



CLINICAL CHARACTERISTICS OF DIFFERENT TYPES OF CRANIAL DYSTONIA: AN OBSERVATIONAL STUDY.

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ABSTRACT

Background: Cranial dystonias have complex phenomenology and heterogenous etiology. Large prospective observational studies would help us in a better understanding and management of this complex disorder.

Objectives: To study the clinic-etiological profile of patients of cranial dystonia attending a movement disorder clinic of a tertiary care teaching institution.

Methods: All the consecutive cranial dystonia patients from October 2017 to September 2019 were enrolled and classified according to the consensus update on phenomenology and classification of dystonia.

Results: Total number of patients with cranial dystonia were 96, with 42(43.8%) females and 54 (56.3%) male, with M: F=1.28:1. Mean age of onset was 42.36 ± 21 years with mean duration of symptoms was 3.38 ± 4.05 years Oromandibular dystonia was the most common type of cranial dystonia (45.8%) followed by Meige syndrome (28%) and blepharospasm (26%). Meige syndrome started as blepharospasm in 85.1%($p<0.001$). Jaw opening dystonia(JOD) was overall the most common (42.3%) type of oromandibular dystonia. In 9.8% idiopathic cases and 28.9% non-idiopathic cases, dystonia started from extracranial region ($p=0.02$). JOD (51.1%) was the most common type of oromandibular movement abnormality in non-idiopathic cranial dystonia where-as in idiopathic cases jaw closure dystonia (JCD) and oro-facial dystonia (OF), (15.7% each) were the most ($p<0.001$).

Conclusion: In present study we observed thatcranial dystonia started one decade earlier than western population. Cranial dystonia with simultaneous extracranial involvement, and starting from the oromandibular region was more likely to be non-idiopathic aetiology.

Keywords: cranial dystonia, blepharospasm. Oromandibular dystonia, Meige syndrome.

INTRODUCTION

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation (1). Cranial dystonia have a complex phenomenology and multifactorial etiology. The various cranial dystonia like blepharospasm, oromandibular dystonia (OMD), and Meige syndrome (MS) (blepharospasm

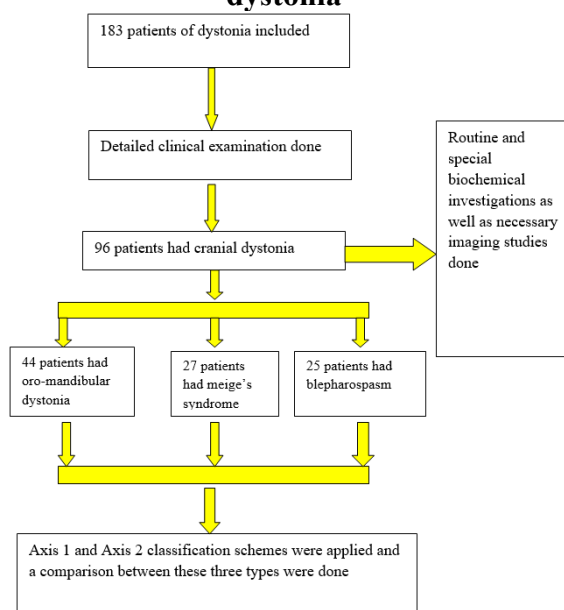
plus oromandibular dystonia) are commonly encountered in clinical practice and represent a diagnostic and therapeutic challenge.

There are only few case series on cranial dystonia from India (2, 3, 4) till date. Therefore larger prospective observational studies will help us in a better identification and recognition of this complex disorder, which causes significant impact on speech and swallowing causing functional impairment. There are several unanswered questions in previous studies, such as; 1) The clinical characteristics of these three types of cranial dystonias are same or different? 2) How the idiopathic and non-idiopathic cranial dystonias are different? and which characteristics will help in identifying non-idiopathic cases? 3) Do all three types of cranial dystonias having same or different tendency to spread to contiguous or non-contiguous segments? The present study aimed to evaluate and compare the clinical characteristics of patients with cranial dystonia attending a tertiary care University hospital.

