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Clinical subtypes of anterocollis in parkinsonian syndromes

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Abstract

Background—Disproportionate anterocollis is a debilitating condition which occurs in the later stages of parkinsonian syndromes and for which there is no effective therapy. Multiple hypotheses have been proposed to explain its underlying etiology, including myopathy of the cervical extensors, and dystonia of the cervical flexors.

Methods—We examined the records of 39 patients (8 prospectively) with anterocollis and parkinsonian syndromes to explore demographics, historical and clinical data, findings from electromyography and response to therapies. We classified our patients based on whether or not they were weak on neck extension and also based on primary diagnosis (PD vs atypical parkinsonian syndrome). Demographic, clinical, historical and EMG features are reported for each group.

Results—There were no significant demographic differences between clinical subtypes, or primary diagnosis. Electromyographic (EMG) findings demonstrated myopathic changes in both groups, although they were more prominent in the group which was weak in extension. Historical features were similar between groups except for dopamine agonist use, which was more common in the myopathic subgroup ($p = 0.02$). There were no other significant clinical differences between clinical subtypes or primary diagnosis with the exception that patients with atypical parkinsonian syndromes had more advanced motor symptoms.

Conclusions—We conclude that anterocollis is a heterogeneous condition in which at least two distinct subtypes exist. Recognizing these subtypes may help guide therapy and future research.

Keywords

Anterocollis; Head drop syndrome; Parkinson's disease; Dystonia; Myopathy

1. Introduction

Anterocollis has been defined as marked neck flexion (>45%), disproportionate to trunk flexion [1,2]. Patients who have this problem are unable to hold their head up in a normal

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posture and may have superimposed laterocollis or torticollis [3]. As a result there is great discomfort and functional impairment. Historically, its presence was considered to be a 'red flag' for a diagnosis of multiple system atrophy (MSA) [4]. However, it has since been reported in levodopa-responsive Parkinson's disease (PD) as well [5]. No effective therapy is available. Neck rigidity, weakness, limitations in range of motion, pseudohypertrophy of the neck extensors, and atrophy of the flexors have all been reported as characteristics of this condition [3,6,7]. Terms used to describe anterocollis in the literature include 'head drop' or 'dropped head syndrome' (DHS) which has been used to imply weakness as a cause [8–11], and 'disproportionate anterocollis' which has been used to imply dystonia as a cause [3,12,13].

Multiple hypotheses have been presented regarding the etiology of anterocollis. Early reports argued that myopathy was the primary etiology, based on the finding of myopathic features on electromyographic (EMG) examinations of the cervical extensor muscles, and some biopsy data [8–11]. More recent studies on camptocormia (presumptively a similar disorder affecting the thoracic and lumbar areas) and anterocollis have also demonstrated myopathy of extensor muscles as well as edema of this musculature on MRI [14,15], suggesting that the hypertrophy of these muscle groups was actually pseudohypertrophy. These studies were limited by the fact that they excluded patients who were not weak in extension. In addition, it has been argued that the EMG findings supporting myopathy were non-specific and there was insufficient normative data to be able to interpret biopsy findings [12]. An alternative hypothesis is that anterocollis is due to dystonia of the neck flexors and that the myopathic changes observed in studies of the extensors were inconsistent and likely secondary [3,12,13].

In this study, we attempted to reconcile some of the conflicting findings described in previous studies by including all phenotypes of this condition. We hypothesize that there may be at least two different subtypes.

2. Methods

All assessments described here had the approval of Emory University's Institutional Review Board. Patients with a clinical diagnosis of PD or atypical parkinsonism [including MSA, progressive supranuclear palsy (PSP), dementia with Lewy Bodies (DLB), or corticobasal degeneration (CBD)] and concurrent anterocollis were recruited from the Movement Disorder clinic at Emory University (between July 2009 and June 2010) either prospectively (8 cases) or retrospectively (31). Medical records were reviewed for all cases. All patients were diagnosed by a movement disorder neurologist using established diagnostic criteria. Patients were considered to have anterocollis if there was a subjective complaint corroborated by an objective finding of anterocollic head posture on exam. There was no minimum degree of flexion so as to include the full spectrum of presentations. Data collected included demographic information, primary diagnosis, stage at the time of enrollment [modified Hoehn and Yahr (H&Y)] and duration of disease. Historical information gathered included duration of parkinsonism, duration of anterocollis, mode of onset, course or progression, presence of pain, disability resulting from anterocollis, dopamine agonist (DA) use, and presence of sialorrhea. DA use was specifically looked at in our population since there have been reports of anterocollis occurring following their administration. Sialorrhea has been reported as a frequent finding and source of worsening quality of life from this condition. Clinical examination information regarding head posture, presence or absence of extensor weakness, extensor hypertrophy, flexor atrophy, and neck rigidity was gathered when available. Prospective clinical evaluations included measurement of degree of anterocollis using a protractor and wall chart [16]. Information regarding EMG or imaging (e.g. cervical spine MRI) and treatment (botulinum toxin, deep brain stimulation

