Management of oromandibular dystonia on a chorea acanthocytosis: a brief review of the literature and a clinical case

Maria Cecilia Pesce Ortega DDS¹,²,⁴, Nicolás Patricio Skármeta DDS¹,²,⁵ and Yaglyn Jarpa Diaz DDS³

¹Faculty of Medicine Clínica Alemana Santiago, Universidad Desarrollo, Santiago, Chile, ²Department of TMD and Orofacial Pain, Dental School of Medicine, Clínica Alemana Santiago – Universidad del Desarrollo, Santiago, Chile, ³Universidad Autonoma, Santiago, Chile, ⁴Institution Director of Advance Occlusion Program, Universidad del Desarrollo, ⁵Clinical Coordinator of Advance Occlusion Program Universidad del Desarrollo.

Background: Chorea acanthocytosis is an extremely rare neurodegenerative condition characterized by neuropsychiatric disturbances, movement disorders, neuropathy, seizures, and acanthocytosis. In this case report, the authors will present the management of the oromandibular movement disorders associated with this disease.

Case Description: This case report describes the focal management of the severe orofacial manifestations associated with this condition. The therapeutic approach adopted to reduce the severe oromandibular movements, dysphagia, and the numerous oral ulcers was selective electromyography (EMG)-guided botulinum toxin application to the inferior head of the lateral pterygoid muscles and masseters. This would be applied to control severe and sudden oromandibular dystonia.

Results: Through this procedure, the authors were able to reduce these severe oral manifestations, which had a major impact on the patient’s quality of life, and temporarily improve vital functions, such as mastication, deglutition, and speech articulation.

Conclusions: Electromyography-guided botulinum toxin application may be a useful tool in the multimodal management of this condition.

Keywords: Chorea acanthocytosis, Movement disorders, Oromandibular dystonia, Electromyography, Botulinum toxin, Neurodegenerative diseases

Introduction

Chorea-acanthocytosis (ChAc) is an extremely rare neurodegenerative disease, inherited by an autosomal recessive pattern with reduced penetrance. It is produced by the mutation of the VPS13A gene, which provides the codification to the protein chorein, which is believed to play an important role in the transportation of molecules through the cellular membrane.¹,²

Chorea-acanthocytosis belongs to a group of genetically diverse conditions called neuroacanthocytosis, which feature movement disorders, progressive neurological degeneration, and the appearance of acanthocytes-type red blood cells (usually 5–50% of the red cells population).³

The prevalence and incidence of this condition still remains unknown, with only 200 existing cases confirmed worldwide. However, it has been estimated that there may be around 1000 cases worldwide because of misdiagnosis of the condition.⁴

The clinical manifestations of ChAc usually begin in early to mid-adulthood, starting with psychiatric disorders, such as personality changes, depression, obsessive compulsive disorder, lack of self restraint, inability to take care of oneself, and even dementia.⁵

Once the primary clinical onset is established, cognitive decline and orofacial dystonia commonly follows. Chorea-acanthocytosis patients may also experience epileptic seizures (about 40% of the cases), and self-inflicted buccal and lingual injuries produced by the uncontrolled oromandibular movements.⁶,⁷ Progressive lingual
Dystonia is also common, altering the function of the motor-speech system (dysarthria) and deglutition (dysphagia). It is also likely that patients may experience other peripheral neuropathies, such as distal amyotrophy and progressive loss or absence of reflexes.

The phenotypic manifestation of this condition is very similar to X-linked recessive McLeod’s neuroacanthocytosis and other conditions, such as Huntington's disease, Juvenile Parkinsons, Tourette’s, and Pantothenate kinase-associated neurodegeneration. Moreover, blood analyses may not always be useful in identifying spiked-type blood cells. Neuroimaging findings, such as atrophy of the caudate nuclei, dilatation of anterior horns of the lateral ventricle, basal ganglia, and putamen alterations, are frequently seen in other conditions as well.

Therefore, absence of formal diagnostic criteria and of an established guide of obligatory findings, added to the low reliability of clinical grounds, dictates that protein-based tests or molecular genetic testing (like a Western Blotting) should be completed to get an accurate diagnosis of ChAc.