MATERIAL AND METHODS

This study was conducted in the Department of Neurology of a tertiary care teaching institute. The study was approved by the institute ethical committee and an informed consent was taken from all patients. All consecutive dystonia patients (n=183) were screened from October 2017 to September 2019. Patients with cranial involvement, with or without additional site of involvement (n=96) were enrolled. A detailed clinical history including age at onset, duration of illness, body distribution of dystonia, additional movement disorder phenotypes, additional neurological/systemic signs, diurnal fluctuations, task specificity, for aetiology patients were asked for drug or toxin exposure and family history. This was followed by a thorough neurological examination. All patients were investigated for routine blood and biochemical investigations (complete blood count, general blood picture, calcium, phosphorous, alkaline phosphatase, liver, renal and thyroid function tests, fundus examination, slit lamp for KF ring, neuroimaging (CT/MRI) were done in all patients. Certain investigations were done depending on the clinical suspicion of disease based on history and examination such as serum copper, Serum ceruloplasmin, 24 hrs urinary copper, ultrasound abdomen, electrodiagnostic studies. We classified cranial dystonia into blepharospasm, oromandibular dystonia and Meige syndrome, according to the consensus update on the phenomenology and classification of dystonia (1). Both Axis 1 and Axis 2 (Flow diagram-1) classification schemes were applied and a comparison between these three types were done. Severity was rated according to Burke–Fahn–Marden (BFM) scale (5).

Figure 1: Showing study participants recruitment and further classification of cranial dystonia



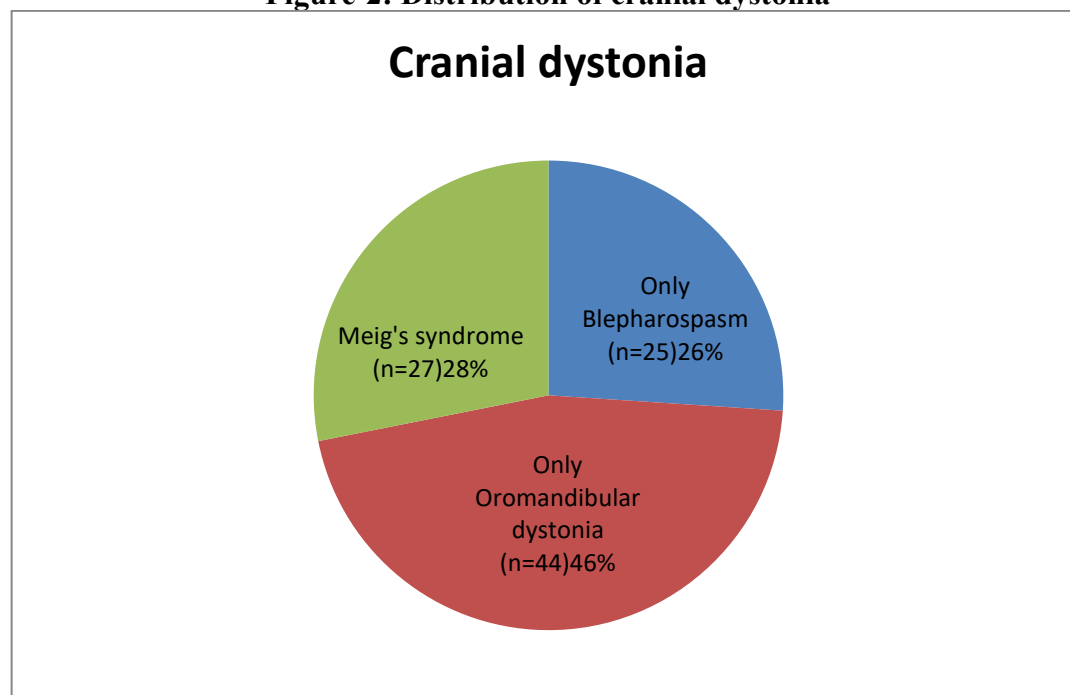
In case of oromandibular movement abnormality were divided into jaw opening dystonia (JOD), jaw closing dystonia (JCD), jaw deviation dystonia (JDD), jaw mixed dystonia (JMD), Oro-facial dystonia (OF) and Oro-facio-lingual dystonia (OFL).

