PRDOA 5 (2021) 100106

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Breathing dystonia in Meige syndrome

Natalie Anne Watson, Lucy Anne Hicklin, Marie-Helene Marion *

Ear, Nose & Throat Department, St George's Hospital, London, United Kingdom

ARTICLE INFO

Keywords:
Breathing dystonia
Meige syndrome
Dyspnoea
Respiratory
Supra-hyoid muscles
Laryngeal dystonia

ABSTRACT

Background: Dyspnoea is rarely mentioned in the clinical description of adult-onset isolated dystonia. In this study, we present the clinical features of 13 patients with Meige syndrome (cranio-cervical dystonia) with breathing difficulties.

Methods: A retrospective case note review was performed of patients presenting with Meige syndrome and shortness of breath, to a neuro-laryngology MDT clinic.

Results: Some patients were severely limited by their breathlessness, but others did not volunteer these symptoms. The majority of patients were referred with the assumption that the larynx was the cause of the problem; however half the patients did not have evidence of laryngeal involvement. Of the patients who had laryngeal involvement, injecting the larynx alone did not always relieve the dyspnoea. The majority of our patients responded to injection of the suprahyoid muscles, including genioglossus, digastric and mylohyoid.

Conclusion: We recommend routinely establishing if the patient with Meige syndrome has signs or symptoms of breathlessness, and establishing the level of the problem, as this can be treated successfully.

1. Introduction

Our joint neuro-laryngology MDT clinic for head and neck movement disorders receives referrals with unexplained breathing problems. Most of the patients are severely affected to limit their physical activity; some have been treated for asthma without benefit and the chest physicians will have examined most and no cause for the breathing problem identified by standard tests.

For this study, we did not include patients with isolated spasmodic dysphonia (SD), laryngeal breathing dystonia due to tardive dystonia, multiple system atrophy, functional diagnoses or other neurological disorders, instead focusing on breathing dystonia related to Meige syndrome.

We present a series of 13 patients with Meige syndrome and dyspnoea. We describe the clinical phenotypes, response to treatment and review the literature.

2. Methods

A retrospective case note review was performed of patients presenting with Meige syndrome and shortness of breath, to a neuro-laryngology MDT clinic, which involves a neurologist (MHM) specialising in movement disorders and an ENT surgeon (LAH), with expertise in cranial and laryngeal dystonia, at a teaching hospital, from 2016 to 2020. The patients were considered to have breathing dystonia if they had a sensation of difficulty in breathing in association with their other symptoms that prevented them from certain activities of daily living. Neurologists or respiratory physicians referred patients, as no cause for dyspnoea was found, or as non-responders to treatment, such as broncho-dilatators. Patients underwent clinical evaluation of their dystonia including laryngoscopy, which allowed inspection of the larynx and supra-glottic area. The patient's description of their breathlessness, when it occurs (at rest, on exertion or while speaking) and the perceived level of obstruction guided our examination and therapeutic strategy. A treatment regimen was then established with botulinum toxin A (BoNT-A) injected into involved muscles with adjunct medication if indicated. All patients received BoNT-A (incobotulinumtoxinA or abobotulinumtoxinA) typically 10–30 u of abobotulinumtoxinA per muscle in the suprahyoid muscles depending on the examination, previous benefit and side effects. The protocol was varied depending on outcome until the ideal protocol was found (Table 2).

Follow up was performed at intervals dictated by patient need, usually at 12–16 weeks. All patients were asked to rate their symptoms including breathlessness from 0 to 100% at follow up visits (0 = no improvement to 100% = back to normal) although this is a subjective measure the patients will usually offer additional evidence such as

* Corresponding author.
E-mail address: dr.mhmarion@londonbtxcentre.co.uk (M.-H. Marion).

https://doi.org/10.1016/j.prdoa.2021.100106
Received 3 July 2021; Received in revised form 8 August 2021; Accepted 23 August 2021
Available online 28 August 2021

return to their normal activities of daily living. All patients are also asked about side effects at each visit with specific attention to dysphagia as this is known to be a potential side effect of injection of neck muscles.

