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Headaches in hypermobility syndromes: A pain in the neck?

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Abstract

Headache and neck pain (cervicalgia) are frequently reported among patients with joint hypermobility but the prevalence and scope of these symptoms has not been studied in the era of contemporary Ehlers-Danlos and hypermobility disorder nosology. We performed a single-center retrospective study on the incidence of head and neck symptoms in 140 patients with hypermobility disorders over a 2-year period. Overall, 93 patients (66%) reported either headache or neck pain with 49 of those (53%) reporting both. Migraine (83%) was the most common headache type among those with headache disorders and cervical spondylosis (61%) the most common pathology among those with neck symptoms. Fifty-nine percent of spondylosis patients who underwent cervical facet procedures reported significant improvement in neck and head symptoms. Of patients with both head and neck complaints, 82% had both migraine and spondylosis, which, when combined with the high response rate to injections raises the possibility of cervicogenic headache. In this large multidisciplinary retrospective study of patients with hypermobility disorders, head and neck symptoms were highly prevalent, with migraine and cervical spondylosis common, often coexisting, and frequently responsive to targeted therapy for the cervical spine suggesting that degenerative spinal pathology may cause or contribute to headache symptoms in some patients with hypermobility disorders.

KEYWORDS

cervical spondylosis, cervicalgia, Ehlers-Danlos syndrome, hypermobility disorder, migraine

1 | INTRODUCTION

Hypermobility disorders refer to a range of conditions including the Ehlers-Danlos syndromes (EDS), sharing the common feature of excessive joint laxity and often leading to musculoskeletal pain and disability. Nosology for this broad family of conditions has evolved since the first comprehensive description of "The Hypermobility Syndrome" (Kirk, Ansell, & Bywaters, 1967). Most recently, the Committee on Hypermobile Ehlers-Danlos Syndrome of the International Consortium on the Ehlers-Danlos Syndromes put forth updated guidelines delineating distinct and stringent diagnostic criteria for hypermobile Ehlers-Danlos syndrome (hEDS) and a range of alternative diagnoses labeled "hypermobility spectrum disorders" (HSDs) (Malfait et al., 2017).

Headaches have been reported as common in hypermobile patients in case series and case-control studies of heritable connective tissue disorders. In one of the largest reported series, headache occurred in 30–40% of patients with EDS (Sacheti et al., 1997). Patients with joint hypermobility syndrome may also report headaches that are more frequent and debilitating than in the general population (Bendik et al., 2011; Puledda et al., 2015). However, interpretation of these results in 2020 is hampered by the fact that prior studies: (a) preceded the most current diagnostic nosology of hEDS and HSD; (b) did not describe the full range of specific headache disorders; and (c) did not address the association of frequently accompanying neck pain in this population (Dolan, Hart, Doyle, Grahame, & Spector, 2003).

To address these needs, we retrospectively assessed the prevalence of all-cause neck pain (cervicalgia) and headache in a population of hypermobile patients evaluated through our multidisciplinary program. We evaluated for specific headache types using International Classification of Headache Disorders (ICHD-3) standards (Headache Classification Committee of the International Headache Society, 2018) for migraine, tension-type headache, cluster headache, new daily persistent headache (NDPH), and cervicogenic headache. Since craniocervical pain is common in these patients and may relate directly to associated hypermobile phenomenon, we also investigated the prevalence of cervical spondylosis, craniocervical instability (CCI), intracranial hypotension (low pressure), Chiari malformation, and vascular lesions (i.e., arterial dissection) according to the most current diagnostic standards and using imaging to confirm diagnoses when available.