Statistical analysis was done using SSPS23 software and Microsoft office Excel statistical software programs. Comparative analysis was performed using the chi-square test or Fisher's exact tests for categorical variables and unpaired student t-test for continuous variables. A p value of less than 0.05 was considered to be statistically significant

RESULTS

AXIS I Total number of patients with cranial dystonia were 96, out of which 42(43.8%) were female and 54 (56.3%) were male with M:F ratio is 1.28:1. Mean age of onset was 42.36 ± 21 years with mean duration of symptoms was 3.38 ± 4.05 years.

Figure-2: Distribution of cranial dystonia



Oromandibular dystonia was the most common type of cranial dystonia ($n=44/96$, 45.8%) followed by Meige syndrome ($n=27/96$, 28%) and blepharospasm ($n=25/96$, 26%).

Cranial dystonia was mostly focal (40.6%). It was a part of segmental body distribution in 31.3% (30/96), generalized body distribution in 19.8% (19/96) and multifocal body distribution in 8.3% (8/96). Among segmental cranial dystonia, 50% (15/30) cases were of Meige syndrome, 33.33% (10/30) had additionally cervical involvement, 10% (3/30) had laryngeal dysphonia and 6.67% (2/30) had additional cervical with upper-limb involvement.

Onset and spread

Dystonia started as blepharospasm in 47.9% cases (46/96), followed by from oromandibular region (33.3%), upper-limb (8.3%), lower-limb (8.3%) and cervical region (2.1%). In 18.7% of patients, the initial site of involvement was extracranial and later it spread to cranial region.

Meige syndrome started as blepharospasm in 85.1% (23/27) of patients and as oromandibular dystonia in 11.1% (3/27) ($p < 0.001$). The mean interval of spread from blepharospasm or oromandibular region to become Meige syndrome was 12.33 ± 18.1 months. In the remaining one patient of Meige syndrome, dystonia started from upper limb.

If cranial dystonia started from oromandibular region, then extra-cranial site involvement was seen in 50% (16/32), but if dystonia started as blepharospasm then later spread to extra-cranial site was seen in only 17.4% (8/46) ($p < 0.001$).

Among patients with blepharospasm-onset dystonia, 50% (23/46) of patient progressed to become Meige syndrome and among them 34.7% (8/23) developed extracranial dystonia but none of the patients in whom cranial dystonia remained restricted to ocular region developed extracranial dystonia ($p = 0.02$). Some or other form of sensory tricks to relieve dystonia were present in 38.5% (37/96) of patients.

Table-1 Severity of ocular involvement in cranial dystonia (n=96)

Characteristics	Severity of ocular involvement	P
Male	4.7±2.3	0.48
Female	5.1±2.1	
With photophobia	5.5±2.1	0.026
Without photophobia	3.7±1.9	
With sensory trick	5.6±0.34	0.004
Without sensory trick	3.8±0.47	

Characteristics of ocular involvement

Ocular involvement was present in 54.2% (52/96) of total cases of cranial dystonia. Photophobia were present in 76.9% (40/52) cases of cranial dystonias with ocular involvement. Ocular involvement were more severe (Table-1) in those patients in whom it was associated with photophobia ($p = 0.026$) and sensory tricks ($p = 0.004$) and there were no significant difference in severity of cranial dystonia with regard to gender ($p = 0.48$).

Characteristics of oromandibular involvement

73.9% (n=71/96) patients of cranial dystonia had oro-mandibular involvement.