or dopaminergic therapy) was collected from the record. Prospective EMGs were performed on paraspinal muscles and other proximal muscles to determine if the process was truly isolated. All prospective EMGs were performed by an experienced electromyographer and neuromuscular specialist (M.B.). Most retrospective EMGs were performed by the same electromyographer. To further minimize variability and eliminate bias, the data for all EMGs (prospective and retrospective) was collected, de-identified, tab-ulated and the same electromyographer (who performed all prospective EMGs) was asked to characterize each case as: 1) No Myopathy, 2) Possibly Myopathic, or 3) Definitely Myopathic.

For the sake of comparison, patients were divided by primary diagnosis (PD vs. atypical parkinsonism) and by the presence or absence of weakness on extension. Because of the retrospective nature of the study (for 31 subjects) some of the data points were not available in all patients. T-tests and Fisher's exact tests were used for comparative analyses.

3. Results

3.1. Demographics and disease specific information

Of the 39 patients identified, 27 had PD and 12 had atypical parkinsonism (7 MSA, 2 PSP, 3 DLB). Mean (SD) age at the time of examination was 74.9 (7.7) years and 61.5% of the patients were male. Information regarding weakness on head extension was available on 31. Of these, 13 (42%) had neck extensor weakness. The mean (SD) duration of parkinsonism and duration of anterocollis was 9.3 (4.5) years and 2.9 (3.4) years, respectively. There were no significant differences in age, gender, duration of illness, or duration of anterocollis between PD and atypical parkinsonism, or between those with extensor weakness and those without extensor weakness (Table 1). However, patients with atypical parkinsonism had on average a significantly higher H&Y score than those with PD ($p=0.002$).

3.2. Electromyography data

Eight of the 18 patients whose neck extensor strength was documented to be normal underwent EMG testing. Five of the eight EMGs were performed prospectively. Only one of the eight EMGs showed definite myopathy on the original report, and this was later interpreted as only possibly myopathic in the blinded interpretation (Table 2a and 2b).

Eight of the 13 patients with documented extensor weakness underwent EMG evaluation. All, but one of the EMGs in this group showed evidence of myopathy of varying degrees of severity. Four of the eight EMGs were performed prospectively, by the same electromyographer. In both the retrospective review of records and the blinded interpretation, only one study lacked definitive evidence of myopathy. This particular patient had significant reduction in cervical range of motion at the time when extensor weakness was documented.

In fact, there were two patients in our cohort who had limitation in cervical range of motion. Clinical data for both patients was gathered prospectively. One patient had PD for 13 years, and anterocollis for 3 years, was strong in extension with $\sim 45^\circ$ anteroflexion, pronounced saggital shift with extensor pseudohypertrophy and flexor atrophy. The first EMG was performed one month after onset of anterocollis and showed early recruitment of small, short duration, moderately polyphasic motor unit action potentials which was isolated to the C7 paraspinal muscles. EMG of the SCMs did not show tonic discharges at rest. Follow up EMG 3 years later performed by the same EMGer showed normal recruitment, long duration at C6/7 short duration at C6/7, moderately polyphasic motor unit action potentials at C4, 6 and 7. The other patient had MSA for 8 years and anterocollis for 5, had 4/5 weakness on extension with 50° anteroflexion, pronounced saggital shift, with extensor pseudo-hypertrophy, levator spasm and flexor atrophy. The first EMG was performed ~ 6 months

after onset of anterocollis. This study showed normal recruitment, amplitude, duration, phase and activation at two paraspinal levels. SCMs were sampled and showed evidence of tonic activation. The second EMG was performed 2 years later and showed slightly reduced recruitment at C5/6 of long duration motor unit action potentials at the same levels, one short duration unit at C7, and mildly polyphasic units at C5-7.