2 | METHODS

We conducted a single-center retrospective study of the incidence and description of head and neck symptoms and etiologies in patients with hypermobility disorders. Subjects were eligible for inclusion if they were referred to our multidisciplinary Cardiovascular Genetics Program for evaluation of Ehlers-Danlos syndrome or a heritable connective tissue disorder between January 1, 2017 and December 30, 2018 and subsequently diagnosed with a hypermobility disorder. The study was conducted under the approval of Mount Sinai's Institutional Review Board (GCO # 19-0883 ISMMS). Electronic health records (EHRs) were reviewed for demographic data and diagnoses of hEDS or HSD documented by a study investigator based on the in-person clinical evaluation. The determination of the specific underlying hypermobility disorder was made by either a cardiovascular genetics (A.R.K. or B.D.G.) or medical genetics (L.M.) specialist based on the Committee on Hypermobile Ehlers-Danlos Syndrome of the International Consortium on the Ehlers-Danlos guidelines for hEDS and HSDs (Malfait et al., 2017). Some patients were subsequently referred to and evaluated by a pain management (A.M.) or headache (A.P. or R.C.) specialist. Expert review of EHR for symptom description, physical examination findings, and imaging results was performed by both a pain management (A.M.) and headache (A.P.) specialist if an in-person neurology or pain evaluation had not been performed. Ascertainment of headache diagnosis was confirmed through review of documentation by applying ICHD-3 criteria (IHS, 2018) to chart review data (A.P.). Additional measures determined included: complaint of head and/or neck discomfort in the history or review of systems; diagnosis of any of the following in the EHR: cervical spondylosis, CCI, low cerebrospinal fluid (CSF) pressure, Chiari malformation, cerebrovascular lesion (i.e., arterial dissection), or other craniocervical diagnosis; and results of any relevant imaging studies. Charts of those patients meeting diagnostic criteria for cervical spondylosis were queried for history and patient-reported efficacy of medial branch block (MBB) or radiofrequency ablation (RFA) procedures for the cervical facet joints (Figure 1). Diagnostic imaging was reviewed (A.M.) when available.

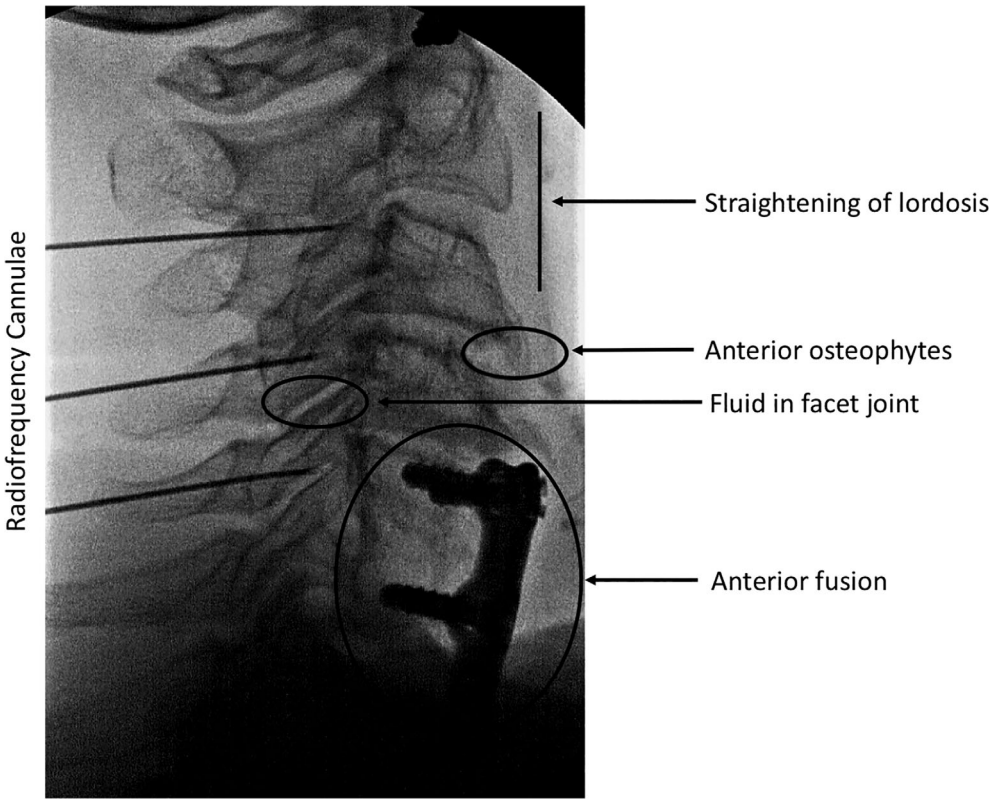

FIGURE 1 Representative fluoroscopic image of spondylosis in hypermobile patient with neck discomfort. Findings commonly associated with spondylosis and seen on imaging include straightening of lordosis, osteophytes, fluid in facet joints. This image additionally shows hardware from a prior anterior fusion, as well as cannuale in plate for a radiofrequency ablation of medial branches

2.1 | Statistics

Fisher's exact test (two-tailed) was used to compare rates of headache and/or neck pain among subjects with diagnoses of hEDS versus HSD. $p < .05$ was considered as statistically significant.