Among different types of oromandibular movement abnormalities, jaw opening dystonia (JOD) were most common (n=30/71; 42.3%) followed by jaw closing dystonia (JCD) (n=15/71; 21.1%), jaw mixed dystonia (JMD) (n=10/71; 14.1%), oro-facio-lingual dystonia (OFL) (n=13/71; 18.3%) and jaw deviation dystonia (JDD) (n=3/71; 4.2%).

The total number of patients with lingual dystonia was 25/71 (35.1%). Lingual dystonia was present in 53.3% (n=16/30) of JOD, 40% (n=4/10) of JMD and 13.3% (n=2/15) of JCD. The difference was significant ($p = 0.033$).

Functional impairment in speech and swallowing were seen in the OMD patients. Impaired speech was seen in 74.6% (n=53) patients, difficulty in mastication in 46.5% (n=33) patients, and in swallowing was seen in 16.9% (n=12) patients. The prevalence of mastication, speech and swallowing problems among JOD were 63%, 90%, 26.7% respectively, among JCD were 60%, 86.7%, 13.3% respectively and among JMD were 50%, 70%, 10% respectively.

AXIS II

Cranial dystonia was idiopathic in 53.1% (51/96) and non-idiopathic in 46.9% (45/96). Although onset of dystonia was early in non-idiopathic cases (38.3 ± 24.5 years) in comparison to idiopathic cases (45.9 ± 16.5 years) but difference did not reach to the significance ($p = 0.077$).

In idiopathic cases only 33.3% (17/51) were had simultaneous extracranial involvement but in non-idiopathic cases 55.6% (25/45) had extracranial involvement ($p = 0.039$). In 9.8% (5/51) idiopathic cases and 28.9% (13/45) non-idiopathic cases, dystonia started from extracranial site and later-on involved the cranial region ($p = 0.02$).

Among cranial onset cases if dystonia started from blepharospasm then 37.5% (12/46) turned out to be non-idiopathic where-as when dystonia started from oromandibular region then 62.5% (20/32) came to be non-idiopathic ($p = 0.002$). In 54.9% (28/51) idiopathic cases were using sensory tricks

but only 20% (9/45) non-idiopathic cases were using sensory tricks and this difference found to be statistically significant ($p=0.001$).

Photophobia was present in 84.6% (11/13) non-idiopathic cases and 74.4% (29/39) idiopathic cases with ocular involvement ($p=0.76$).

Most common type of oromandibular movement abnormality in non-idiopathic cranial dystonia was JOD (23/45; 51.1%) where-as in idiopathic cases JCD and oro-facial movement (8/51; 15.7% each) were the most ($p<0.001$). Tremor was present in 23.5% (12/51) idiopathic cases and 37.8% (17/45) non-idiopathic cases ($p=0.18$).

Most common non-idiopathic etiology was drug-induced dystonia ($n=16/45$; 35.6%) followed by Wilson's disease (28.9%). Other etiologies were post-surgery (17.8%), post-infection (4.4%), birth insult (4.4%), young onset Parkinson's disease($n=1$), post-trauma($n=1$), paroxysmal kinesogenic dyskinesia($n=1$) and NBIA($n=1$).

