PATHOLOGY

Identifying Pain Subtypes in Patients With Craniofacial Lesions of Fibrous Dysplasia/McCune-Albright Syndrome

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Background: Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is a genetic disorder, marked by bone lesions, often affecting the craniofacial skeleton. Pain is a prevalent yet heterogeneous symptom reported by patients with craniofacial FD. Effective treatments are currently lacking, posing a significant clinical challenge to patient care.

Purpose: This preliminary study examined pain profiles in craniofacial FD and aimed to identify subtypes of patients based on pain phenotypes and emotional health.

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Study Design, Setting, Sample: A prospective, cross-sectional study involving 15 patients with FD/MAS, conducted at Boston Children's Hospital and Massachusetts General Brigham's Hospitals.

Predictor/Exposure/Independent Variable: Headache frequency, craniofacial pain severity, neuropathic pain quality, pain interference, allodynia, photophobia, depression, and anxiety were assessed using clinical questionnaires.

Main Outcome Variable(s): The primary outcome variable was the symptom profile derived from standardized clinical questionnaires and analyzed using principal component analysis and K-means clustering.

Covariates: Covariates included demographic data, diagnosis, and lesion location(s).

Analyses: Principal component analysis and K-means clustering of patient-reported measures of pain and emotional health were performed. Analysis of variance was conducted to determine significant differences among patient subtypes. Statistical significance was set at ($P < .05$).

Results: The study included 15 subjects with FD/MAS, with a mean age of 36.2 (13.9) years, including 1 male. Clustering analysis identified 3 subtypes of patients with distinct symptom profiles. Cluster 1 (n = 2) averaged 70 (28.3) headache days in a 90-day period, pain level of 7.5 (0.7) on a 0-10 scale, and severe anxiety, depression, allodynia, photophobia, and pain interference. Cluster 2 (n = 7) patients reported an average of 5.4 (7.5) headache days, an average pain level of 2.7 (2.6), mild or no anxiety, depression, allodynia, photophobia, and pain interference. Cluster 3 (n = 6) patients displayed a mixed symptom profile with an average of 47.3 (36.4) headache days and a pain level of 5.25 (1.4). Notably, patients with temporal and skull base lesions were predominantly found in Clusters 1 and 3, which exhibited the most severe symptomatology.

Conclusions and Relevance: This study establishes a basis for future longitudinal research aimed at understanding underlying pain mechanisms and evaluating the response to personalized pain management strategies in subtypes of patients with craniofacial FD.

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Fibrous dysplasia (FD) is a rare genetic disorder arising from a postzygotic missense mutation in the GNAS locus that alters the GαS transcript. This gain-of-function mutation leads to the replacement of healthy bone and marrow with pre-osteoblastic fibro-osseous tissue that has a structurally abnormal matrix, decreased mineralization, and thinner cortex. As a result, fractures, deformity, musculoskeletal weakness, and pain often occur.[1] Lesions may be present in a single bone (monostotic FD) or in multiple bones (polyostotic FD) in the axial, appendicular, and/or craniofacial skeletons. McCune-Albright syndrome (MAS) is a diagnosis characterized by FD accompanied by hyperfunctioning endocrinopathies and hyperpigmented skin.[2,3] The craniofacial skeleton is one of the most commonly involved regions.[4] Patients with craniofacial lesions may experience a range of neurological and ophthalmological manifestations such as vision loss, hearing loss, headache, migraine, orofacial pain, and facial deformity.[5-9]

Pain is a predominant and frequently debilitating symptom of FD. However, this pain is heterogeneous, and the underlying mechanisms are not fully understood.[10,11] Effective pain treatment remains a major clinical challenge, as patients often exhibit inconsistent responses to traditional analgesics and bisphosphonates.[12] Adding to the complexity of pain management is a well-known dissociation between skeletal disease burden and the intensity of pain reported by patients.[7,13] Coexisting psychological factors may also exacerbate pain perception.[14,15]

The variability in the presentation of pain phenotypes necessitates a comprehensive approach to characterize pain in patients with FD/MAS. By delineating the spectrum of pain experiences, treatment strategies can be tailored to patient subtypes, potentially improving clinical outcomes and prognoses. We hypothesize that there are distinct subtypes of symptom presentation in patients with craniofacial FD. This prospective, exploratory study aimed to *1)* determine subtypes of symptom presentation in patients with craniofacial FD based on headache frequency, craniofacial pain severity, neuropathic pain quality, allodynia, photophobia, and anxiety and depression, and *2)* identify if secondary characteristics (age, diagnosis, and lesion location) corresponded with symptom subtypes.