3 | RESULTS

During the 2-year study period, 140 patients were evaluated for and diagnosed with a hypermobility disorder. Initial consultations were requested by primary care providers, rheumatologists, orthopedists, pain management specialists, neurologists, or self-referred and performed by a study investigator (A.R.K., B.D.G., or L.M.). The reason for the initial consultation was "joint hypermobility," "rule out Ehlers-Danlos syndrome," or "evaluate for connective tissue disorder." The average age was 34.6 ± 12.8 years (range 13–72) and 93% were female (F = 130, M = 9, transgender = 1). Most patients (71%) were diagnosed with either hEDS or generalized HSD (G-HSD), and the remainder were diagnosed with either an alternate HSD or a rarer form of EDS (Table 1). Eight patients (6%) were classified as having an unspecified hypermobility disorder.

Head and neck complaints were common among patients with hypermobility disorders and included headache, subjective neck instability or "clicking," neck pain, facial pain, and combinations thereof with 93 (66%) endorsing one or more of these symptoms (either as chief complaint or documented in "review of systems" or "history of present illness" in the medical record); 49 (53%) of these reported concomitant headache and neck pain. Notably, 44 (31% of all 140 patients) endorsed a head and/or neck symptom as their chief complaint at the time of the initial hypermobility evaluation, indicating that these symptoms were the primary concern.

Across the different hypermobility diagnoses, the rate of head and neck complaints was highest in those with hEDS but also present in the majority of patients with HSDs (Table 1). Significantly more patients with hEDS had head and/or neck symptoms (48, 86%) compared to those with an HSD (40 out of 73 total HSD patients, 55%; $p = .0002$). Prevalence of head and neck symptoms was not statistically different between patients with the different subtypes of HSD (G-HSD, L-HSD, and H-HSD) but was significantly lower for each than for hEDS ($p = .0001$, .0001, and .0006, respectively).

In total, 80 patients reported headache. Of these, 66 (83%) were determined to have migraine by reported diagnosis, in-person evaluation (by a neurologist specializing in headache medicine), or chart review of symptoms. For the remainder of participants, two had tension-type headache, two had cluster headache, and one had NDPH. Nine patients evidenced mixed or unclear headache types for which a primary headache could not be determined (Table 2).

Of the 62 patients with neck pain, the commonest etiology confirmed on imaging was cervical spondylosis; this was identified as the etiology in 42 patients (68%), encompassing those with spondylosis alone or with additional diagnoses (Table 3). Of the four patients who had multiple anatomic findings in the cervical spine, all included spondylosis as one of the codiagnoses. Low CSF pressure was observed in six cases total (one in conjunction with spondylosis), followed by CCI in three (all of which were associated with concurrent spondylosis), Chiari malformation in two, and arterial dissection in one patient. A total of 12 patients did not evidence any anatomic

TABLE 1 Prevalence of headache and/or neck symptoms reported in the hypermobile cohort

		Headache and/or neck pain
Diagnosis	***N***	***N* (%)**
hEDS	56	48 (85.7)
G-HSD	44	23 (52.3)
L-HSD	19	10 (52.6)
H-HSD	10	7 (70.0)
Other	8	5 (62.5)
vEDS	2	0 (0)
cEDS	1	0 (0)
Total	140	93 (66.4)

Abbreviations: cEDS, classical EDS; EDS, Ehlers Danlos syndrome; G-HSD, generalized HSD; hEDS, hypermobile EDS; H-HSD, historical HSD; HSD, hypermobility spectrum disorder; L-HSD, localized HSD; other, patient with hypermobility not meeting criteria for above or other well-characterized disorder; vEDS, vascular EDS.

TABLE 2 Headache diagnoses among hypermobility patients reporting head pain

Specific headache diagnoses	*N* (%)
Migraine	66 (82.5)
Mixed/unspecified	9 (11.3)
Tension	2 (2.5)
Cluster	2 (2.5)
NDPH	1 (1.3)
Total headache	80

Abbreviation: NDPH, new daily persistent headache.

TABLE 3 Etiologic diagnoses among hypermobility patients reporting neck pain

Diagnoses related to neck pain	*N* (%)
Spondylosis alone	38 (61.3)
Spondylosis with CCI	3 (4.8)
Spondylosis with LP	1 (1.6)
Unspecified	12 (19.4)
LP alone	5 (8.1)
Chiari malformation	2 (3.2)
Vascular	1 (1.6)
Total	62

Abbreviations: CCI, craniocervical instability; LP, low cerebrospinal fluid pressure.