Table-2 Characterises of cranial dystonia of different aetiology

Characteristics		Idiopathic n=51	WD n=13	Drug n=16	Post surgery n=8	Perinatal insult n=2	Post- infectio n n=2	NBIA n=1	Post- trauma n=1	YOPD n=1	PKD n=1	P
Age of onset (years)		45.9 ± 16.6	11.4 ± 4.1	54.4 ± 17.7	58.4 ± 7.9	6.75 ± 6.71	57.7 ± .3	12.0	53.0	25.0	19.5	<0.001
Duration of illness (years)		3.8 ± 4.5	5.0 ± 4.8	1.9 ± 2.8	1.1 ± 0.6	5.2 ± 3.9	1.75 ± 1.76	3.0	4.0	3.0	0.5	0.483
Types of cranial dystonia (N)	BS	20	0	0	3	0	1	0	1	0	0	<0.001
	OMD	12	13	14	0	2	1	1	0	0	1	
	M	19	0	2	5	0	0	0	0	1	0	
Extra-cranial involvement N (%)		17(33.3)	13(100)	6(37.5)	1(5.5)	2(100)	0(0)	1(100)	0(100)	1(100)	1(100)	<0.001
Types of oro-mandibular involvement	JOD	7	11	6	2	2	0	1	NA	1	0	<0.001
	JCD	8	2	4	1	0	0	0		0	0	
	JDD	0	0	1	0	0	1	0		0	1	
	JMD	6	0	4	0	0	0	0		0	0	
	OFL	2	0	1	0	0	0	0		0	0	
	OF	8	0	0	2	0	0	0		0	0	
Speech and swallow severity score		1.97 ± 2.6	9.4 ± 5.2	2.9 ± 2.1	0.8 ± 1.8	7.5 ± 2.1	1	8.0	NA	1.0	1.0	<0.001
Oro-mandibular abnormal movement severity score		3.1 ± 1.4	4.3 ± 2.1	4.6 ± 2.4	3.3 ± 1.6	5.0 ± 1.4	4.5	4.5	NA	2.0	3.0	0.227
Blepharospasm severity score		4.8 ± 2.1	NA	3.0 ± 2.1	6.2 ± 2.2	NA	4.5	NA	8.0	NA	3.0	0.177

NBIA (Neurodegeneration with brain iron accumulation), YOPD (Young onset Parkinson disease), WD (Wilson's disease), PKD (paroxysmal kinesigenic dyskinesia), n(number), NA (not applicable).

Age of onset of dystonia was significantly different among different aetiology ($p<0.001$). Cranial dystonia due to inherited causes i.e. Wilson's disease (WD), Neurodegeneration with brain iron accumulation (NBIA), Young onset parkinson's disease (YOPD) and perinatal birth insult had early age of onset, where as cranial dystonia due to acquired causes(i.e. drug induced, post surgery and post-traumatic) had older age of onset than idiopathic cases. ($p<0.001$). Duration of disease were not significantly different among cranial dystonia of different aetiologies ($p=0.483$). Types of cranial involvement was also significantly different among different causes($p<0.001$). None of the drug induced cranial dystonia had ocular involvement without oromandibular involvement. In Wilson's disease all cases of cranial dystonias were of oromandibular dystonia. In Wilson's disease and drug-

induced cases most common type of oromandibular involvement was jaw opening dystonia whereas in idiopathic cases most common type was jaw closing dystonia and Oro-facial movement without jaw involvement ($p<0.001$). Speech and swallowing abnormalities were most severe in Wilson's disease ($p<0.001$) although severity of oromandibular movement and ocular involvement was not significantly different among different aetiologies ($p=0.227$). Positive Family history was present in 7.3% of patients. There was no significant difference between different types of cranial dystonia ($p=0.738$).

Table-3 Comparison between different types of cranial dystonia

		BLEPHAROSPASM M (n=25)	OROMANDIBULAR DYSTONIA (n=44)	MEIGE'S SYNDROME (n=27)	P
Age of onset		45.7 ± 15.5	36.39 ± 25.8	49.02 ± 13.3	0.03
M:F		13:12	30:14	11:16	0.068
Duration of illness		3.57 ± 4.2	3.75 ± 4.8	2.59 ± 2.1	0.47
Extra-cranial involvement		2/25(8%)	28/44(63.6%)	12/27(44.5%)	<0.001
Photophobia		21/25(84%)	NA	19/27(70.4%)	0.2
Sensory tricks		19/25(76%)	4/44(9.1%)	14/27(51.9%)	<0.001
Types of oromandibular involvement	JOD	NA	21	9	0.063
	JCD		9	6	
	JDD		2	1	
	JMD		7	3	
	OFL		3	0	
	OF		2	8	
Mouth score		NA	4.1 ± 1.9	3.2 ± 1.4	0.64
Severity score of ocular involvement		5.2±1.8	NA	4.7±2.4	0.377
Causes					<0.001
Idiopathic		20 (80%)	12 (27.3%)	19 (70.4%)	
Non-idiopathic		5 (20%)	32 (72.7%)	8 (29.6%)	