Methods

STUDY DESIGN/SAMPLE

This prospective, cross-sectional study (NCT04125 862) was approved by Boston Children's Hospital and the Massachusetts General Brigham Institutional Review Boards. The study sample was drawn from patients with FD/MAS who were recruited via local physician referrals, the FD/MAS Alliance, and the National Institute

of Dental and Craniofacial Research Natural History study (NCT00001727). Eligible subjects had a confirmed diagnosis of monostotic FD, polyostotic FD, or MAS (defined by polyostotic FD, endocrine/thyroid involvement, and skin hyperpigmentation). Inclusion criteria required written informed consent prior to study participation. For subjects under 18 years of age, informed consent was obtained from a guardian along with assent from the patient. Diagnoses were verified by review of the patients' medical and imaging records, including whole-body sodium ^{18}F-fluoride positron emmision tomography, computed tomography, and/or magenetic resonance imaging. This study represents the second phase of investigation using this patient cohort, building upon previously published findings to explore additional variables.[16]

VARIABLES

The study's key variables were organized into predictor, outcome, and covariate groups. Predictor variables included headache frequency and craniofacial pain severity (including headache pain), neuropathic pain quality, pain interference, allodynia, photophobia, and depression and anxiety symptoms, all of which were assessed using standardized clinical questionnnaires. The main outcome variables included the principal components, cluster assignments, cluster centers, and the percentage of variance explained by the principal component analysis (PCA) and subsequent k-means clustering. Covariates included demographic data, diagnosis (monostotic, polyostotic, or MAS), number of craniofacial FD lesions, and lesion locations.

DATA COLLECTION METHODS

Study participants described the location, severity (0-10 pain scale), and frequency of headache in the last 90 days.[17] The presence of neuropathic-like pain was determined using the painDETECT questionnaire.[18] The Brief Pain Inventory was used to assess pain interference on 7 aspects of daily life (general activity, mood, walking, work, relations with others, sleep, and enjoyment of life).[19] Additionally, subjects completed the allodynia symptom checklist and photophobia questionnaire.[20,21] The Hospital Anxiety and Depression Scale (HADS) was used to assess depression- and anxiety-related mood symptoms.[22]

DATA ANALYSIS

PCA was conducted using questionnaire scores for headache frequency, craniofacial pain severity, neuropathic pain quality, pain interference, allodynia, photophobia, depression, and anxiety. Missing data were addressed by imputing the mean value of the cohort where necessary. A PCA approach was used to reduce dimensionality in the data set while retaining at least 80% of the total variance. Three principal components were used. Following PCA, k-means clustering was applied. PCA and k-means algorithms were implemented using scikit-learn's PCA and KMeans modules, respectively. The k-means clustering algorithm, configured with a predetermined number of clusters (k = 3) established through exploratory analysis, partitioned the data into 3 distinct categories based on feature similarity within each cluster. Characteristic features were analyzed within each cluster for clinical relevance within the cohort.

Further statistical analyses were conducted using R Studio (version 2023.09.0). A one-way analysis of variance was performed to determine significant differences between clusters (or patient subtypes). Prior to the analysis of variance, the assumptions of normality and homogeneity of variances were evaluated using the Levene's test. Statistical significance was set at a P value of less than .05.

