Sleep and other Non-motor Symptoms in Patients with Idiopathic Oromandibular Dystonia and Meige Syndrome: A Questionnaire-based Study

Somdattaa Ray, Bindu Kutty¹, Pramod Kumar Pal, Ravi Yadav
Departments of Neurology and ‘Neurophysiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Abstract

Introduction: Non-motor symptoms are an essential cause of comorbidity in generalized and focal dystonia. However, there are few studies on dystonia involving the craniofacial regions. Methods: We studied non-motor symptoms in patients with oromandibular dystonia (OMD) and Meige syndrome using a questionnaire, and validated instruments for depression, anxiety, REM behaviour disorder, restless leg syndrome, sleep quality, excessive daytime sleepiness, and self-esteem. The severity of dystonia and blepharospasm was also studied. Results: Nineteen patients with OMD were recruited into the study. Among patients with OMD, depression was seen in 63.6% (n = 7), sleep impairment in 27.3% (n = 3), excessive daytime sleepiness in 27.3% (n = 3), and poor self-esteem in 18.2% (n = 2) of the patients. Among patients with Meige syndrome, depression was seen in 37.5% (n = 3), sleep impairment in 12.5% (n = 1), excessive daytime sleepiness in 25% (n = 2), low self-esteem in 25% (n = 2) of the patients. Conclusion: This study highlights the significant frequency of depression and sleep disturbances in patients with idiopathic OMD and Meige syndrome.

Keywords: Depression, sleep, Meige syndrome, nonmotor, oromandibular dystonia

Introduction

Non-motor symptoms are a significant cause of comorbidity and distress in patients with dystonia.[1] The cortico-striato-thalamo-cortical loops are implicated in dystonia,[1] and they also play a role in the pathogenesis of the non-motor syndrome of dystonia.[2] Basal ganglia have a role in emotions, and in dystonia, emotional dysregulation could be the result of basal ganglia dysfunction.[1]

Oromandibular dystonia (OMD) consists of spasmodic movements of muscles of mastication, facial, and lingual musculature resulting in sustained or patterned jaw opening or closure or a combination of these movements.[4,5] Tardive dyskinesia forms a significant group of patients with OMD.[6] OMD may occur in isolation or association with blepharospasm (Meige syndrome).[7] and spasmodic dysphonia.[8] Meige syndrome forms a substantial part of idiopathic craniofacial dystonia. It has been reported in 22% of the patients, while OMD is relatively uncommon, with the incidence being 5% among all dystonia.[9]

Patients with OMD face stigma because of disfigurement, communication, and feeding problems that could also give rise to many non-motor symptoms.[10] Moreover, the worsening of OMD with activities such as reading, eating, looking up and down, walking, watching television[5,9] further deteriorates the quality of life. These may be associated with multiple non-motor symptoms (depression, anxiety, sleep disturbances, loss of self-esteem). The non-motor syndrome has been described in depth in focal dystonia.[11-15]

Non-motor symptoms in OMD are less well studied. Non-motor symptoms in OMD and Meige syndrome were first described in a paper by Marsden. Among nine patients with OMD, all had eating difficulty, four patients reported swallowing difficulty, and three patients reported depression before the onset and during the illness. Among 17 patients with Meige syndrome, 13 patients reported difficulty speaking, five patients reported difficulty swallowing, and five patients reported psychiatric disturbances before the onset and during the illness.[17] Novaretti et al. studied non-motor symptoms in focal dystonia. One group had 28 patients that included blepharospasm and five patients with cranial dystonia. This group reported significantly higher anxiety, depression, and sleep impairment compared to other dystonia, such as cervical dystonia and focal hand dystonia.[16] Fabbri et al. also studied non-motor symptoms among a group of 28 patients with blepharospasm that included seven patients...
with OMD.[14] As OMD is a rare disorder and data is sparse from the Indian perspective, we envisaged to evaluate the non-motor symptoms in OMD and Meige syndrome.

