Phase Specific Pain Localization in Cluster Headache Patients.

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Abstract

Background and Objective:

Applying local treatments like neuromodulation or injections for cluster headache, requires exact knowledge of the anatomical structures and pain topography. However studies with emphasis on exact pain localization are rare although local treatments are increasingly used for patients in whom systemic pharmacotherapy is ineffective or contraindicated. Here, survey results with emphasis on exact pain location in cluster headache attacks for onset of pain, peak pain and radiation of pain, are presented.

Methods:

Data from 631 respondents were collected for 23 months using an online survey composed of 117 questions on pain location, epidemiology, and clinical features. 5260 datapoints on 44 pain locations were analyzed.

Results:

There is a periorbital concentration of pain during onset and peak phases of attacks. Pain locations outside the periorbital region were reported more frequently during radiation when compared to the onset and peak of attacks. Dorsal (occipital/nuchal) pain is more frequent during onset and radiation compared to peak: onset pain (13%) vs. peak pain (6%), $p < 0{,}001$. Pain radiation (22%) vs. peak pain (6%), $p < 0{,}001$. There is no significant difference in dorsal pain frequencies for pain radiation (22%) vs. onset (13%), $p = 0{,}552$. Furthermore, single pain spots differ significantly in frequency during the three attack phases.

Conclusions:

Analysis of the pain location data shows phase specific frequencies and distributions of pain location during the three stages of a cluster headache attack. Single pain spots differ significantly in frequency during the three attack phases. Dorsal pain is more frequent during onset and radiation, compared to peak. Extra-orbital pain locations are more frequent during pain radiation. These findings will help to better understand cluster headache and might help to identify further target structures for local treatments.

Key Findings

- Different pain locations can be observed during the onset and peak and radiation phases of a cluster attack. Single pain locations are statistically significantly different in frequency during the three phases of an attack.
- Dorsal pain is mainly present during the onset and radiation phase of an attack and less frequent during peak pain.

- Differences in the patterns of pain location might help identify further target structures for (local) treatments.
- Patient satisfaction with available treatments is low.

Background And Aim

Although cluster headache has been known for many years, major CH surveys with emphasis on pain localization are rare(1–4). Results from previous international cross-sectional surveys on CH describe demography(2,5,6), clinical characteristics including symptoms(2,4,6,7), and diagnostic and therapeutic challenges(8–10). Current pharmaceutical management of CH(11)¯(12) including preventive treatment involves substances like triptans, prednisolone, lithium, verapamil and others which, especially when used by patients in high doses over long periods of time, have the potential for side effects like cardiac events(13), fatigue, nausea, tremor, depression, increased serum glucose and others(12). Neuromodulatory approaches like non-invasive vagus nerve stimulations(14), Sphenopalatine Ganglion Stimulation(15), Percutaneous Bioelectric Current Stimulation(16) or Greater Occipital Nerve blocks(17) are increasingly used for patients in whom systemic pharmacotherapy is ineffective or contraindicated(18). Applying neuromodulatory treatments requires exact knowledge of the anatomical structures and pain topography relevant for CH. However, few surveys evaluate exact topographic pain locations in CH patients. This article highlights frequencies and distributions of 44 pain locations during the onset, peak and radiation phases of cluster headache attacks in order to analyze phase-specific pain locations. This is to contribute to a better understanding of pain topography of CH in order to identify further targets and helping to improve effectiveness for local treatments.

Methods And Materials

The data were collected from October 2015 to August 2017 using a German online cross-sectional survey. Respondents were invited to the survey by email from German headache centers and by links placed in online self-help groups.

The questionnaire was developed by the authors with the participation of patients from a CH self-help forum. The survey was composed of 117 questions of different types: multiple choice, multi-select, fill-in questions, drop-down selections, numeric rating scales and image maps (see Additional file 1). In addition to pain localization, data on epidemiological aspects, diagnosis, clinical features and treatment were collected.

Collection of pain location data

Patients were asked to choose pain locations via multiple response questions for onset (“which area hurts first?”), peak (“during the attack: where is the most severe pain?”) and radiation (“where does the pain radiate to?”).

In order to achieve a high resolution of the pain topography, patients had to select up to 5 of 44 points per phase distributed on a realistic representation of the ventral and dorsal head including neck and shoulder region (Fig. 1).