3. Results

13 patients with Meige syndrome and breathing difficulties were identified. The clinical features of the cohort are summarised (Tables 1 & 2). There was a female predominance (11/13), age of onset averaged 57 years (range 42–72).

We found six patients with laryngeal involvement; four had adductor spasmodic dysphonia (SD), two had intermittent stridor.

Among the 13 Meige patients, all patients, except one, had clinical signs of supra-hyoid muscles involvement such as rhythmic movements of the submental muscles described as a "frog-like" movement (video 1), "double chin" posture, with posterior sagittal shift of head on neck [1], and so called "Donald duck" voice due to involvement of the base of tongue (genioglossus). We did not have any patients with isolated or associated chest and diaphragmatic dysfunction.

All patients received BoNT-A injections into the affected muscles (Table 2). The entire laryngeal group had injections into the larynx, however this did not improve the dyspnoea, except in one patient with stridor. In all patients, except one with only laryngeal injections, injection of at least one suprahyoid muscle was performed. Following treatment, 11 patients had a dramatic clinical improvement (50–90%) in dyspnoea and three patients rated their improvement at 50% or less. Side effects were seen in two patients with transient dysphagia and two had transient dysphonia all of which did not require medical intervention.

4. Discussion

Dyspnoea is rarely mentioned in the clinical description of adult onset isolated dystonia [2]. The main focus of breathing difficulties in dystonic patients has been on inspiratory laryngeal dystonia [3–7], since laryngeal stridor with immobile VC was first recognised as being dystonic and not paralytic in dystonic patients [3,4].

Marsden and Sheehy [8] found in a cohort of 53 patients with Meige syndrome, respiratory difficulties in 7%, thought to be due to dystonic spasm affecting the respiratory muscles. In a small number of patients with adult onset dystonia, dyspnoea has been studied with functional respiratory tests [9] and with electrophysiological recordings of the respiratory muscles [10]. They showed respiratory upper airway or diaphragmatic dysfunction.

However, chest and diaphragmatic dysfunction as a cause of breathing dystonia have been described in only one isolated case [11] and, in a 900 patient review [12], only in two patients with a combination of adductor spasmodic dysphonia and paradoxical diaphragmatic and abnormal chest wall movement.

As is typical in Meige syndrome [13,14], all our patients developed an initial focal dystonia (including BSP), which progressively spread to involve the tongue muscles, pharynx and larynx, all of which can contribute to narrowing of the airway and hence dyspnoea. The anatomical distribution of muscle involvement (Table 2) demonstrated dystonic contractions at many different levels, which makes the analysis of the dystonia complex. The dystonic spasms are task specific and variable, so may not be seen on laryngoscopy. Accurate analysis of the symptoms and clinical observation of patients performing triggering tasks is essential.

We accept that the cohort described is subject to potential bias as referrals to our clinic selected those with swallowing, speaking, breathing difficulties or anterocollis posture, in addition to BSP. We cannot comment on the prevalence of dyspnoea in a "standard" Meige syndrome population; however, we suspect breathing difficulties may be under-reported, as such symptoms may not be the primary focus at presentation.

In our cohort, most of the patients with laryngeal involvement had spasmodic dysphonia and only 2 had true respiratory laryngeal involvement with inspiratory stridor on exercise. The laryngeal phenotype with Adductor SD responded well to BoNT-A injection into the larynx, with the majority (5/6) reporting a response of greater than 50% improvement in their symptoms, however 5/6 patients were also injected in the suprahyoid muscles. Patients may have spasmodic dysphonia, as part of their dystonia complex, but this may not be the cause of their breathlessness.

Of the two patients with stridor, one had a good response but was injected in the larynx and base of tongue; the other patient was only injected in the larynx and did not experience any improvement.

Mention should be made of another concept in this area. Inducible laryngeal obstruction (ILO) is described as inappropriate, transient, reversible narrowing of the larynx in response to exercise and anxiety [15]. Failed responders in both groups may share common factors with ILO. The high levels of anxiety in dystonic patients [16] may contribute to the triggering of an ILO-like reaction. Recognising the features of ILO is clinically important, as patients may benefit from respiratory physiotherapy and speech and language input, rather than BoNT-A.