TABLE 4 Prevalence of diagnoses related to neck pain according to underlying hypermobility diagnosis

	N (%)					
Diagnosis	**Spondylosis**	**LP**	**Chiari**	**CCI**	**Vascular**	**Multiple**
hEDS	22 (39.3)	4 (7.1)	2 (3.6)	1 (1.8)	-	1 (1.8)
G-HSD	11 (25.0)	2 (4.5)	-	1 (2.3)	-	2 (4.5)
L-HSD	6 (31.6)	-	-	1 (5.3)	-	1 (5.3)
H-HSD	3 (30.0)	-	-	-	1 (10)	-

Note: "-" indicates *N* = 0.
Abbreviations: CCI, craniocervical instability; G-HSD, generalized HSD; hEDS, hypermobile Ehlers-Danlos syndrome; H-HSD, historical HSD; HSD, hypermobility spectrum disorder; L-HSD, localized HSD; LP, low cerebrospinal fluid pressure.

abnormalities on imaging or exam. The rate of spondylosis among patients with the various hypermobility disorders was similar (Table 4); this was identified in 22 (39%) of those with hEDS and 20 (27%) of those with all-cause HSD (p = .2).

An association between migraine and cervical spondylosis has been described in the general population (Lin, Huang, Chuang, Lin, & Kao, 2018) and since migraine and spondylosis were the most common headache and neck pain diagnoses, respectively, in our cohort (observed in 47% and 30% of the total hypermobility cohort), we investigated whether these conditions may correlate. Indeed, 40 out of the 49 patients reporting both head and neck pain were found to have coexisting migraine and spondylosis (82% of those reporting both symptoms, 43% of patients with any head or neck pain). Of all patients with spondylosis, a total of 22 (52%) underwent either MBB or RFA, with 13 (59%) reporting significant (>80%) improvement in head and/or neck symptoms.

4 | DISCUSSION

Head and neck pain prevalence were high, occurring in 66% of all hypermobile patients assessed. Of the etiologies queried, migraines and cervical spondylosis were the commonest findings and with substantial overlap, together accounting for 43% of patients with a hypermobility disorder who endorsed either head or neck discomfort and 82% of those who reported both types of pain during the initial evaluation.

Migraine was the most common headache type reported (47% of total population, 83% of all headaches), consistent with previous studies in patients with joint hypermobility syndrome. Jacome (1999) examined 18 patients with EDS and found that all reported chronic headaches and 67% had some form of migraine. Hakim (2004) conducted a case-control study of 170 patients with hypermobility diagnosed using the Beighton criteria and found that 40% suffered from migraines compared to 20% in a healthy control group. A study of 28 patients by Bendik et al. (2011) with joint hypermobility syndrome found that 75% had migraine. Importantly, this last study and another (Puledda et al., 2015) have shown that migraine is more debilitating and frequent in patients with joint hypermobility syndrome compared to healthy controls; for example, the hypermobile group in the 2011 Bendik et al. study had an average number of 10.5 headache days per month while the control group had an average number of 5.6 days of headache per month. Our findings are consistent with these in terms of severity, with 44 of the 93 (47%) patients with head or neck pain rating this as their chief complaint, though frequency was not tallied.

NDPH has also been reported to occur frequently in this patient population. It is characterized by a headache that is daily from onset and is often refractory to pharmacologic therapies. Rozen, Roth, and Denenberg (2006) reported that 11 out of 12 patients enrolled in their study with primary NDPH had cervical spine joint hypermobility and 10 out of those 12 participants had evidence of widespread joint hypermobility as determined by Beighton score. Rozen's case series looked at patients with NDPH and then assessed for hypermobility after the headache diagnosis was made. In our series evaluating a hypermobile population and then investigating headache, only one patient was deemed to have NDPH by expert case review, suggesting that this headache type is not frequent in this population; further study on the association of NDPH and hypermobility is probably warranted.

Little data are available on tension-type headache in patients with EDS and other hypermobility syndromes and it has not been a strongly linked diagnosis. A single review did note tension-type headaches to have a similar prevalence but higher frequency of occurrence in patients with hypermobility syndromes compared to controls (Bendik et al., 2011). Two patients in our case series had evidence of tension-type headaches, which is lower than the reported prevalence of 30–78% in the normal population; however, most patients with tension-type headache do not seek medical care, and the numbers observed in our population are similar to those who present for headache specialist evaluation and are diagnosed using the same criteria used in this study (Jensen, 2017).