Treatment is purely symptomatic and should be focused on a multimodal approach; it may include feeding assistance, speech therapy, mechanical protective devices, and pharmacological treatment for epilepsy and behavioral disorders.

In this article, the authors will present a report of the clinical management of the oromandibular dystonia associated with ChAc.

Case Report
A 35-year-old woman diagnosed with ChAc was referred to an Orofacial Pain Unit. The patient presented with a medical family history of healthy non-consanguineous parents and an older brother diagnosed with ChAc in 2006. At consultation, the main complaint was the presence of severe clenching/grinding produced by rapidly and abrupt dystonic uncontrollable oromandibular movements, and stereotypic orofacial movements consisting of facial grimacing and blepharospasms. Trouble with food mastication, speech articulation, and the appearance of multiple and repeated oral ulcers because of the irrepresible mandibular movements were also part of the patient’s clinical manifestations.

In this particular case, the early clinical manifestations began in 1998 with slight personality changes and diurnal teeth grinding. A few years later, the patient started with epileptic seizures and mild involuntary movements that kept progressing until she was unable to work. In 2010, the diagnosis of ChAc was confirmed through Western Blot testing, revealing the absence of expression of the protein chorein. This was supplemented with consistent blood work and MRI findings. Since then and until the referral, the patient complied with symptomatic medical treatment, consisting of an anxiolytic (2 mg of clonazepam per day) and an antiepileptic (100 mg of lamotrigine per day) and 24 hours a day/7 days a week-wear oral appliance.

In spite of treatment, one of the major concerns of the patient was frequent and numerous oral ulcers and the progressive and systematic aggravation of the involuntary orofacial dystonic movements (Figures 1–3).

To assess the severity and duration of the movement disorders, the authors used the Unified Dystonia Rating Scale (UDRS) (See Supplement 1), because it includes a more detailed assessment of the orofacial area. The authors also used a brief evaluation questionnaire to assess
Pesce Ortega et al. Oromandibular dystonia on a chorea acanthocytosis

Figure 2 Orofacial dyskinesia.

Figure 3 Blepharospasms.

the patients’ impression of change, using a Global Rating Change Scale (GRC).18 (See Supplement 2).

A video in resting position was recorded following UDRS’s protocol19 to assess the amount of involuntary orofacial/oromandibular dystonias.

Furthermore, the most predominant movements during these events were facial grimacing and blepharospasms triggered by swallowing, and dystonic oromandibular laterotusive abrupt movements with sustained clenching/grinding (Table 1).

Based on a careful analysis of the movement disorder observed, an electromyography (EMG)-guided application of onabotulinum toxin (BOTOX®, Irvine, CA, USA) was administered to the inferior head of lateral pterygoid muscles (ILPM). Also, Botox® applications were administered to both masseters, and the oral appliance was replaced.

Allergan’s Electromyograph Signal Amplifier® (Irvine, CA, USA) was used to determine the location of the ILPM. Once it located the puncture site (Figure. 4), a needle-electrode was inserted 3–4 cm until it was in contact with muscle, which was corroborated using the EMG through isometric contraction of the ILPM by asking the patient to do a counter-resistance protrusive movement (Figure 5). After the correct positioning of the electrode was finally established, 35U of BoTox® were injected through the needle electrode per ILPM (Figure. 6). Another 15U were injected per masseter, concluding the treatment with the oral appliance.

Table 1 Before onabotulinum toxin application.

| Motor severity | Duration* | Total |
|----------------|-----------|-------|
| Eyes and upper face | 3 | 2.5 | 5.5 |
| Lower face | 2 | 1.5 | 3.5 |
| Jaw and tongue | 3 | 3.5 | 6.5 |
| Larynx | 1 | 0.5 | 1.5 |
| Neck | 0 | 0 | 0 |
| Overall rating | 17 | |

Table illustrates the severity and duration of the dystonia on the craniocervical region using UDRS, prior to the onabotulinum toxin application. Motor severity is scored from 0 (none) to 4 (extreme). Duration is scored from 0 (none) to 4 (Constant with predominance maximal intensity movements).