54% of our dystonic patients with respiratory difficulties did not have evidence of laryngeal involvement. The majority of the non-laryngeal cohort responded well following injections in the suprahyoid muscles with 83% having greater than 50% improvement. The suprahyoid muscles injected (anterior digastric, myelo-hyoid muscles) in our patients are those involved in tongue stability. The genioglossus plays an essential role in both enlarging and stabilizing the upper portion of the respiratory tract [17]. When affected by dystonia, these muscles can interfere with the breathing and swallowing by preventing normal tongue mobility.

Several of the patients will have pre-existing dysphagia due to the dystonia, which typically improves after injection due to improvement in tongue function.

Meige [18] reported that the facial convulsions could extend to the muscles of the pharynx, jaw, mouth floor and tongue. This phenotype found in our cohort correlates with those that have been described by Waln and Ledoux [19] and Norby [20]. In the Ledoux series, 7/114 patients with Meige syndrome presented with a combination of late-onset apraxia of eyelid opening and antecollis [18]; one of these seven patients had "air hunger" thought to be due to laryngeal dystonia, although it did not improve following TA-LCA injections and required a tracheostomy and may indeed have been Meige syndrome without laryngeal involvement. Interestingly, the published pictures of these patients showed flexion of the head on the neck, with a "double chin"

Table 1
Clinical phenotype of Meige patients with dyspnoea and supra-hyoid dystonic muscles involvement.

Meige syndrome with dyspnea	Sex	Mean age of onset	BSP	Frog movements	Double chin posture	"Donald Duck" Voice	Palate
with laryngeal involvement n = 6	5F/1M	53 years (45–61)	6/6	1/6	2/6	1/6	1/6
without laryngeal involvement n = 7	6F/1M	61 years (42–72)	7/7	5/7	2/7	3/7	1/7

BSP: Blepharospasm – "Frog" movements: rhythmic movements of the submental muscles, "Double chin" posture: posterior sagittal shift of head on neck. "Donald Duck" Voice: related to base of tongue dystonia.

Table 2
Clinical features of Meige patients with dyspnoea and muscle selection for BoNT injections.

Phenotype of Meige	Meige with laryngeal involvement						Meige without laryngeal involvement						
	F	M	F	F	F	F	F	M	F	F	F	F	F
Age at onset (years)	61	52	50	45	58	53	42	61	72	63	53	63	72
Site of involvement													
BSP	+	+	+	+	+	+	+	+	+	+	+	+	+
Palatal	−	+	−	−	−	−	−	+	−	−	−	(+)	−
Tongue base	−	−	−	−	+	−	+	+	−	−		+	−
Frog	−	−	−	−	−	+	+	+	+	+	+	−	−
Double chin	+	−	−	+	−	−	−	−	−	+	−	−	+
Larynx (TA/LCA)	+	+	+	+	+	+	(+)	−	−	−	−	−	−
Treatment													
Chemodenervation - BoNTA													
Orbicularis oculi	+	+	+	+	+	+	+	+	+	+	+	+	+
Palatoglossus	−	+	−	−	−	−	−	+	−	−	−	(+)	−
Anterior digastric muscles	+	−	−	+	−	+	+	−	+	+	+	−	+
Mylohyoid muscles	−	−	+	−	−	+	+	−	(+)	−	−	−	−
Genioglossus	−	−	−	−	+	−	(+)	+	+	−	−	+	−
Masseter	−	−	+	−	−	−	−	−	−	+	−	−	−
Longus coli	(+)	−	−	+	−	−	−	−	−	(+)	−	−	+
Longus capitii	−	−	−	−	−	−	−	−	−	+	−	−	+
Sternohyoid	−	−	−	−	−	+	−	−	−	+	+	−	−
Sternocleidomastoid	+	−	−	+	−	−	−	−	−	+	−	−	+
Platysma	−	−	−	−	+	−	+	−	−	−	−	−	−
Trapezius	−	−	−	−	−	−	−	−	−	+	−	−	−
Supraglottis	−	−	−	−	−	−	−	−	−	−	−	+	−
TA-LCA complex	+	+	+	+	+	+	(+)	−	−	−	−	(+)	(+)
Medical treatment													
Trihexyphenidyl	+	−	+	−	−	+	+	−	−	+	−	−	−
Clonazepam	−	−	−	−	−	+	+	−	−	−	−	+	−
Side effects													
Diplopia	−	−	−	+	−	−	+	−	+	+	−	−	−
Breathy Dysphonia	−	−	−	−	−	+	−	−	−	−	−	+	−
Dysphagia	−	−	+	−	−	−	−	−	−	−	−	−	+
Outcome for dyspnoea													
<50% response	−	−	+	−	−	−	+	−	−	+	−	−	−
50–90%response	+	+	−	+	+	+	−	+	+	−	+	+	+