Results

PARTICIPANT CHARACTERISTICS

A total of 15 participants were included in the study, comprising 14 females and 1 male. The mean age was 36.2 years (range, 12-61 years). The distribution of FD and MAS subtypes was as follows: monostotic FD N = 1 (6.7%), polyostotic FD N = 10 (66.7%), and MAS N = 4 (26.7%). Patients had a range of 1 to 4 craniofacial FD lesions. A total of 35 craniofacial FD lesions were identified with sodium ^{18}F-fluoride positron emmision tomography/computed tomography and/or non-contrast magenetic resonance imaging.[16]

SYMPTOM PRESENTATION AND CLASSIFICATION

Headache and craniofacial pain were experienced by all patients except for patient 2 (Fig 1). Patient 7 did not describe pain from headache, but noted a mild level of craniofacial pain, particularly near the orbits. Patient 14 did not experience headaches or craniofacial pain but did describe pain in the upper neck, which could be related to an FD lesion in the cervical spine. Six patients (patients 8, 9, 10, 11, 12, and 14) had FD lesions in the cervical spine; however, no patterns emerged in the symptomatic presentations reported by these patients. One patient, patient 10, experienced vision loss and patient 14 reported diplopia. Hearing loss was not reported by any study participant.

Headache frequency varied between patients, with 9 patients reporting 20 headaches or less in the proceeding 90 days and 5 patients reporting 50 headaches or more. The number of days with headaches in the last 90 days was not reported for patient 1; this missing

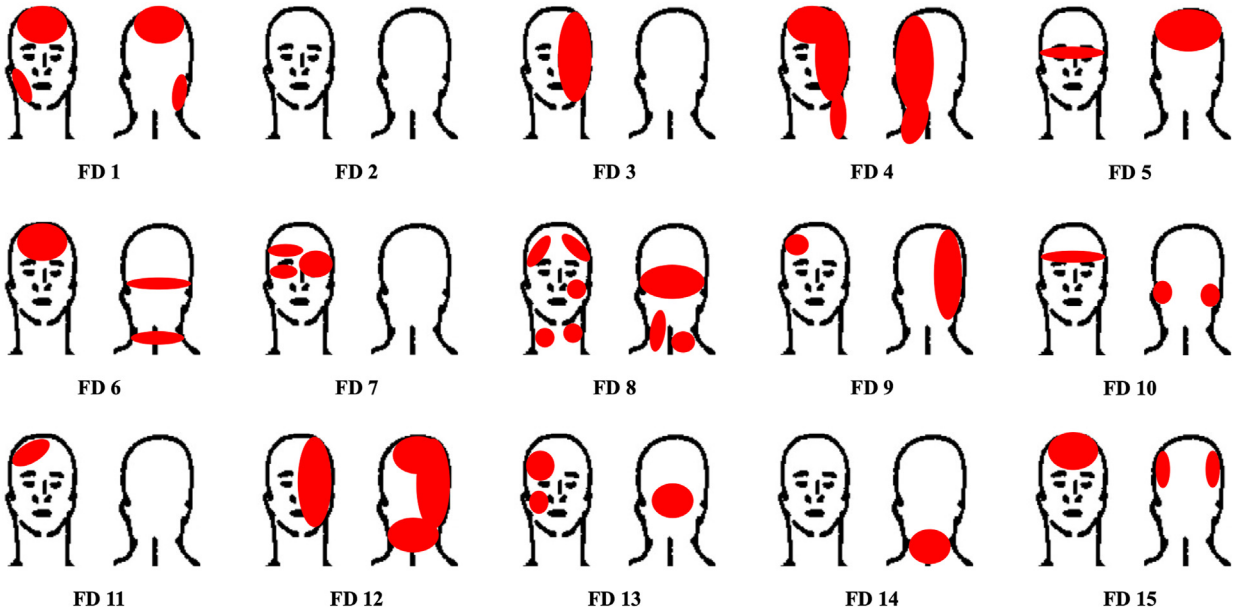

FIGURE 1. Self-reports of pain distribution in patients with FD/MAS. During study visits, study participants marked the location (*red regions*) of headache and craniofacial pain. Patient 2 reported no pain, while patient 14 described pain in the upper neck but did not experience headaches or craniofacial pain. FD/MAS, fibrous dysplasia/McCune-Albright syndrome.

