Paris) 163 (5) (2007) 589–591.
[14] P. Coutinho, C. Andrade, Autosomal dominant system degeneration in Portuguese families of the Azores Islands. A new genetic disorder involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions, Neurology 28 (7) (1978) 703–709.
[15] M. Bologna, A. Berardelli, The cerebellum and dystonia, Handb. Clin. Neurol. 155 (2018) 259–272.