These points were defined by consensus among the authors and involved feedback from CH patients. Selection criteria were the authors' clinical experience, peripheral sensory innervation of the head including neck and shoulder regions (Nn.V1-V3, C2-C4), and known localization points for occipital nerve blocks(17), botulinumtoxin injections(19) and acupuncture points for trigeminal headache(20).

Inclusion criteria

Not all survey questions had to be answered mandatorily. However, incomplete questionnaires were excluded. Further inclusion criteria consisted of gender, patients > 18 years old and physician-confirmed cluster headache diagnosis date (Fig. 2).

Duplicates and data integrity

Respondents were only able to complete one survey. Duplicate entries were technically prevented. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics committee vote

The cross-sectional survey was anonymized; therefore the investigation was released by the responsible authority without the need for an ethics vote (Ethics Committee of the North Rhine Medical Association, Düsseldorf, application No. 272/2015).

Patient consent

Within the survey, patients gave us online consent to process and publish their anonymized data.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0.0.1 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0.0.1. Armonk, NY: IBM Corp.).

Frequencies of pain locations at onset, peak, and radiation are presented as percentages. Mean and median were used as measures of central tendency. Durations are presented as means or medians and interquartile ranges.

The Friedman test was used to determine significant changes per point during the course of the three stages of a cluster headache attack. Pairwise comparison of the three stages was then performed using the McNemar or Wilcoxon tests in order to identify significant differences in frequencies between pain location points. Group comparisons were performed using Chi-square and Fisher exact test. A pvalue below 0.05 was considered statistically significant. P-values of multiple comparisons have been adjusted

using the Bonferroni method. Visualizations were performed using Apple Numbers 10.1. Any missing values are marked in the results.

Results

From 10/2015 to 08/2017, a total of 1327 cluster headache patients were recruited. According to inclusion criteria, final analysis included data from 631 respondents (episodic cluster headache: 64% [n: 406/631], chronic cluster headache: 36% [n: 225/631]). The cCH to eCH ratio was 1:1.8. The female (42%, n: 267/631) to male (58%, n: 364/631) ratio was 1:1.36.

Median age at onset of CH symptoms was 25 years (SD ± 11.37, range: 4–62, n: 622/631) and the median age of first diagnosis (by a physician) was 33 years (SD ± 10.38, range: 8–63, n: 631/631). In 89% (n: 559/631) of the patients, the diagnosis was made by a neurologist, in 11% (n: 72/631) by an unspecified type of physician, whereby 44% (n: 279/631) self-diagnosed before the diagnosis was made by a physician.

Pain characteristics and accompanying symptoms

Sensory quality: The five most frequently reported pain qualities during cluster headache were sharp (24%, n: 160/631), piercing (18%, n: 120/631) pressing (12.5%, n: 84/631), burning (11%, n: 74/631) and pulsating (10%, n: 65/631).

Accompanying vegetative symptoms: Most respondents (86% n: 544/631) reported vegetative symptoms during CH attacks. The five most common symptoms were lacrimation (71% n: 448/631), stuffy nose (59%, n: 369/631), red eyes (58%, n: 36/631), ptosis (122%, n: 408) and runny nose (46%, n: 293/631). Miosis was reported by 19% (n: 122/631) of respondents. Restlessness was reported by 85% (n: 533/628, missings: 3).

Treatment

Pharmacotherapy: In 89% (n: 563/631) of respondents, CH was treated with medication including oxygen for acute or prophylactic purpose.

Acute treatment: 87% (n: 540/631) of respondents received acute treatment, consisting of triptans in various applications (nasal spray [38%, n: 238/631], sumatriptan injections [32%, n: 205/631], tablets [23%, n: 144/631]) and oxygen inhalation [71%, n: 384/543, missings: 88]).

Prophylactic treatment: Prophylactic treatment was received by 54% (n: 344/564, missings: 67) of respondents: Verapamil (75%, n: 262/349, missings: 282), topimarate (429%, n: 38/346, missings: 285), lithium (9%, n: 33/346, missings: 285).

The median satisfaction (NRS: 0 = no effect, 10 = complete absence of pain) with drug treatment (prophylactic and acute) was rated at 6 (n: 564/631, missings: 167, SD ± 2.6, IQR 4).