CRANIO®: The Journal of Craniomandibular & Sleep Practice 2016 VOL. 34 NO. 5

Figure 4 Shows the location of the needle insertion between the following anatomic landmarks: the lower border of the zygomatic arch, the posterior border of the coronoid process, and the anterior border of the condylar neck.
The reevaluation of the patient was scheduled 2, 4, 6, 12, and 16 weeks after the Botox® application. During these evaluations, the authors noticed a substantial decrease of severity and suddenness of the movement disorder, and an important improvement on the patient's impression of change (Tables 2 and 3). At week 12, after initial onabotulinum toxin application, the procedure was repeated using the same doses without any adverse effects. No further controls were scheduled because the patient died unexpectedly from a cardiac arrest, possibly related to ChAc.

**Discussion**

So far, there is no curative or disease-modifying treatment available for ChAc, and the management remains purely symptomatic. All neuroacanthocytosis are relentlessly progressive and eventually fatal. Chorea-acanthocytosis runs a chronic progressive course, often leading to major disability within a few years. Life expectancy is short, with an age of death ranging from 21 to 68 years. Therefore, recognition of the treatable complications of this disease is the most important aspect in the management of the condition, especially when these complications can have a major impact upon the quality of life. Anxiolytics or antidepressants may be effective in the treatment of neuropsychiatric manifestations, and seizures are usually responsive to standard anticonvulsants.

The movement disorders presented in this condition can be categorized as hyperkinetic disorders (excessive and abnormal involuntary movements).

Hyperkinetic movement disorders include tremors, dystonia, chorea, tics, tardive dyskinesia, and myoclonus, among others. In this particular case, the most predominant involuntary movements were oromandibular dystonia and blepharospasms, also known in the literature as Meige's syndrome.

Dystonia is defined as a neurological disorder dominated by a sustained muscle contraction that causes repetitive and patterned abnormal movements. It can be presented as slow sustained spasms, or rapid and jerky-like movements. The hyperkinetic phenomenology of

| Motor severity | Duration | Total |
|----------------|----------|-------|
| Eyes and upper face | 1 | 0.5 | 1.5 |
| Lower face | 0 | 0 | 0 |
| Jaw and tongue | 1 | 0 | 0 |
| Larynx | 1 | 0 | 0 |
| Neck | 0 | 0 | 0 |

*Duration is scored from 0 (none) to 4 (constant with predominance of maximal intensity movements).
neuroacanthocytosis is highly variable, and the diagnosis should focus on the accompanying findings, more than the rhythmicity or nature of the movements.  

Pharmacological treatments of dystonia, except for chemodenervation, is poorly documented, and no evidence-based recommendations can be made to guide prescribing. Most treatment studies done on neuroacanthocytosis patients were undertaken in Huntington's disease using neuroprotective schemes for symptomatic control of the condition. In this perspective, the most promising therapeutic approach in Huntington's disease-associated chorea is the use of tetrabenazine, which produces selective depletion of dopamine in nerve terminals. However, there is not enough evidence to support this therapeutic approach in ChAc.

The therapeutic use of botulinum toxin in hyperkinetic movement disorders is well documented and proven to be effective in reducing focal dystonia, spasms, and spastic movement disorders. The action mechanism of botulinum toxin is common to all its serotypes, interfering with neural transmission by blocking the release of acetylcholine (Ach), which is the principal neurotransmitter of the neuromuscular complex. The toxin acts in the presynapses of the motor neurons, producing muscle paralysis, by the chemodenervation of the neuromuscular junction.

One of the most important aspects of the use of botulinum toxin is the correct determination of the muscular group affected in the movement disorder. Intramuscular injection is determined based on clinical evaluation and patient information, but is not always an accurate method. Electromyography is a very helpful tool in identifying deep muscle groups not noticeable by inspection or palpation, and allows the practitioner to perform a selective intramuscular puncture in deep muscles with abnormal activity, averting other muscular groups that may not be affected in the disorder.

To record the electrical activity of the muscle, the practitioner must consider that there are many hundreds of muscle fibers belonging to a single motor unit and distributed widely throughout the cross section of the muscle. Consequently, to have an effective pick-up region with the electrode, the needle must transfix over four to six fibers of a single motor unit. In this case report, the detection of the ILPM, located in the deep infratemporal region, was made with the needle electrode, because of the impossibility of noticing the muscle through palpation or inspection. Once the correct location was established, the ILPM Botox® injection was given.