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value was replaced with the average number of days with headache for the entire patient cohort (31 days). The average pain severity (0-10) experienced also varied within the cohort, with a range of 0-8. Using the painDETECT scale, 11 patients had scores ranging between 0 and 12 and were negative for having neuropathic pain, while the remaining 4 patients fell within the unclear to positive range

Table 1. PATIENT-REPORTED SYMPTOMS

Patient ID	Days w/Headache per 90 Days	Average Pain (0-10)	PainDETECT	HADS* Depression	HADS* Anxiety	Allodynia	Photophobia	Mean Pain Interference
1	NA	4	12	14	12	11	8	2.57
2	0	0	0	0	1	0	3	0
3	20	5	8	0	10	0	0	2
4	90	4	16	4	7	1	11	4.29
5	3	6.5	20	3	2	1	6	3.86
6	90	4	6	4	3	4	3	5.29
7	0	0	12	8	10	0	0	6.86
8	50	7	32	20	21	11	10	8.86
9	50	6	10	2	3	2	10	4.71
10	3	5	4	5	5	2	4	0.43
11	11	4	5	2	6	0	0	0.86
12	90	8	28	13	15	11	8	9.14
13	20	7	6	7	6	4	2	5.43
14	0	0	8	5	10	0	0	3.86
15	4	5	3	1	5	0	5	0.57
Mean (SD)	29.07 (35.46)	4.37 (2.58)	11.33 (9.16)	5.87 (5.74)	7.73 (5.39)	3.13 (4.29)	4.67 (3.98)	3.91 (2.91)

Note: Allodynia: None: 0-2; Mild: 3-5; Moderate: 6-8; Severe: 9+.
Photophobia: None: 0-2; Mild: 3-5; Moderate: 6-8; Severe: 9+.
Mean (standard deviation[SD]) are provided.
* Hospital Anxiety and Depression Scale.

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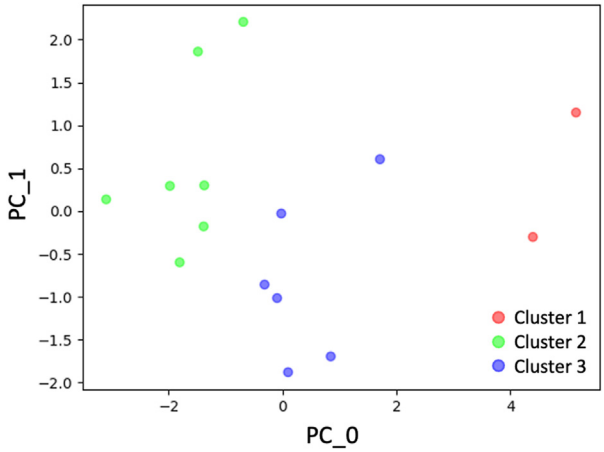

FIGURE 2. K-means clustering analysis of symptomatic data. Scatter plot illustrating k-means clustering (k = 3) of symptomatic data from 15 patients, including headache frequency, average craniofacial pain severity (including headache pain), painDETECT score, allodynia, photophobia, HADS depression score, HADS anxiety score, and pain interference. HADS, Hospital Anxiety and Depression Scale; PC, Principal Component.

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(Table 1). Using the allodynia checklist, 3 patients had severe allodynia, 2 patients had mild allodynia, and the remaining 10 patients had no allodynia. Photophobia was more common; 3 patients reported experiencing severe photophobia, 3 patients reported moderate photophobia, and 4 reported mild photophobia. Based on the HADS, mild to severe levels of depression were reported by 4 patients and mild to severe levels of anxiety were reported by 6 patients.

Using the Brief Pain Inventory, patients reported varying levels of pain interference (0-10) in 7 aspects of daily life: general activity, mood, walking, work, relations with others, sleep, and enjoyment of life. Mean pain interferences per patient ranged from 0 to 9.1. Patients reported the highest levels of interference with mood (mean: 4.7) and normal work (mean: 4.6). Patients reported utilizing various analgesics to treat pain and in an intermittent manner (ie, tramadol, gabapentin, sumatriptan, ibuprofen, and acetaminophen).