There is no published data regarding cluster headaches in patients with hypermobility. In our population, two patients were found to have cluster headaches, which is slightly higher than the reported prevalence estimated to be 0.1–0.4% in a non-hypermobile population (Fischera, Marziniak, Gralow, & Evers, 2008), particularly as the majority of patients in our population were women and cluster headaches are more common in men. However, the observed incidence was still low and a larger population study would be necessary to evaluate if there is truly a correlation.

Many patients in this cohort self-reported as having migraine, but a high proportion of these had coexisting neck pain, likely meeting criteria for cervicogenic headache. Distinguishing cervicogenic headache from

migraine is diagnostically challenging, particularly in the setting of chart review. Patients with migraine often report neck pain; however, those with true neck pathology as the etiology of their pain may in fact have cervicogenic headache with migrainous-type features or may have a mixed picture of both (Hall, Briffa, & Hopper, 2008). The ICHD-3 defines cervicogenic headache as a "headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain (IHS, 2018, p. 150)." Range of motion of the neck is often painful and the headache patients experience is worsened by various neck maneuvers. The criteria also discuss that the headache must have developed temporally in relation to the cervical disorder and improved if the cervical disorder resolved; diagnostic blockade of the related nerve supply relieves the headache. Hypermobility syndromes may predispose to cervical spine injuries and pain (cervicalgia) through laxity of supporting ligaments and increased vertebral range of motion resulting in spondylosis (Dolan et al., 2003). In the present study, almost half of patients (45%) with hypermobility and head and/or neck discomfort were observed to have cervical spondylosis not only clinically but as diagnosed by X-ray or magnetic resonance imaging (Figure 1). Of note, in keeping with prior studies, the majority of observed spondylosis included the C5-6 vertebral level, corresponding to the most mobile segment of the cervical spine and suggesting a causative mechanism (Castori et al., 2015). Since more than half of those with spondylosis reported significant improvement with intervention (RFA or MBB), it is plausible that head/neck symptoms in these individuals were cervicogenic in nature. Further study on the prevalence of cervicogenic headache and treatment efficacy in patients with hEDS and HSD is warranted since these invasive procedures can carry risk and may not be appropriate for all patients.

Excess motion of the cervical spine and particularly the upper cervical spine can result in instability with the potential for positional brainstem, spinal cord, or nerve root compression. Symptoms include acute intermittent onset of neurologic deficits associated with particular movements. Data regarding prevalence of CCI in hypermobility syndromes are limited but ligamentous laxity of the cervical spine is well recognized to occur (Milhorat, Nishikawa, Kula, & Dlugacz, 2010) and has separately been identified as a risk factor for CCI (Menezes & Traynelis, 2008); use of databases to aggregate data in this population due to rarity of documented cases has been further identified as an area of need (Henderson Sr et al., 2017). Three patients in this case series were ultimately diagnosed with CCI, with only one patient requiring bracing and surgical intervention. Interestingly, all patients with CCI also evidenced symptomatic and imaging-confirmed severe spondylosis, consistent with pathology resulting from increased mobility. Although CCI appears to be a rare complication of hypermobility disorders, considering that it can cause irreversible neurologic injury, diagnostic work-up of concerning symptoms is justified and may be warranted prior to situations where the cervical spine may be manipulated, such as during general anesthesia, physical therapy, or chiropractic maneuvers (Wrobel & Thompson, 2011).

Meningeal involvement with spontaneous CSF leakage has also been described in various hypermobile syndromes and is thought to occur from excessive distension (ectasias), rupture (cysts), or microfenestrations of the dura due to weakened connective tissue elements. In the present study, six patients demonstrated low pressure symptoms, four of which had confirmed CSF leak (three spontaneous and one iatrogenic) and three of these patients were responsive to epidural blood patch. A study of 18 patients with spontaneous CSF leak by Schievink, Gordon, and Tourje (2004) found that 38% had a known connective tissue disorder (including Ehlers-Danlos but also Marfan syndrome) or signs of hypermobility on exam. A later study by Liu, Fuh, Wang, and Wang (2011) found that 23% of patients with spontaneous intracranial hypotension had joint hypermobility as assessed by Beighton score, though authors state this was not significant compared to controls (16.4%) and specific hypermobility type was not queried. Larger studies likely need to be conducted to better describe the relationship of particular hypermobility and connective tissue disorders with intracranial hypotension, but the incidence in our study population adds to evidence of a link.