**Material and Methods**

The study was conducted at the Department of Neurology, NIMHANS, a tertiary health care referral centre in South India. Patients above the age of 18 years with idiopathic OMD and Meige syndrome were recruited from outpatient clinics of neurology and movement disorders clinic from August 2016 to September 2018. Patients with dystonia were excluded from the study if symptoms were secondary to drug exposure or were associated with dystonia of any other body part and other movement disorder or secondary to an underlying neurological disorder, as evident by abnormal MRI. Patients were also excluded from the study if they had a prior history of psychiatric disorder. The institutional ethical board provided the ethics approval. Informed written consent was taken before the study, hence conforming to the ethical standards laid down by the Declaration of Helsinki. Approval from ethics committee was obtained on 7.8.2015.

After obtaining sociodemographic details, a brief clinical history, including the history of drug intake, family history of neurological disorders, were enquired. Besides, patients were asked regarding their current medication and response to the medication. History of treatment with botulinum injection was obtained. Patients were clinically examined to ascertain the phenomenology, presence of other coexisting movement disorders, presence of lower motor neuron or upper motor neuron lesions, cerebellar lesions, or abnormal sensory findings.

The severity of blepharospasm was rated using Jankovic Rating Scale (JRS). The severity of OMD was scored using the Unified Dystonia Rating Scale (UDRS).

Patients were evaluated for REM behavior disorder using the Mayo sleep questionnaire,[17] restless leg syndrome using RLS rating scale, and the International Restless leg syndrome study group rating scale.[18] The excessive daytime sleepiness was scored using the Epworth Sleepiness Scale (ESS). Patients with ESS greater than 10 had excessive daytime sleepiness.[19] Self-esteem was determined using Rosenberg self-esteem scale. For self-esteem, the following was the cutoff: low self-esteem (0–15), normal self-esteem (15–25), high self-esteem (25–30).[20] Sleep quality was assessed using Pittsburgh Sleep Quality Index (PSQI). Patients with PSQI greater than five were considered as poor sleepers.[21] Anxiety was estimated using Hamilton anxiety scale (HAM-A), and a score of >14 was abnormal.[22] Depression was evaluated using Hamilton depression scale (HAMD- D). For depression, the following was the cutoff: no depression (0–7), mild depression (8–16), moderate depression (17–23), and severe depression (≥24).[23]

**Statistics**

The sociodemographic details with the clinical details, details of medication, the severity of the symptoms, and the questionnaire results were entered into MS Excel worksheet, and data were analyzed using SPSS 22. The data were checked for normality using the Kolmogorov–Smirnov test and descriptive statistics such as the mean, standard deviation, frequency, percentage were obtained for all the variables. To estimate differences between the groups, ANOVA and to identify differences in groups, post hoc tests (Bonferroni) were applied. Pearson’s or Spearman correlation coefficient was used as and when applicable. The statistical significance was placed at 0.05.

**Results**

**Demographic details and clinical features—**

Nineteen patients with OMD were recruited into the study. Isolated idiopathic OMD was seen in 11 patients (male-5, female-6), and OMD with accompanying blepharospasm (Meige syndrome) was seen in eight patients (males- 8, females-0). The mean age of onset of the disease in patients with OMD was 52.7 ± 12.0 years, and patients with Meige syndrome is 50.2 ± 11.9 years [Table 1].

Twenty-seven percent of the patients with OMD (n = 3) reported sleep difficulty as the initial manifestation. One patient with Meige syndrome had presented with neck pain. Among patients with Meige syndrome, the onset of symptoms in the ocular area was seen in 100% (n = 8) of the patients. One patient with OMD had a family history of movement disorder. Among patients with OMD, 36.3% (n = 4) of patients reported impairment in occupation, 90.9% (n = 10) of the patients reported social embarrassment, 36.3% (n = 4) reported sleep disturbances, 36.3% (n = 4), reported impairment in activities of daily living. Among patients with Meige syndrome, 62.5% (n = 5) of patients reported impairment in occupation, 100% (n = 8) of the patients reported social embarrassment, 37.5% (n = 3) reported decreased sleep, 62.5% (n = 5) reported impairment in activities of daily living.