+ present/involved, - not present/not involved, (+) previous but not current injection site, "Frog" movements: rhythmic movements of the submental muscles, "Double chin" posture: posterior sagittal shift of head on neck.

posture, which indicates an involvement of not only the deep cervical flexors but also the supra-hyoid muscles [21].

In the retrospective study by Norby *et al.*, [20] a "hyoid muscle dystonia" is described as a sub-phenotype of Meige syndrome with voice changes, anterior neck tightness and dysphagia. No breathing difficulties were mentioned but on laryngoscopic examination, abnormal contractions of laryngeal/pharyngeal space attributed to the dystonic hyoid muscles were seen. As in our cohort, all the patients had visible contractions of the suprahyoid muscles (frog movements – video 1).

We accept that the lack of a robust measure to quantify the degree of dyspnoea pre- and post-treatment and the small number of patients involved make this a difficult area to study accurately. Work to evolve such a measure in the future would be helpful.

We believe that the involvement of suprahyoid muscles is the main cause of the dyspnoea of this specific Meige phenotype, based on our clinical findings, previous descriptions in the literature [19,20] and therapeutic results.

5. Conclusion

Dyspnoea in dystonic patients has been attributed to laryngeal involvement but we have shown that this is often not the case. Detailed clinical examination of patients to identify suprahyoid involvement is as important as laryngoscopic examination for breathless patients. Breathing dystonia does not always include the laryngeal muscles and may be due to upper airway obstruction from palatal, suprahyoid muscles or tongue base dystonia. It is also important to consider non-dystonic symptoms such as ILO.

6. Disclosures

We performed a retrospective case note study. The treatment that the patients received was according to our normal protocols, consents procedures and followed the Trust's ethical guidelines. Informed written patient consent was obtained from every patient prior to the botulinum toxin injection procedure. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding source

The authors declare that there is no funding source for this study.

8. Financial disclosures for the previous 12 months

N.A.W, L.A.H. MHM declare that there are no additional disclosures to report.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.prdoa.2021.100106.

References

[1] J.M. Flowers, L.A. Hicklin, M.-H. Marion, Anterior and posterior sagittal shift in cervical dystonia: a clinical and electromyographic study, including a new EMG approach of the longus colli muscle, Mov. Disord. 26 (13) (2011) 2409–2414.

[2] A. Albanese, K. Bhatia, S.B. Bressman, M.R. DeLong, S. Fahn, V.S.C. Fung, M. Hallett, J. Jankovic, H.A. Jinnah, C. Klein, A.E. Lang, J.W. Mink, J.K. Teller, Phenomenology and classification of dystonia: a consensus update, Mov. Disord. 28 (7) (2013) 863–873.

[3] A. Blitzer, M.F. Brin, Laryngeal dystonia: a series with botulinum toxin therapy, Ann. Otol., Rhinol. Laryngol. 100 (2) (1991) 85–89.

[4] M.-H. Marion, P. Klap, M. Cohen, A. Perrin, Stridor and focal laryngeal dystonia, Lancet 339 (8791) (1992) 457–458.

[5] A. Blitzer, M.F. Brin, K. Simonyan, L.J. Ozelius, S.J. Frucht, Phenomenology, genetics, and CNS network abnormalities in laryngeal dystonia: a 30-year experience, Laryngoscope 128 (2018) S1–S9.