In previous reports, the assessment of the severity and functional difficulties produced by oromandibular dystonia were also made through subjective methods, featuring video recordings, and VAS scores to evaluate disability and effectiveness of the treatment. Improvement of oromandibular lateral and protrusive dystonic movements is mainly because of the rigid limitation of horizontal movements, in which ILPM is most important. Reports that there are no significant side effects to ILPM botulinum toxin application, and the ability of patients to masticate or swallow was unaltered.

There are no other reports of similar interventions on this condition; thus, there is no certainty of the long-term permanence or effectiveness of the treatment. Hsiung et al., in a 10-year follow-up study, suggests that long-term botulinum toxin applications are safe for focal treatment on various movements disorders, and adverse reactions are minor. For this reason, a rigorous follow-up with periodic assessments using the same evaluation methods will be programmed. Future applications will be rescheduled when signs and symptoms start reappearing or if an increase of disability is noticed.

Conclusions
The case described illustrates how the use of EMG-guided botulinum toxin application can be incorporated as a useful tool in the multimodal management of this rare condition. Furthermore, the clinical improvement presented by the patient after the toxin application highlights the importance of identifying the correct muscle group involved in the movement disorder, and how focal therapy can temporarily improve vital functions, such as mastication, deglutition, and speech.

Supplementary material
The supplemental material for this paper is available at http://dx.doi.org/10.1179/2151090315Y.0000000027

Disclaimer Statements
Contributors All the authors contributed to the patient’s care and preparation of the manuscript.

Funding None.

Conflict of interest None of the authors have conflict of interest.

Ethics approval None.

Patient consent Obtained.

Acknowledgements
To Magdalena Reynolds.