Chiari malformation type I describes a developmental disorder wherein the cerebellar tonsils protrude below the foramen magnum, often associated with occipital and suboccipital headaches. In the hypermobile patient population, pseudo-Chiari malformations must be ruled out as low pressure headache due to CSF leak can produce tonsillar herniations mimicking Chiari anatomy; this has been described in prior case reports of patients with connective tissue disorders (Johnston, Jacobson, & Besser, 1998; Owler, Halmagyi, Brennan, & Besser, 2004; Sharma, Sharma, & Chacko, 2001). If there is a question of etiology then orthostasis, magnetic resonance or computed tomographic imaging findings of low pressure, or recent history of dural puncture are likely to provide clues as to the correct diagnosis (Schievink et al., 2011). We identified only two individuals with Chiari malformation (both with hEDS) in our study population and six CSF leaks (four in hEDS and two in G-HSD) indicating that these complications may be rare among patients with hEDS and HSD.

Vascular abnormalities, including vertebral artery tortuosity and dissection, internal carotid artery dissection, and aberrant subclavian artery, have been reported in association with EDS but more frequently in the vascular (vEDS) and classical (cEDS) forms (Debette & Leys, 2009; Dittrich et al., 2007; Martin et al., 2006). The incidence of head or neck pain attributed to a vascular source was low in our case series, with only one patient identified as having spontaneous cerebrovascular dissection. The underlying diagnosis in this case was hEDS, determined on clinical grounds and further confirmed through the absence of any pathogenic variants in *COL3A1*, *COL1A1*, *COL5A1*, or *COL5A2*. Although this study was not designed to specifically assess for frequency and significance of head and neck symptoms in EDS subtypes, it is notable that none of the patients with vEDS ($N = 2$) or cEDS ($N = 1$) reported head or neck symptoms.

In the study population, four patients had more than one finding to account for their head and/or neck discomfort. The largest overlap was between spondylosis and CCI (N = 3) with one case of spondylosis and low pressure. Cervical spondylosis and Chiari malformation has previously been reported to coexist at a significantly higher rate in patients with connective tissue disorders compared to controls, 58% versus 12% in one study (Milhorat, Bolognese,

Nishikawa, McDonnell, & Francomano, 2007); however, we did not see any such overlap in our case series. Echoing prior reviews on the subject matter, given the potential for underlying widespread connective tissue involvement in some hypermobility syndromes, practitioners must be vigilant in assessing if multiple causes are present (Castori et al., 2015).

Limitations of this study include those common to retrospective chart review, namely incomplete reporting, patient self-reporting, and potential for overinterpretation. To the extent possible, this was limited by the inclusion of consistent specific verbiage on the evaluation intake, use of supporting imaging when available, separate evaluation by specialists in each relevant field, and in-person evaluation by at least one study investigator (and often more) for each patient included in the analysis. Demographically, our study was comprised of 93% women, which complicates comparison with other head and neck pain cohorts but is also likely to be representative of the hypermobile population. An additional consideration is that these patients were referred to our tertiary care center for consultation from a large catchment area, which limited opportunities for additional assessment or clarification of patients with unclear or multiple diagnoses. Finally, this retrospective study was not designed to assess the outcomes of specific treatment modalities for patients with head and neck discomfort in the setting of an underlying hypermobility disorder; while specific interventions were found to be successful, we do not have longitudinal follow-up on most to comment on durability of the effects. Future studies may benefit from inclusion of these data.

Given the prevalence of head and neck pain observed in our hypermobile population, it would be prudent for physicians to screen for these symptoms when evaluating patients with generalized hypermobility. Constant or severe neck pain or chronic daily headaches can suggest the need for further work up as opposed to more common, self-limited and episodic variants. Clues to cervical pathology can be found if there is neck or head pain reproduced with movement or position, if hypermobility of the neck is noted on exam, or if there is pain to palpation over the cervical facets. Initial work up with plain X-rays of the cervical spine in extension and flexion can be very revealing, often showing exaggerated range of motion, spondylosis, or translational listhesis with degenerative changes in excess of expected for age, especially in younger patients. Referrals to pain management and headache medicine can be useful in helping to manage pain over the long term as many of these patients can benefit from additional advanced imaging and interventional procedures for neck pain as well as pharmacologic treatment for their headaches.