**Medication history**

Patients were treated with baclofen, clonazepam, trihexyphenidyl, and tetrabenazine. Among patients with OMD, dose range of tetrabenazine was 25–100 mg, clonazepam was 0.25 mg to 1.5 mg, trihexyphenidyl was 2–12 mg, and dose range of baclofen was 10–30 mg Among patients with Meige’s syndrome, dose range of clonazepam was 0.5–0.75 mg, and trihexyphenidyl was 4–10 mg. One patient was treated with tetrabenazine 50 mg and none of the patients were treated with baclofen. Among patients with OMD, 54.5% (n = 6) of the patients were on three or more medications.

Among patients with Meige syndrome, 27.2% (n = 3) were on three or more drugs, and 30% were on two drugs. Three patients with OMD and two patients with Meige syndrome (50 units) were treated with botulinum toxin with satisfactory response. The patients were on botulinum toxin prior to the assessment.

**Sleep and excessive daytime sleepiness**

Among OMD, 27% (n = 3) of the patients reported poor quality of sleep, and 27.3% (n = 3) of the patients had excessive
daytime sleepiness. One patient reported REM behavior disorder. Among patients with Meige syndrome, 25% (n = 2) of the patients had excessive daytime sleepiness. Poor sleep quality was seen in 12.5% (n = 1) of the patient with Meige syndrome. Restless leg syndrome was reported by one patient of OMD and Meige syndrome each.

**Anxiety, depression, and self-esteem**

Among OMD, depression was present in 63.7% (n = 7) of the patients. Of these, mild depression in 27.2% (n = 3), moderate depression in 27.3% (n = 3) of the patients, and severe depression was present in 9% (n = 1) of the patients. Twenty-five percent (n = 2) of the patients reported anxiety. Among these patients, 18.2% (n = 2) of the patients had low self-esteem, 72.7% (n = 8) of the patients had normal self-esteem.

Among patients with Meige syndrome, moderate depression was found in 25% (n = 2) of the patients and severe depression in 12.5% (n = 1) of the patients. Restless leg syndrome was reported by one patient of OMD and Meige syndrome each.

Based on the severity of symptoms, patients were advised medical management. Five patients with Meige syndrome and four patients with OMD were treated for depression, anxiety, and sleep related problems as part of their non-motor symptoms.

**Discussion**

In our study, we assessed the non-motor symptoms in patients with primary OMD. However, many of these patients also were noted to have blepharospasm (Meige syndrome). These patients were either asymptomatic or had minimal symptoms referable to blepharospasm. These patients reported depression, anxiety, poor self-esteem, and excessive daytime sleepiness.

Patients with tardive dyskinesia were excluded from the study as they could be having psychiatric disturbances resulting in neuroleptic intake that could be a confounding factor.

Sleep disturbances have been extensively studied among patients with cervical dystonia and blepharospasm but not in OMD. Sleep impairment is described in 44–72% of patients with cervical dystonia.[12,13,24-26] In blepharospasm, sleep disturbances have been observed in 55–75% of the patients.[12,13,25] In our study, impaired sleep quality was observed in 3 (35%) patients of OMD and 1 (10%) patient with Meige syndrome. A possible explanation for the low

| Parameter                  | Oromandibular dystonia (n=11) | Meige syndrome (n=8) |
|----------------------------|-------------------------------|----------------------|
| Male                       | 5 (45.5%)                     | 8 (100%)             |
| Female                     | 6 (54.5%)                     | 0                    |
| Age at presentation (in years) | 57.1±13.2        | 57.1±7.2             |
| Age of onset (in years)    | 52.7±12.0                     | 50.2±11.9            |
| Duration of illness (in years) | 4.4±4.5          | 3.1±2.4              |