ANALYSIS

PCA produced 3 principal components with a total variance of approximately 84.7%. The k-means clustering analysis on symptomatic data from 15 patients identified 3 distinct clusters, each representing different symptom profiles (Fig 2):

Cluster 1 (N = 2 patients): The mean (SD) number of days with headache in a 90-day period for patients in Cluster 1 was 70 (28); range: 50-90. Patients reported pain suggestive of a neuropathic-like pain profile on the PainDETECT scale 30(2.8); range: 28-32. Patients exhibited severe allodynia, moderate to severe photophobia, severe levels of depression and anxiety, and high levels of pain interference.

Cluster 2 (N = 7 patients): The mean (SD) number of days with headache in a 90-day period for patients in Cluster 2 was 5 (8); range: 0-20. Patients reported pain negative for a neuropathic component on the PainDETECT scale 6(3.9); range: 0-12. Patients demonstrated mild to no allodynia and photophobia along, little to no signs of depression, mild to no anxiety, and minimal pain interference.

Table 2. SUMMARY OF CLUSTER CHARACTERISTICS

Study Measures	Cluster 1 (n = 2)	Cluster 2 (n = 7)	Cluster 3 (n = 6)	*P*
Days w headache per 90 days	70 (28.3)	5.4 (7.5)	47.3 (36.4)	.009
Average pain of headache (0-10)	7.5 (0.7)	2.7 (2.6)	5.25 (1.4)	.02
PainDETECT	30 (2.8)	5.7 (3.9)	11.7 (5.6)	.0001
HADS-Depression	16.5 (4.9)	3 (3.0)	5.7 (4.4)	.003
HADS-Anxiety	18 (4.2)	6.7 (3.5)	5.5 (3.7)	.004
Allodynia	11 (0)	0.3 (0.8)	3.8 (3.8)	.0006
Photophobia	9 (1.4)	1.7 (2.2)	6.7 (3.7)	.008
Mean pain interference	9 (0.2)	2.1 (2.5)	4.4 (1.1)	.002
Age	48.5 (3.5)	33 (18.2)	35.8 (15.5)	.514
Patients with MAS	100%	28.5%	0%	
Number of craniofacial lesions	3 (0)	2.3 (1.3)	2.2 (1.2)	.682
Patients with a temporal lesion	100%	0%	50%	
Patients with a skull base lesion	100%	14.3%	50%	

Note: Mean (standard deviation) are provided.

Abbreviations: MAS, McCune-Albright Syndrome; HADS, Hospital Anxiety and Depression Scale.

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Cluster 3 (N = 6 patients): The mean (SD) number of days with headache in a 90-day period for patients in Cluster 3 was 47 (36); range: 3-90. PainDETECT scores were unclear for neuropathic-like pain 11.7(5.6); range: 6-20. Patients reported moderate to severe photophobia, but mild to no allodynia. Patients also reported mild or no depression and anxiety and mild pain interference.

Cluster characteristics are summarized in Table 2. Notably, temporal or skull base lesions were common in Clusters 1 and 3, which had the most severe symptom presentations. Cluster 1 demonstrated a neuropathic-like pain phenotype and included only patients with both a skull base and temporal lesion. This may indicate a more profound and complex manifestation of symptoms in patients with lesions in temporal and skull base regions.

Discussion

The aim of this study was to classify patients with craniofacial FD, hypothesizing the existence of distinct subtypes characterized by specific patterns of pain-related symptoms and emotional health parameters. Three distinct clusters of symptom profiles using PCA and k-means clustering were identified. Cluster 1 demonstrated frequent headaches, severe craniofacial pain, robust pain interference, and neuropathic-like pain presentation as well as severe allodynia, photophobia. anxiety, and depression. Cluster 2 contained patients experiencing a milder symptomatology with low levels of pain, pain interference, allodynia, photophobia, and mild or no anxiety and depression. Cluster 3 was characterized by a mixed symptom profile with mild to severe pain-related symptom presentation. These findings underscore the complex and heterogeneous nature of pain, the impact of pain, and emotional dysfunction occurring in craniofacial FD.