5 | CONCLUSIONS

This is the first large retrospective study to quantify the prevalence of a range of head and neck abnormalities among patients with hypermobility disorders in the context of the modern nosology of such diagnoses. Head and neck complaints were reported in more than half of all patients but were significantly more prevalent in hEDS than the HSDs. We found a strikingly high incidence of migraine and cervical spondylosis, with the two conditions often coexisting. Therapeutic benefit for head and neck pain was noted in more than half of the subgroup of these patients who underwent MBB or RFA for spondylosis, suggesting the possibility of cervicogenic headache, though additional research is required to more accurately determine diagnosis, reproducibility, and longevity of these benefits. Other craniocervical causes of head and neck pain, including low CSF pressure, Chiari malformation, CCI, and arterial dissection, were also identified, but less frequently. The work-up for head and neck discomfort in individuals with hypermobility disorders should be based upon symptomatology but clinicians should consider the above diagnoses in the differential.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Anuj Malhotra, Amy R. Kontorovich, and Anna Pace conceived of the presented idea, designed the research study, and drafted the manuscript. Tania Ruiz Maya, Anuj Malhotra, Anna Pace, and Amy R. Kontorovich performed the main data collection with additional contributions from Rachel Colman, Bruce D. Gelb, and Lakshmi Mehta. Amy R. Kontorovich and Anuj Malhotra performed the data analyses. Rachel Colman, Bruce D. Gelb, and Lakshmi Mehta provided critical feedback in the analyses and manuscript. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Bendik, E. M., Tinkle, B. T., Al-shuik, E., Levin, L., Martin, A., Thaler, R., & Martin, V. T. (2011). Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia*, *31*, 603–613. https://doi.org/10.1177/0333102410392606

Castori, M., Morlino, S., Ghibellini, G., Celletti, C., Camerota, F., & Grammatico, P. (2015). Connective tissue, Ehlers-Danlos syndrome(s), and head and cervical pain. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *169*, 84–96. https://doi.org/10.1002/ajmg.c.31426

Debette, S., & Leys, D. (2009). Cervical-artery dissections: Predisposing factors, diagnosis, and outcome. *The Lancet Neurology*, *8*, 668–678. https://doi.org/10.1016/s1474-4422(09)70084-5

Dittrich, R., Heidbreder, A., Rohsbach, D., Schmalhorst, J., Nassenstein, I., Maintz, D., & Kuhlenbaumer, G. (2007). Connective tissue and vascular phenotype in patients with cervical artery dissection. *Neurology*, *68*, 2120–2124. https://doi.org/10.1212/01.wnl.0000264892.92538.a9

Dolan, A., Hart, D., Doyle, D., Grahame, R., & Spector, T. (2003). The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: The Chingford study. *Journal of Rheumatology*, *30*, 799–803.

Fischera, M., Marziniak, M., Gralow, I., & Evers, S. (2008). The incidence and prevalence of cluster headache: A meta-analysis of

population-based studies. *Cephalalgia*, *28*, 614–618. https://doi.org/10.1111/j.1468-2982.2008.01592.x

Hakim, A. J. (2004). Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? *Rheumatology*, *43*, 1194–1195. https://doi.org/10.1093/rheumatology/keh279

Hall, T., Briffa, K., & Hopper, D. (2008). Clinical evaluation of cervicogenic headache: A clinical perspective. *Journal of Manual & Manipulative Therapy*, *16*, 73–80. https://doi.org/10.1179/106698108790818422

Headache Classification Committee of the International Headache Society (IHS). (2018). The international classification of headache disorders, 3rd edition. *Cephalalgia*, *38*, 1–211. https://doi.org/10.1177/0333102417738202

Henderson, F. C., Sr., Austin, C., Benzel, E., Bolognese, P., Ellenbogen, R., Francomano, C. A., … Voermans, N. C. (2017). Neurological and spinal manifestations of the Ehlers-Danlos syndromes. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *175*, 195–211. https://doi.org/10.1002/ajmg.c.31549

Jacome, D. (1999). Headache in Ehlers-Danlos syndrome. *Cephalalgia*, *19*, 791–796. https://doi.org/10.1046/j.1468-2982.1999.1909791.x

Jensen, R. H. (2017). Tension-type headache - The normal and most prevalent headache. *Headache*, *58*, 339–345. https://doi.org/10.1111/head.13067

Johnston, I., Jacobson, E., & Besser, M. (1998). The acquired chiari malformation and syringomyelia following spinal csf drainage: A study of incidence and management. *Acta Neurochirurgica*, *140*, 417–428. https://doi.org/10.1007/s007010050119