Non-pharmaceutical treatment: 32% of respondents (n: 202/627, missings: 4) received non-pharmaceutical treatment for CH: occipital nerve stimulation (7%, n: 16/234, missings: 297), stimulation of the pterygopalatine ganglion (7%, n: 16/231, missings: 400), percutaneous direct current stimulation (11%, n: 25/227, missings: 404), non-invasive transcutaneous vagal nerve stimulation (20%, n: 45/226, missings: 405) and acupuncture (50%, n: 111/226, missings: 405).

The median satisfaction (NRS: 0 = no effect, 10 = complete absence of pain) with non-drug treatment was rated at 3 (n: 99/631, missings: 532, SD ± 3.4, IQR 6).

Pain localization during stages of CH attacks

For pain location, patients could select up to 5 points; however, mean responses per phase (onset:peak:radiation) were 3:3:2.2. Lateralization: 49% (n: 310/631) reported only right-sided pain, 41% (n: 250/631) only left-sided pain and 10% (n: 63/631)) reported side changes between attacks. Pain location varied during the course of a CH attack. (Fig. 3)

Table 1:
Comparison of pain location [1-44] frequencies for onset. peak and radiation

Loc.	Onset		Peak		Radiation		Onset vs. peak	Onset vs. radiation	Peak vs. radiation
	n	%	n	%	n	%	p	p	p
1	12	1.9%	13	2.06%	12	1.9%	3.0000	3.0000	3.0000
2	6	0.95%	8	1.27%	17	2.69%	2.3220	0.0810	0.2790
3	7	1.11%	11	1.74%	11	1.74%	1.0320	1.4430	3.0000
4	27	4.28%	30	4.75%	17	2.69%	2.0340	0.5250	0.2400
5	56	8.87%	61	9.67%	16	2.54%	1.6530	*p < 0.001*	*p < 0.001*
6	27	4.28%	16	2.54%	28	4.44%	0.1890	3.0000	0.2460
7	26	4.12%	12	1.9%	32	5.07%	*0.0090*	1.5120	*0.0090*
8	9	1.43%	9	1.43%	21	3.33%	3.0000	0.1140	0.1140
9	20	3.17%	26	4.12%	22	3.49%	0.7140	2.6040	1.9530
10	79	12.52%	101	16.01%	32	5.07%	*0.0480*	*p < 0.001*	*p < 0.001*
11	144	22.82%	157	24.88%	51	8.08%	0.8610	*p < 0.001*	*p < 0.001*
12	242	38.35%	322	51.03%	54	8.56%	*p < 0.001*	*p < 0.001*	*p < 0.001*
13	45	7.13%	48	7.61%	35	5.55%	2.2650	0.8460	0.5130
14	26	4.12%	20	3.17%	30	4.75%	0.9810	2.0310	0.6090
15	5	0.79%	6	0.95%	11	1.74%	3.0000	0.6300	0.9960
16	39	6.18%	43	6.81%	41	6.5%	1.9050	2.7300	2.7300
17	89	14.1%	105	16.64%	46	7.29%	0.2430	*p < 0.001*	*p < 0.001*
18	193	30.59%	214	33.91%	46	7.29%	0.2970	*p < 0.001*	*p < 0.001*
19	153	24.25%	190	30.11%	47	7.45%	*p < 0.001*	*p < 0.001*	*p < 0.001*
20	49	7.77%	60	9.51%	41	6.5%	0.5340	1.3020	0.1860
21	41	6.5%	35	5.55%	74	11.73%	1.2510	*p < 0.001*	*p < 0.001*
22	8	1.27%	9	1.43%	30	4.75%	3.0000	*p < 0.001*	*p < 0.001*
23	8	1.27%	17	2.69%	29	4.6%	0.1470	*p < 0.001*	0.2220
24	80	12.68%	74	11.73%	59	9.35%	1.7430	0.2220	0.6090
25	129	20.44%	135	21.39%	57	9.03%	1.9440	*p < 0.001*	*p < 0.001*