Jaw opening dystonia (JOD), jaw closing dystonia (JCD), jaw deviation dystonia (JDD), jaw mixed dystonia (JMD), oro-facio dystonia (OF) and oro-facio-lingual dystonia (OFL), NA (not applicable), M (male), F (female)

Patients of oromandibular dystonia had significantly younger age of onset than patients of blepharospasm and Meige syndrome ($p=0.03$)

There was no gender difference ($P=0.068$) between these three types of cranial dystonias although Meige syndrome were more prevalent in females whereas oro-mandibular dystonia and blepharospasm were more common among males.

Among different types of cranial dystonias, oromandibular dystonia was commonly associated with other extracranial dystonias whereas in patients with blepharospasm and Meige syndrome, dystonia was mostly limited to cranial distribution ($p<0.001$). There was no significant difference in the prevalence of photophobia in blepharospasm with or without associated oro-mandibular dystonia ($p=0.2$). Sensory tricks were more commonly used by patients of blepharospasm than patients of Meige syndrome and of oro-mandibular dystonia ($p<0.001$). Types and severity of oro-mandibular movement abnormalities among oro-mandibular dystonia and Meige syndrome were not significantly different ($p=0.063$). There was no significant difference in severity of ocular involvement between blepharospasm and Meige syndrome ($p=0.37$). Most of the blepharospasm

and Meige syndrome were idiopathic where-as most of the oromandibular dystonia were non-idiopathic ($p<0.00$).

In Oro-mandibular dystonia non-idiopathic cases were mostly due to drug induced (14/32; 43.75%) and Wilson's disease (13/32; 40.62%). Other aetiologies being birth-insult($n=2$), YOPD($n=1$), post herpes-zoster infection ($n=1$), NBIA ($n=1$). 62.5% Non-idiopathic Meige syndrome (5/8) was post-operated cases of cataract or glaucoma, 2 cases were drug induced and 1 case had PKD. Among non-idiopathic blepharospasm cases, 60%(3/5) patients had history of surgery for eye conditions, 1 had history of head injury and 1 patient had history of conjunctivitis before development of blepharospasm.

DISCUSSION

We found that cranial dystonias were more prevalent among males than females which contradicts findings from previous studies (6,7,8). This could possibly be explained by an existing geographical variation or a bias due to various prevailing socio-cultural reasons. The average age of onset of cranial dystonia in our study, is in the 5th decade which is a decade earlier as compared to their western counterparts (6,8,9,10,11). This could be due to possibly different genetic and epigenetic factors, which needs to further explored in long term studies.

Cranial dystonia starting from oromandibular region had a greater risk of extracranial spread than blepharospasm onset cases ($p<0.001$). Also, if blepharospasm spread to the oromandibular region then there was a high chance ($p=0.02$) of extra-cranial spread, than when it remained restricted to the ocular region alone.

Gender ($p=0.48$) did not predict severity of ocular involvement but presence of photophobia ($p=0.026$) and sensory tricks ($p=0.004$) did. We found that JOD was most common type of oromandibular movement abnormality. Photophobia was present in 76.9% of cases. In previous studies prevalence of photophobia was variable from 32%-74%(6,7) among blepharospasm, which is consistent with the results of our study.

In present study, most common type of dystonia which occurred simultaneously with OMD in the segmental form was blepharospasm (80%) which is comparable with a previous studies (11).