[6] S. Payne, S. Tisch, I. Cole, H. Brake, J. Rough, P. Darveniza, The clinical spectrum of laryngeal dystonia includes dystonic cough: observations of a large series, Mov. Disord. 29 (6) (2014) 729–735.

[7] V. Woisard, X. Liu, M.C.A. Bes, M. Simonetta-Moreau, Botulinum toxin injection in laryngeal dyspnea, Eur. Arch. Otorhinolaryngol. 274 (2) (2017) 909–917.

[8] Marsden C, Sheehy M. Spastic dysphonia, Meige disease, and torsion dystonia. Neurology. 1982;32(10):1202.

[9] N. Braun, A. Abd, J. Baer, A. Blitzer, C. Stewart, M. Brin, Dyspnea in dystonia: a functional evaluation, Chest 107 (5) (1995) 1309–1316.

[10] A. Lagueny, P. Burbaud, G. Le Masson, F.X. Bergouignan, X. Ferrer, J. Julien, Involvement of respiratory muscles in adult-onset dystonia: a clinical and electrophysiological study, Movem. Disorders 10 (6) (1995) 708–713.

[11] R. Mehanna, J. Jankovic, Respiratory disorders associated with dystonia, Mov. Disord. 27 (14) (2012) 1816–1819.

[12] A. Blitzer, M.F. Brin, C.F. Stewart, Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): a 12-year experience in more than 900 patients, Laryngoscope 108 (10) (1998) 1435–1441.

[13] G. Defazio, A. Berardelli, G. Abbruzzese, V. Coviello, F. Carella, M.T. De Berardinis, G. Galardi, P. Girlanda, S. Maurri, M. Mucchiut, A. Albanese, M. Basciani, L. Bertolasi, R. Liguori, N. Tambasco, L. Santoro, G. Assennato, P. Livrea, Risk factors for spread of primary adult onset blepharospasm: a multicentre investigation of the Italian movement disorders study group, J. Neurol. Neurosurg. Psychiatry 67 (5) (1999) 613–619.

[14] G. Abbruzzese, A. Berardelli, P. Girlanda, R. Marchese, D. Martino, F. Morgante, L. Avanzino, C. Colosimo, G. Defazio, Long-term assessment of the risk of spread in primary late-onset focal dystonia, J. Neurol. Neurosurg. Psychiatry 79 (4) (2008) 392–396.

[15] J.T. Olin, E. Westhoff (Carlson), Exercise-induced laryngeal obstruction and performance psychology: using the mind as a diagnostic and therapeutic target, Immunol. Allergy Clinics 38 (2) (2018) 303–315.

[16] B. Ellement, Y. Jasaui, K. Kathol, E. Nosratmirshekarlou, T. Pringsheim, J. Sarna, B. L. Callahan, D. Martino, Social cognition in cervical dystonia: phenotype and relationship to anxiety and depression, Eur. J. Neurol. 28 (1) (2021) 98–107.

[17] W. Qin, Y.B.H. Zhang, B.L. Deng, J. Liu, H.L. Zhang, Z.L. Jin, MiR-17-5p modulates mitochondrial function of the genioglossus muscle satellite cells through targeting Mfn2 in hypoxia, J. Biol. Regul. Homeost. Agents 33 (3) (2019) 753–761.

[18] H. Meige, Les convulsions de la face. Une forme clinique de convulsion faciale. Bilaterale et mediane (1), Rev. Neurol. 21 (1910) 437–443.

[19] Waln O, LeDoux MS. Blepharospasm plus cervical dystonia with predominant anterocollis: a distinctive subphenotype of segmental craniocervical dystonia. Tremor Other Hyperkinetic Movem. 2011;1.

[20] E. Norby, D. Orbelo, E. Strand, J. Duffy, D. Ekbom, J. Bower, J. Matsumoto, Hyoid muscle dystonia: a distinct focal dystonia syndrome, Parkinsonism Related Dis. 21 (10) (2015) 1210–1213.

[21] L.A. Hicklin, M.-H. Marion, Endoscopic injection of the Longus Capiti muscle in the treatment of dystonic head flexion, Movem. Disorders Clin. Practice 7 (3) (2020) 293–297.