| First symptom              |
|----------------------------|----------------|
| Involuntary movement       | 8 (72.7%)     |
| Neck pain                  | 0             |
| Difficulty in speaking     | 3 (27%)        |
| Most disabling symptom     |
| Difficulty in carrying out ADL | 2 (18.1%)   |
| Pain                       | 1 (9.00%)      |
| Social interaction impairment |
| Difficulty speaking        | 7 (63.6%)      |
| Discomfort over face       | 2 (18.1%)      |
| No disabling symptoms      | 0              |

| Table 2: Non-motor symptoms in idiopathic oromandibular dystonia and Meige syndrome |
|---------------------------------|-----------------|-----------------|
| Parameters                      | Oromandibular dystonia (n=11) | Meige syndrome (n=8) |
|---------------------------------|-------------------------------|----------------------|
| Depression n (%)                | 7 (63.6%)                     | 3 (37.5%)             |
| HAM-D (mean±SD)                 | 10.4±7.5                     | 9.25±9.8             |
| Sleep - n (%)                   | 3 (27.3%)                     | 1 (12.5%)             |
| PSQI (mean±SD)                  | 3.8±1.7                      | 3.5±1.9              |
| EDS - n (%)                     | 3 (27.3%)                     | 2 (25%)               |
| ESS (mean±SD)                   | 7.8±3.5                      | 6.9±5.7              |
| Low self-esteem - n (%)         | 2 (18.2%)                     | 2 (25%)               |
| Rosenberg self-esteem scale (mean±SD) | 18.8±5.9     | 20±6.3               |
| Anxiety - n (%)                 | 2 (25%)                      | 1 (16.7%)             |
| HAM-A (mean±SD)                 | 9.4±6.8                      | 7.3±6.9              |
| RLS (mean±SD)                   | 1 (9%)                       | 1 (12.5%)             |
| MOCA (mean±SD)                  | 20.9±9.9                     | 22.2±6.5             |
| UDRS (mean±SD)                  | 5.3±2.6                      | 12.4±9.85            |
| JRS (mean±SD)                   | NA                           | 5.7±1.58             |

EDS - excessive daytime sleepiness JRS - Jankovic rating scale. ESS - Epworth Sleepiness Scale, UDRS - Unified Dystonia Rating Scale, PSQI - Pittsburgh Sleep Quality Index, HAM-A - Hamilton Anxiety Rating Scale, HAM-D - Hamilton Depression Rating Scale, RLS - Restless Leg Syndrome

In our study, impaired sleep quality was observed in 3 (35%) patients of OMD and 1 (10%) patient with Meige syndrome. A possible explanation for the low
prevalence of sleep disturbances in our study could be the fact that a significant proportion (>50% of patients in each group) of our patients were on benzodiazepines that could have led to earlier sleep onset and longer sleep time.\textsuperscript{[27]} We did not find a correlation between the degree of dystonia and sleep disturbances. Moreover, there was no correlation between excessive daytime sleepiness and sleep impairment. Excessive daytime sleepiness could be the consequence of the side effects of medication or a primary disturbance in dystonia.\textsuperscript{[15]} Sleep disturbances because of an intrinsic mechanism in dystonia, rather than a secondary symptom, have been postulated\textsuperscript{[12,26]} that is evident by lack of improvement of sleep quality with botulinum toxin while there was an improvement in cervical dystonia severity.\textsuperscript{[25,26]}

Depression was observed in 66.6% (n = 8) patients with OMD and 50% (n = 5) in patients with Meige syndrome in our study, but the anxiety was less common among them. Berman et al. studied non-motor symptoms in lower cranial dystonia in 39 patients. Based on BDI, 29% of patients, and based on HAM-D, 20.5% of the patients had depression in their study. This is much less than the percentage of patients with depression in our study. Based on HAM-A, 46.2% of their patients had anxiety.\textsuperscript{[28]}