Again lingual dystonia was significantly associated with JOD and JMD than with JCD (53.3%, 40%, and 13.3%, respectively, $p = 0.033$) these findings were similar to the previous studies (11).

In patients of cranial dystonia if there is simultaneous extracranial site involvement then there is high risk of non-idiopathic aetiology. If dystonia started from extracranial region and later-on spread to cranial region then chance of finding non-idiopathic aetiology is higher than dystonia started from cranial region. But among cranial onset cases if dystonia started from oro-mandibular region then risk of non-idiopathic aetiology is higher than blepharospasm onset cases.

Certain clinical features can predict aetiology of cranial dystonia such as presence of sensory tricks and JOD type of dystonia. Where-as presence of photophobia and tremor did not predicted types of aetiology. Sensory tricks were more prevalent in idiopathic cases similar to a previous reported study (12) and jaw opening dystonia in non-idiopathic cases.

The chance of development of Meige syndrome was more if dystonia started as blepharospasm rather than Oro-mandibular dystonia ($p<0.001$) Severity of ocular involvement between blepharospasm and Meige syndrome and severity of oro-mandibular abnormal movement between blepharospasm and oro-mandibular dystonia was not significantly different.

In a recent meta-analysis on OMD, genetic and presumed genetic (idiopathic), along with tardive etiologies accounted for the vast majority of isolated oromandibular dystonia in adulthood (13). Also drugs were the commonest cause of acquired oromandibular dystonia (13) similar to our study.

CONCLUSIONS

In the current hospital-based, study we found that cranial dystonia started a decade earlier than western population. Oromandibular dystonia was the commonest type of cranial dystonia. Onset with blepharospasm had the highest chance of progression to Meige syndrome, while oromandibular onset had a higher risk of extracranial spread. If cranial dystonia had simultaneous extracranial involvement, then possibility of underlying secondary aetiology was high. Drugs and Wilson's disease were most common non-idiopathic aetiology of cranial dystonia.

Limitations

We have not been able to perform genetic analysis in our patients because of financial constraints. TRODAT or other functional imaging was not done due to the non-availability of the same at our institute.

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Reviewer 1:

The authors have analysed a series of 96 patients presenting with cranial dystonia.

1. In the "Axis II", the authors mention that "Cranial dystonia was idiopathic in 53.1% (51/96) and non-idiopathic in 46.9% 163 (45/96)". One of the major drawback of this study is the absence of genetic testing in all the 96 patients. It appears incorrect to label a group of patients, lacking abnormality on biochemical or radiological investigations, as idiopathic in the absence of genetic testing. Probably many (or at least few) of these patients might have been reclassified to non-idiopathic group (esp. hereditary/ genetic) rather than idiopathic group. Can the authors explain their stand on this ?

2. The authors write in the "Introduction" that "There are only few case series on cranial dystonia from India (2, 3, 4) till date. Therefore larger prospective observational studies will help us in a better identification and recognition of this complex disorder, which causes significant impact on speech and swallowing causing funtional impairment." There study appears a "cross-sectional" study rather than a prospective follow-up study. In fact, the data collected from the patient was something which had affected them in the past... like which group of muscles were first involved and so on... a big disadvantage of this is the "recall bias". I was wondering how there study is different from other case-series reported from India as far as the study design in concerned.

3. On the other hand, I would suggest the authors that if they had followed each of these patients for a couple of years, they can write the average follow-up period and discuss the evolution of symptoms based on their examination findings during the follow-up. This may proved a better picture of "cranial dystonia" as they have mentioned in the introduction.

4. I understand that when the authors write in "methodology" that "classified cranial dystonia into blepharospasm, oromandibular dystonia and Meige syndrome, according to the consensus update on the phenomenology and classification of dystonia(1)", they meant regarding the presence of dystonia at the time of presentation. I would suggest them to mention "at the time of presentation" in the methodology. A major concern here is that few of these dystonia may advance and get classified in a different label as their disease progresses.