Loc.	Onset		Peak		Radiation		Onset vs. peak	Onset vs. radiation	Peak vs. radiation
26	36	5.71%	25	3.96%	67	10.62%	0.2730	*0.0030*	*p < 0.001*
27	15	2.38%	12	1.9%	32	5.07%	1.9920	0.0600	*0.0090*
28	12	1.9%	13	2.06%	17	2.69%	3.0000	1.3230	1.6680
29	32	5.07%	28	4.44%	58	9.19%	1.8510	*0.0120*	*0.0030*
30	19	3.01%	21	3.33%	55	8.72%	2.5170	*p < 0.001*	*p < 0.001*
31	6	0.95%	7	1.11%	16	2.54%	3.0000	0.1230	0.2340
32	11	1.74%	8	1.27%	13	2.06%	1.6470	2.5170	1.1490
33	9	1.43%	10	1.58%	14	2.22%	3.0000	1.0770	1.5690
34	40	6.34%	25	3.96%	25	3.96%	0.0750	0.2040	3.0000
35	42	6.66%	19	3.01%	45	7.13%	*p < 0.001*	2.4600	*0.0030*
36	15	2.38%	4	0.63%	31	4.91%	0.0570	0.0720	*p < 0.001*
37	4	0.63%	0	0%	15	2.38%	0.3750	0.0570	*p < 0.001*
38	10	1.58%	5	0.79%	21	3.33%	0.6810	0.2160	*0.0030*
39	18	2.85%	10	1.58%	23	3.65%	0.4020	1.5660	0.1110
40	44	6.97%	24	3.8%	36	5.71%	*0.0090*	1.1220	0.3810
41	6	0.95%	1	0.16%	14	2.22%	0.1890	0.3450	*0.0030*
42	15	2.38%	6	0.95%	22	3.49%	0.0660	0.8880	*0.0090*
43	20	3.17%	4	0.63%	25	3.96%	*0.0030*	1.5660	*p < 0.001*
44	19	3.01%	5	0.79%	30	4.75%	*0.0090*	0.3810	*p < 0.001*

Onset

The top 10 frequencies for ventral points are: 12, 18, 19, 11, 25, 17, 24, 10, 5, 20. The top 10 frequencies for dorsal points are: 40, 35, 34, 43, 44, 39, 36, 43, 32, 38.

Most pain locations at onset (as well as in peak pain) are reported periorbital. However, during onset, occipital (point 40) and nuchal (point 35) pain locations differ significantly in frequency compared to during peak pain and radiation. (Fig. 4).

Peak

The top 10 frequencies for ventral points are: 12, 18, 19, 11, 25, 17, 10, 24, 5, 20. The top 10 frequencies for dorsal points are: 34, 40, 35, 39, 33, 32, 42, 44 ,38, 43.

Pain location frequency is mainly congruent with onset (in and around the eye), except for dorsal points. Significant differences compared to radiation are reported for: (peri) orbital (5, 11, 12, 18, 19), frontal (10) and temporal (25) pain locations. (Fig. 5).

Radiation

The top 10 ventral points are: 21, 26, 24, 29, 25, 30, 12, 11, 19, 18. The top 10 dorsal points are: 35, 40, 36, 44, 34, 43, 39, 42, 38, 37.

For onset and peak pain, the most frequent pain locations are located peri-orbitally. However, for pain radiation, the most frequent pain locations are significantly different (Fig. 6). Pain is less often reported in and around the eye and is more frequently reported in the following locations: maxillary (21, 26) mandibular (27,22), temporal (29) (pre- and post-) auricular (30, 42), parietal (23), occipital (38), nuchal (35), wing of nose (7), regio-suprascapularis (36, 44), regio-interscapularis (37) regio-scapularis (41).

General observations on pain location

Retroorbital pain is reported by 86% (n: 545/631) of patients. Periorbital pain localization can be further discriminated into the medial (5) and lateral (19) corners of the eye as well as supra- (11, 18) and infraorbital (13, 20) regions.

Patients reported fewer locations and less peri-orbital involvement during pain radiation (n: 1418) (Fig. 7) compared to onset (n: 1893) and peak pain (n: 1949), but dorsal pain locations (points 32–44) were reported more frequently during pain radiation and onset versus peak pain.

Comparison of dorsal pain locations (32–44) for:

Peak pain (6%, n: 121/1949) vs. onset (13%, n: 253/1893), $p < 0{,}001$.

Pain radiation (22%, n: 314/1418) vs. onset (13%, n: 253/1893), $p = 0{,}552$.

Pain radiation (22%, n: 314/1418) vs. peak pain (6%, n: 121/1949), $p < 0{,}001$.