3.3. Historical data

Information regarding clinical history was available on 33 of the 39 patients; however, not all historical aspects were available for each category (Table 3). Patients who developed anterocollis with extensor weakness were more likely to have been on DAs at onset than patients without extensor weakness (88% vs. 20%; $p=0.02$). Anterocollis was progressive and disabling for the majority of patients studied. Most patients complained of cervical pain and sialorrhea throughout the course of their anterocollis.

3.4. Examination data

Information regarding clinical exam findings was available on 38 of 39 patients. Almost all of the examination findings were similar between the different patients in this cohort (Table 4). However, it is worth mentioning that patients with atypical parkinsonism tended to have more extensor weakness (55%), compared to patients with PD (35%, $p=n.s.$). There were no other significant differences between atypical parkinsonism and PD patients with regards to head posture, presence of flexor atrophy, extensor hypertrophy or rigidity. Of the patients who had flexor atrophy, extensor hypertrophy was seen in 75% (9/12). Patients without extensor weakness were not more likely to have superimposed laterocollis and/or torticollis as one would expect if anterocollis was indicative of a dystonic phenotype [13].

3.5. Treatment data

Treatment trials and clinical response data was available in eleven patients. Six received dopaminergic therapy with no benefit. Four patients had trials of botulinum toxin; of these, two had no response, and two had modest benefit. One patient had bilateral subthalamic nucleus deep brain stimulation (STN-DBS) and reported subjective improvement in head posture post-operatively, objective observations prior to surgery were not available to corroborate this report.

4. Discussion

We report our experience with 39 patients suffering from parkinsonian syndromes and concurrent anterocollis of varying degrees of severity. This is the largest cohort reported with this condition to date. Prior studies examining anterocollis have reported conflicting findings. An early report of 7 patients with anterocollis found that all had myopathic features on EMG; however, all seven had neck extensor weakness [8]. Similarly, a recent study reported myopathic findings on biopsy of 19 cases with anterocollis; all nineteen were described as having 'weakness in the neck extensor musculature'. There was no evidence of dystonia in any [17]. Conversely, Van de Warrenburg et al. studied 15 anterocollis cases and reported that EMG changes were not compatible with a primary myopathy. The majority of the patients they studied had no extensor weakness [13]. Others concluded that dystonia was the underlying feature of this condition after performing studies on small groups of patients lacking extensor weakness [3]. Finally, Yoshiyama et al. studied seven patients, three of whom had documented extensor weakness. They performed EMGs on two patients, one of whom had extensor weakness; both EMGs were normal [7].

If, in fact, anterocollis is a heterogeneous condition with at least two distinct subtypes, as we propose, our findings would be consistent with all of these previous reports. This conclusion

reconciles conflicting findings in the literature. It is important to recognize the heterogeneous nature of this condition when defining it and when developing inclusion and exclusion criteria for future clinical trials. Findings from studies of anterocollis that exclude patients whose neck extensors are either weak or not weak should not be generalized to the entire population of anterocollis patients. Future reports regarding therapeutic interventions, or studies addressing the pathophysiology of anterocollis should either include both subtypes, or clarify that their results apply only to the subtype being studied. Evidence to support a heterogeneous presentation of this condition is emerging [18].

We found two outliers in our cohort. These were two patients with long duration of anterocollis, who had relatively fixed neck postures. These two patients had a relatively long course of anterocollis and had early and late EMG studies which changed from myopathic to neurogenic in the PD case, and from normal to neurogenic in the MSA case. Although these patients may be excluded from some anterocollis cohorts, we feel it is important to include this subtype in our cohort and describe our findings. Many skeletal deformities in Parkinsonian syndromes lead to reduction in range of motion, and contracture [1,2]. We speculate this is the case with these two cases, but cannot confirm this without careful prospective study.

Although this condition was historically thought to be indicative of MSA, and is indeed more common in this condition, there have been several reports of anterocollis in PD [3], DLB [19] and PSP [20]. In our cohort, we confirmed that anterocollis occurs in all of these conditions. The occurrence of anterocollis in patients with parkinsonism should continue to raise suspicion for atypical parkinsonism, since it is more common in these syndromes, but it is certainly not specific neither for atypical parkinsonism in general nor for a specific atypical parkinsonian syndrome. Regarding patients with neck extensor weakness and myopathic findings on EMG, we do not have complete documentation regarding comprehensive investigations to exclude the presence of any underlying neuromuscular disease. In the prospective patients, we did ensure the process was isolated.