5. Unfortunately, I could not see any of the tables with the manuscript. I would request the authors to kindly submit their tables as they have mentioned in the manuscript.

6. In the "Result" section and the subsection titled "Distribution of cranial dystonia", the authors have written "Oromandibular dystonia was the most common type of cranial dystonia (n=44/96, 108 45.8%) followed by Meige syndrome (n=27/96, 28%) and blepharospasm 109 (n=25/96, 26%)." In the next paragraph they again write, "Cranial dystonia was mostly focal (40.6%). It was a part of segmental body 111 distribution in 31.3% (30/96), generalized body distribution in 19.8% (19/96) and multifocal body distribution in 8.3% (8/96). Among segmental cranial dystonia, 50% (15/30) cases were of Meige syndrome, 33.33% (10/30) had additionally cervical involvement, 10% (3/30) had laryngeal dysphonia and 6.67% (2/30) had additional cervical with upper-limb involvement." It is very confusing to understand few things If we take or-mandibular and blepharospasm as focal dysotnias, there combined percentage in >> 40.6%, while the authors write that cranial dystonia was mostly focal (40.6%) in the subsequent sentence. I was wondering if the authors can clear the timepoints of patient's symptoms/ examiner's assessment ??

7. While describing the non-idiopathic cases, I would suggest the authors to kindly answer the following, "Break-up of post-drug cases?; what was the surgery in their post-surgery case? which particular infection was detected in their post-infective case? How did they confirm birth insult... was it radiologically or clinically+radiologically ? what was the trauma in their post-traumatic cases ?

what was the manifestation of PKD....was it genetically proven ? What was the genetic diagnosis of NBIA ... I mean which subtype ?"

8. In the first paragraph under discussion, the authors write, "We found that cranial dystonias were more prevalent among males than females which contradicts findings from previous studies(6,7,8)." All the three studies which the authors have compared here include ONLY blepharospasm cases" I would suggest authors to take into consideration several of the larger series including other type of cranial dystonia. They can refer to a nice review by Pandey and Sharma et al. 2017 in JNS.

9. In the discussion the authors write that "The chance of development of Meige syndrome was more if dystonia started as blepharospasm rather than Oro-mandibular dystonia ($p < 0.001$)" I would suggest the authors to please discuss briefly the hypothesis or reason(s) behind this.

10. In the limitations, the authors write that "TRODAT or other functional imaging was not done due to 304 the non-availability of the same at our institute." I was wondering how the presence of "TRODAT or functional imaging" would have helped them to reclassify their patients in the AXIS-II. Please explain this.

In fact, absence of "genetic testing" in their patients is the biggest limitation of their study and its presence might have had significant implications on their results and conclusions.

11. There are several typographical errors.. e.g., SPSS has been written as SSPS... and so on.

Reviewer 2:

Thank you very much for asking me to review the manuscript titled "Clinical characteristics of different types of cranial dystonia: An observational study."

I appreciate the efforts of authors in conducting the study and drafting the manuscript.

The observations from the study are indeed interesting. However, there are some areas of concerns, which need to be clarified before considering for the publication.

The authors should enlist the complete inclusion & exclusion criteria. It is not clear whether they excluded the PD or other atypical parkinsonism cases. The authors have mentioned that one patient had 1 YOPD. If authors have included combined dystonias, I expect more representation of such cases in their cohort. But, there is no mention of combined dystonia in results or discussion. These points need to be clarified.

Authors have mentioned that they will do the BFM scoring, but the data is not available.

The results section is exhaustive to read. Authors can use tables & graphs to represent some part of their data. Though the subheadings mention tables, I could not find them in the bundled doc.

The other limitations, like the lesser representation of childhood/adolescent onset dystonia, lack of supporting radiology/ functional images, disability/severity score, and treatment, should be acknowledged.

The manuscript requires further editing for the language and grammar. My edits and other minor comments can be found in the draft attached.

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