References
1 Bader B, Velayos-Baeza A, Walker RH, Danek A. Dominant transmission of chorea-acanthocytosis with VPS13A mutations remains speculative. Acta Neuropathol. 2009;117(1):97–8.
2 Velayos-Baeza A, Lévecque C, Dobson-Stone C, Monaco AP. The function of chorein. In: Walker RH, Saiki S, Danek A, editors. Neuroacanthocytosis syndromes II. Berlin: Heidelberg: Springer; 2008, p. 87–105.
3 Ichiba M, Nakamura M, Kusumoto A, Mizuno E, Kurano Y, Matsuda M, et al. Clinical and molecular genetic assessment of a chorea-acanthocytosis pedigree. J Neurol Sci. 2007;263(1-2):124–32.
4 Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. Orphanet J Rare Dis. 2011;6:68.
5 Danek A, Jung HH, Melone MAB, Rampoldi L, Broccoli V, Walker RH. Neuroacanthocytosis: new developments in a neglected group of dementing disorders. J Neurol Sci. 2005;229(2-3):171–85.
6 Organizing Committee, Andermann E, Danek A, Irvine G, Jung HH, Rampoldi L, et al. Second International Neuroacanthocytosis Symposium: expanding the spectrum of choreatic syndromes: Montreal Neurological Hospital and Institute. April 17-19. Mov Disord. 2005;20(12):1673–94.
7 Scheid R, Bader B, Ott DV, Merkenschlager A, Danek A. Development of mesial temporal lobe epilepsy in chorea-acanthocytosis. Neurology. 2009;73(17):1419–22.
8 Fontenelle LF, Leite MAA. Treatment-resistant self-mutilation, tics, and obsessive-compulsive disorder in neuroacanthocytosis: a mouth guard as a therapeutic approach. J Clin Psychiatry. 2008;69(7):1186–7.
9 Bader B, Walker RH, Vogel M, Proesigel M, McIntosh J, Danek A. Tongue protrusion and feeding dystonia: a hallmark of chorea-acanthocytosis. Mov Disord. 2010;25(1):127–9.
10 Schneider SA, Lang AE, Bader B, Danek A, Bhatia KP. Characteristic head drops and axial extension in advanced chorea-acanthocytosis. Mov Disord. 2010;25(10):1487–91.
11 Rampoldi L, Danek A, Monaco A. Clinical features and molecular bases of neuroacanthocytosis. J Mol Med. 2002;80(8):475–91.
12 Walterfang M, Looi JCL, Styn M, Walker RH, Danek A, Niethammer M, et al. Shape alterations in the striatum in chorea-acanthocytosis. Psychiatry Res. 2011;192(1):29–36.
13 Prohaska R, Sihon OCM, Rudnicki DD, Danek A, Hayflick SJ, Verhaag EM, et al. Brain, blood, and iron: perspectives on the roles of erythrocytes and iron in neurodegeneration. Neurobiol Dis. 2012;46(3):607–24.
14 Walker RH, Jung HH, Dobson-Stone C, Rampoldi L, Sano A, Tison F, et al. Neurologic phenotypes associated with neuroacanthocytosis. Neurology. 2007;68(2):92–8.
15 Dobson-Stone C, Rampoldi L, Bader B, Velayos Baeza A, Walker RH, Danek A, et al. Chorea-acanthocytosis. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong C-T, eds. GeneReviews®. Seattle (WA): University of Washington; 1993.
16 Walker RH, Danek A, Dobson-Stone C, Guerrini R, Jung HH, Lafontaine A-L, et al. Developments in neuroacanthocytosis: expanding the spectrum of choreatic syndromes. Mov Disord. 2006;21(11):1794–805.
17 Comella CL, Leurgans S, Wuu J, Stebbins GT, Chmura T. Rating scales for dystonia: a multicenter assessment. Mov Disord. 2003;18(3):303–12.
18 Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther. 2009;17(3):163–70.
19 Burke RE, Fahm S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology. 1985;35(1):73–7.
20 Karkheiran S, Bader B, Roohani M, Danek A, Shahidi GA. Chorea-acanthocytosis: report of three cases from Iran. Arch Iran Med. 2012;15(12):780.
21 Al-Ashmi A, Jansen AC, Badhwar A, Dubeau F, Tampieri D, Shustik C, et al. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. Epilepsia. 2005;46(8):1256–63.
22 Le Doux MS. Meige syndrome: what's in a name? Parkinsonism Relat Disord. 2009;15(7):483–9.
23 Jankovic J. Treatment of hyperkinetic movement disorders. Lancet Neurol. 2000;9(9):844–56.
24 Cardoso F, Seppi K, Mair KJ, Wenning GK, Poewe W. Seminar on chorea. Lancet Neurol. 2006;5(7):589–602.
25 Albanese A, Barnes MP, Bhatia KP, Fernandez-Alvarez E, Filippini G, Gasser T, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES task force. Eur J Neurol. 2006;13(5):433–44.
26 Adam OR, Jankovic J. Symptomatic treatment of Huntington disease. Neurother J Am Soc Exp Neurother. 2008;5(2):181–97.
27 Jankovic J. Disease-oriented approach to botulinum toxin use. Toxicon. 2009;54(5):614–23.
28 Hallett M, Benecke R, Blitzer A, Comella CL. Treatment of focal dystonias with botulinum neurotoxin. Toxicon. 2009;54(5):628–33.
29 Simpson L. The life history of a botulinum toxin molecule. Toxicon. 2013;68:40–59.
30 Mills KR. The basics of electromyography. J Neurol Neurosurg Psychiatry. 2005;76(Suppl_2):ii32–5.
31 Møller E, Bhatia KP, Fernandez-Alvarez E, Filippini G, Gasser T, et al. Treatment of perioral dystonia with botulinum toxin in 4 cases of Meige's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(5):544–9.
32 Møller E. The chewing apparatus. An electromyographic study of the action of the muscles of mastication and its correlation to facial morphology. Acta Physiol Scand Suppl. 1966;280:1–229.
33 Møller E, Bhatia M, Wackenfelt S, Regeur L. Treatment of perioral dystonia with botulinum toxin in 4 cases of Meige's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(5):544–9.
34 Hsiung G-YR, Das SK, Ranawaya R, Lafontaine A-L, Suchowsky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord. 2002;17(6):1288–93.