Kirk, J. A., Ansell, B. M., & Bywaters, E. G. (1967). The hypermobility syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. *Annals of the Rheumatic Diseases*, *26*, 419–425. https://doi.org/10.1136/ard.26.5.419

Lin, W. S., Huang, T. F., Chuang, T. Y., Lin, C. L., & Kao, C. H. (2018). Association between cervical spondylosis and migraine: A nationwide retrospective cohort study. *International Journal of Environmental Research and Public Health*, *15*, 587–597. https://doi.org/10.3390/ijerph15040587

Liu, F. C., Fuh, J. L., Wang, Y. F., & Wang, S. J. (2011). Connective tissue disorders in patients with spontaneous intracranial hypotension. *Cephalalgia*, *31*, 691–695. https://doi.org/10.1177/0333102410394676

Malfait, F., Francomano, C., Byers, P., Belmont, J., Berglund, B., Black, J., & Tinkle, B. (2017). The 2017 international classification of the Ehlers-Danlos syndromes. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *175*, 8–26. https://doi.org/10.1002/ajmg.c.31552

Martin, J. J., Hausser, I., Lyrer, P., Busse, O., Schwarz, R., Schneider, R., & Grond-Ginsbach, C. (2006). Familial cervical artery dissections. *Stroke*, *37*, 2924–2929. https://doi.org/10.1161/01.str.0000248916.52976.49

Menezes, A. H., & Traynelis, V. C. (2008). Anatomy and biomechanics of normal craniovertebral junction (a) and biomechanics of stabilization (b). *Child's Nervous System*, *24*, 1091–1100. https://doi.org/10.1007/s00381-008-0606-8

Milhorat, T. H., Bolognese, P. A., Nishikawa, M., McDonnell, N. B., & Francomano, C. A. (2007). Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation type I in patients with hereditary disorders of connective tissue. *Journal of Neurosurgery: Spine*, *7*, 601–609. https://doi.org/10.3171/spi-07/12/601

Milhorat, T. H., Nishikawa, M., Kula, R. W., & Dlugacz, Y. D. (2010). Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. *Acta Neurochirurgica*, *152*, 1117–1127. https://doi.org/10.1007/s00701-010-0636-3

Owler, B. K., Halmagyi, G. M., Brennan, J., & Besser, M. (2004). Syringomyelia with Chiari malformation; 3 unusual cases with implications for pathogenesis. *Acta Neurochirurgica*, *146*, 1137–1143. https://doi.org/10.1007/s00701-004-0323-3

Puledda, F., Viganò, A., Celletti, C., Petolicchio, B., Toscano, M., Vicenzini, E., & Di Piero, V. (2015). A study of migraine characteristics in joint hypermobility syndrome a.k.a. Ehlers-Danlos syndrome, hypermobility type. *Neurological Sciences*, *36*, 1417–1424. https://doi.org/10.1007/s10072-015-2173-6

Rozen, T., Roth, J., & Denenberg, N. (2006). Cervical spine joint hypermobility: A possible predisposing factor for new daily persistent headache. *Cephalalgia*, *26*, 1182–1185. https://doi.org/10.1111/j.1468-2982.2006.01187.x

Sacheti, A., Szemere, J., Bernstein, B., Tafas, T., Schechter, N., & Tsipouras, P. (1997). Chronic pain is a manifestation of the Ehlers-Danlos syndrome. *Journal of Pain and Symptom Management*, *14*, 88–93. https://doi.org/10.1016/s0885-3924(97)00007-9

Schievink, W. I., Dodick, D. W., Mokri, B., Silberstein, S., Bousser, M. G., & Goadsby, P. J. (2011). Diagnostic criteria for headache due to spontaneous intracranial hypotension: A perspective. *Headache: The Journal of Head and Face Pain*, *51*, 1442–1444. https://doi.org/10.1111/j.1526-4610.2011.01911.x

Schievink, W. I., Gordon, O. K., & Tourje, J. (2004). Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: A prospective study. *Neurosurgery*, *54*, 65–71. https://doi.org/10.1227/01.neu.0000097200.18478.7b

Sharma, P., Sharma, A., & Chacko, A. G. (2001). Syringomyelia in spontaneous intracranial hypotension. *Journal of Neurosurgery*, *95*, 905–908. https://doi.org/10.3171/jns.2001.95.5.0905

Wrobel, C. J., & Thompson, E. M. (2011). Joint hypermobility and the spine: Part II. *Contemporary Neurosurgery*, *33*, 1–4. https://doi.org/10.1097/01.CNE.0000403891.30232.ff

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