This study confirms previous reports of a relationship between DA use at the time of symptom onset and the development of anterocollis [3,5,21–23] and this data has been reviewed recently [24]. All of these reports have suggested a dystonic etiology, and at least one case reported normal extensor EMG [22]. Our findings show that patients who developed myopathic anterocollis were more likely to be on DAs ($p=0.02$). In other reports, there was a more direct association, with symptom onset soon after initiation treatment with DAs, or increasing dose, and symptoms improvement or resolution upon its discontinuation. In our study we simply report an association where patients who developed myopathic changes were more likely to be treated with DAs at the onset of symptoms. If there was a true causal association between DA and development of dystonic anterocollis, one may argue peak dose dystonia as a possible etiology. However, if a true causal association was confirmed between DA treatment and myopathic anterocollis, one may speculate more direct damage to the extensor muscles, possibly explaining the described fibrotic changes reported on biopsy. Further studies with larger sample sizes would need to be conducted to prove a true causal relationship, and if present, begin to elucidate the underlying mechanism.

The primary limitations of this study are the largely retrospective nature of data collection. Future studies should focus on understanding the pathophysiology of parkinsonian dystonias, as well as focal myopathies in parkinsonian syndromes. Prospective studies taking into consideration all clinical subtypes of anterocollis and performing repeat investigations starting soon after the onset of anterocollis are warranted to confirm the value of this clinical distinction.

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Table 1

Demographics.

	PD (n=27)	Atypical parkinsonism (n=12)	p-value	Extensor weakness (n=13)	No extensor weakness (n=18)	p-value
Age in years mean (SD)	74.5 (7.5)	75.7 (8.5)	0.7	76.5 (7.8)	72.2 (8.0)	0.2
Gender n (%) male	19 (70.4%)	5 (41.7%)	0.2	6 (46.2%)	14 (77.8%)	0.1
Duration of Parkinsonism in years mean (SD)	10.1 (4.7)	7.6 (3.8)	0.1	8.2 (3.6)	9.2 (4.5)	0.5
Duration of anterocollis mean (SD)	3.1 (3.9)	2.6 (2.3)	0.7	2.2 (2.4)	3.8 (4.1)	0.3
Modified H&Y Stage	3.2 (0.9)	4.3 (0.9)	0.002*	3.7 (1.0)	3.5 (1.0)	0.6

Table 2a

EMG findings of all patients (prospective and retrospective).

	Number	No myopathy	Possibly myopathic	Definite myopathy
Neck extensor weakness	8	1	0	7
No neck extensor Weakness	8	5	2	1 (mild)

Note: For patients who had two separate EMGs, only the more recent prospective EMG was used in this table.

Table 2b

EMG findings. (Prospective only).

	Number	No myopathy	Possibly myopathic	Definite myopat
Neck extensor weakness	4	0	2	2
No neck extensor weakness	5	2	3	0

Note: These EMGs were all done prospectively by one electromyographer, the EMG data was then de-identified and the same electromyographer rated each study based on the data alone.

Table 3

Historical details.

	PD (n=27)	Atypical parkinsonism (n=12)	p-value	Extensor weakness (n=13)	No extensor weakness (n=18)	p-value
Acute/subacute onset	7/14	0/5	0.1	3/6	3/12	0.3
Progressive course	12/14	5/5	>0.9	5/6	10/11	>0.9
DA at onset	7/15	2/4	>0.9	7/8	2/10	0.02*
Disabling	18/19	10/10	>0.9	12/12	12/13	>0.9
Painful	10/12	6/7	>0.9	8/9	7/9	>0.9
Sialorrhoea	8/11	9/10	0.6	6/8	10/12	>0.9

Table 4

Clinical findings.

	PD (n=27)*	Atypical parkinsonism (n=12)	p-value	Extensor weakness (n=13)	No extensor weakness (n=18)	p-value
Extensor weakness	7/20	6/11	0.4	-	-	-
Pure anterocollis	21/26	10/11	0.6	11/12	13/18	0.4
Flexor atrophy	8/13	4/7	1.0	6/8	6/12	0.4
Extensor hypertrophy	6/16	4/8	0.7	4/10	6/14	1.0
Neck rigidity	19/22	10/10	0.5	9/11	15/16	0.5

* n values represent the total number in each category, however, the denominators in each column represent the number of cases where there was available data for each category.