The identification of distinct symptom subtypes in patients with craniofacial FD/MAS has significant clinical implications, especially for patients who have both craniofacial deformities based on FD lesions, plus headaches or craniofacial pain. Tailoring treatment strategies based on these subtypes could enhance pain management and lead to improved patient outcomes. For instance, patients in Cluster 1 may benefit from targeted neuropathic pain treatments and psychological support, due to the high scores on painDETECT and HADS. In contrast, the minimal symptoms reported by patients in Cluster 2 suggest that a more conservative strategy of surveillance might be appropriate to reduce the risk of side effects from unnecessary medications. For Cluster 3, where a mixed symptom profile was observed, a more nuanced treatment approach that considers both analgesic and psychological interventions may be warranted based on individual need.

A notable association was observed between specific lesion locations (skull base and temporal lesions) and the severity of symptoms, particularly in Clusters 1 and 3. Moreover, it is well-known that patients with FD lesions in the midface (zygomatic/maxillary complex and orbits) have pain.[23-25] In contrast, no associations were observed between symptom severity and number of craniofacial lesions. This suggests that lesion location, particularly in regions with rich nerve supplies, may influence the severity and quality of pain in FD patients more than the number or extent of lesions (skeletal burden).[26,27] The presence of depressive symptoms and anxiety was prominent in Cluster 1. These patients also reported higher mean pain interference, indicating the impact of pain on their daily activities and quality of life. Such findings point to the need for comprehensive psychological assessment in patients demonstrating depressive symptoms and anxiety, which are known to exacerbate pain perception and can complicate pain treatment efforts.[28-30] A multidisciplinary, holistic approach that incorporates psychological support may improve patient outcomes.

The varied presentation of pain-related symptoms suggests potential different underlying mechanisms contributing to the complex pain phenotypes in patients with craniofacial FD. Patients in Cluster 1 reported severe allodynia, a symptom associated with neuropathic or inflammatory pain states.[31-34] This heightened sensitivity to innocuous stimuli is theorized to result from central sensitization, where the central nervous system becomes hyper-responsive and amplifies pain signals.[35,36] Additionally, moderate to severe photophobia was notably prevalent in Clusters 1 and 3. Photophobia can also be associated with central sensitization, where the hyper-responsiveness of the central nervous system affects sensory perception.[37,38]

The findings of this study align with previous research documenting the heterogeneity of pain among patients with FD/MAS.[10,39,40] Similar to prior studies, a dissociation was observed between skeletal disease burden and reported pain severity.[7,13] Furthermore, no associations were discovered between number of craniofacial lesions and any pain-related symptoms. The presence of neuropathic-like pain quality has been previously identified within a cohort of FD/MAS patients,[41] but the additional assessment of allodynia, photophobia, and pain interference provides new insights into the manifestation in patients with craniofacial FD. These findings highlight the need for further exploration into the neuropathic aspects of FD-related pain, including investigation into

treatment potential of gabapentinoids for neuropathic pain analgesia.

Multiple limitations of this study should be considered. While the prospective design and comprehensive symptom assessment allowed for a detailed analysis of symptomatology in our patient cohort, the cross-sectional nature of the study prevents assessment of symptom progression over time. Another limitation of this study is the lack of specificity and potential overlap between headache pain and craniofacial pain as patients with FD/MAS often found it difficult to dissect various forms of pain. Future studies could benefit from a more refined questionnaire that better differentiates between these 2 pain types and their compex interplay to improve diagnostic accuracy. Only 2 patients were under 18 years of age. A more extensive study of pediatric patients could provide valuable insights into craniofacial lesion symptomatology during childhood. Another potential study limitation is that there was only 1 male patient included, which differs from the reported gender distribution.[42,43] We also recognize the limited sample size; however, this is an inherent challenge given the rarity of FD/MAS.

Future research should focus on expanding the study cohort to validate these findings in a larger, more diverse population. Longitudinal studies are needed to explore the dynamic nature of symptom progression and evaluate the efficacy of different treatment approaches over time. Additionally, an investigation into the underlying biological mechanisms driving the different pain profiles is essential for providing insights into possible novel therapeutic targets for FD/MAS.

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