Psychiatric disturbances were studied in a closely associated disorder, spasmodic dysphonia. Aronson et al. reported psychiatric symptoms in 68% of the patients with spasmodic dysphonia. Anxiety and depression were reported in 39% of patients with spasmodic dysphonia. Gundel et al. reported that 41.7% of the patients with spasmodic dysphonia reported psychiatric disturbances in the form of adjustment disorders, mood disorders, panic disorders.\textsuperscript{[29]} Psychiatric disorders correlated with the severity of the symptoms\textsuperscript{[29]} that were not replicated in our study. Almost all the patients reported social embarrassment, while only four patients reported low self esteem. Social embarrassment and low self-esteem are pivotal factors that could have contributed to depression. Psychiatric symptoms could be the result of the interplay between distorted body image, low self-esteem,\textsuperscript{[11]} and intrinsic factors. Pathophysiology of psychiatric and non-motor symptoms in dystonia has been traced to dysfunctional cortico-striato-thalamo-cortical circuits,\textsuperscript{[30]} increased cortical plasticity, reduced inhibition, and structural alterations in the brain.\textsuperscript{[12]} Among patients with depression, low DAT binding to striatal receptors has been reported.\textsuperscript{[30]} Among patients with cervical dystonia and depression, decreased DAT binding to the striatal receptors and D2, D3 receptors are found, thus, explaining the possible reason for depression among patients with cervical dystonia.\textsuperscript{[11]} The serotoninergic system is also dysfunctional among patients with cervical dystonia. Low levels of serotonin metabolites have been observed among focal dystonia. A decreased level of 5 hydroxy indole acetic acid in the cerebrospinal fluid of the patient with dystonia indicates ineffective serotonergic activity.\textsuperscript{[12,31]} Recently, studies have demonstrated that serotonin receptor binding is decreased in putamen while it is accentuated in the dorsal raphe nucleus among patients with cervical dystonia. The serotonin receptor binding in dorsal raphe nuclei has a correlation with sleep disturbances, pain, and motor disability. Interestingly, no correlation between SERT (sertraline receptor) binding and mood disorders could be discerned.\textsuperscript{[34]} REM sleep is governed by serotonin activity. Inhibition of serotonin pathways, particularly the projections to dorsal raphe nucleus, is essential for the generation of REM sleep.\textsuperscript{[35]} Hence, enhanced SERT binding could result in poor sleep because of poor REM sleep generation. Whether abnormalities of SERT binding could link poor sleep with depression among patients with dystonia, remains to be explored.

Restless leg syndrome was reported in one patient of OMD and Meige syndrome. Restless leg syndrome has been reported in 18% of the patients with cervical dystonia.\textsuperscript{[23]} Both hypodopaminergic state and iron deficiency have been postulated in the causation of restless leg syndrome. D2 receptor binding was found to be low in caudate and putamen among patients with restless leg syndrome.\textsuperscript{[25,36]}

To the best of our knowledge, this is the first study that describes non-motor symptoms exclusively in primary OMD and Meige syndrome patients. Similar precipitating factors as dystonia may be responsible for these non-motor symptoms in our study group [Figure 1].

A limitation of our study is the small sample size, but given the rarity of the disorder, the results gave valuable insight into the non-motor symptoms. Moreover, the data available on this aspect is sparse. We hope that this study paves the way for more extensive studies on cranial dystonia.

The study highlights the distressing aspect of non-motor symptoms of the OMD. Large multi-center studies with a higher number of patients are needed, as this disorder is rare. The coexisting non-motor comorbidities in patients with OMD add to the misery of the patients, and so they need to be addressed by the treating clinician to provide more comprehensive care.

Figure 1: The spectrum of Nonmotor symptoms in primary oromandibular dystonia and meige syndrome
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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