Discussion

The survey is the largest conducted in Germany among cluster headache patients to date and the only article describing phase-specific pain dynamics in CH patients. Comparable survey-based studies with a different focus have been conducted in the US (2), Germany(4,21) France(1), Denmark(7,22) and the Netherlands(8), but this study on pain location patterns is novel as it highlights differences and commonalities with respect to frequencies and distribution of pain locations during onset, peak pain and pain radiation. Different pain locations can be observed during pain onset and peak of a cluster attack. Single pain locations are statistically significantly different in frequency during the three phases. Dorsal

pain is mainly present during onset and radiation phases of an attack and less frequent during the peak phase. During onset and peak there is a peri-orbital pain focus that can be further discriminated into medial and lateral corners the eye as well as supra- and infraorbital regions.

Data on demographics and epidemiology (male to female ratio, eCH to cCH ratio, diagnostic delay) as well as clinical characteristics (pain features and accompanying. vegetative symptoms) are in line with results of other published CH surveys. It has to be taken into account that adverting the survey in headache centers and among the members of the self-help groups might explain the high proportion of chronic cluster headache patients in terms of a selection bias.

Furthermore, patients report a dissatisfaction with current management of cluster headache especially with neuromodulatory methods.

We were able to investigate further pain locations in addition to the locations described by diagnostic criteria (severe or very severe unilateral orbital, supraorbital and/or temporal) in the IHS ICHD-3 classification(23). Our findings of pain location are in line with previous publications(3,4); however, by explicitly asking patients to discriminate between onset, peak and radiation, we were able to show differences on a per-point basis (pain locations 1–44) thus making it possible to resolve those pain regions into more detail. This might have been overlooked in the past because peri-orbital pain is so dominant that other pain locations were not mentioned if they were not specifically asked for.

Patients report a simultaneous occurrence or radiation of ventral (Nn. V1-V3, locations 1–31) and dorsal pain (dorsal: area of distribution from Nn. C1-C4, locations 32–44), which is also described in cervicogenic headache(24). The fact that the cervical and occipital innervation is connected to the trigeminal nerve system through various structures (e.g. trigeminocervical complex(25)) supports our findings on ventral and dorsal pain from a neurophysiological perspective and may help in identifying further target structures for treatment.

In recent years, along with pharmacotherapy, local stimulation procedures have evolved(26). While topographic pain patterns may be of secondary significance for drug treatment, the described pain patterns and locations might serve as possible targets for non-pharmaceutical approaches especially when the CH is drug-resistant. Given our findings, it could be important or even mandatory to carefully examine the exact pain locations before selecting the appropriate neuromodulating approach. For example, a cluster headache that develops in the dorsal parts of the head or the occipital/nuchal area might respond differently to locally applied treatments (like electrical stimulation or nerve blockades) than a CH that starts from periorbital areas. For the dorsal cluster, a local nerve block or implantation of an ONS stimulator might be more promising, whereas in a cluster exclusively around the eye, stimulation of the pterygopalatine ganglion (SPG)(27) might be more suitable.

Limitations

CH is a disease with a low prevalence compared to other forms of headache. To reach as many patients as possible, a survey conducted online is well accepted. In respect to demographics and major clinical features, our findings are in line with other published studies, thereby confirming the external validity of our data. As the number of questions increased, the number of answers decreased for some questions. This may have distorted the results, especially in the areas of data on patient satisfaction with current management of CH. While all cases were reportedly diagnosed by a doctor, the method does not allow to verify whether cluster headache or another form of (trigeminal autonomic) headache was present. We considered IHS ICHD-3 criteria but could not validate the diagnostic quality of the questionnaire. In order to minimize recall/information bias for questions related to the past, we explicitly asked the patients to relate those questions only to observations of the last two years

Conclusions

Analysis of the pain location data shows phase specific frequencies and distributions of pain location during the three stages of a cluster headache attack. Single pain spots differ significantly in frequency during the three attack phases. Dorsal pain is more frequent during onset and radiation, compared to peak. Extra-orbital pain locations are more frequent during pain radiation. These findings will help to better understand CH and might help to identify further target structures for local treatments.

Abbreviations

CH: cluster headache; eCH: episodic cluster headache; cCH: chronic Cluster Headache; ICHD-3: International Classification of Headache Disorders – 3rd edition; NRS: numeric rating scale (0-10; 0 = no pain, 10 = max. pain); SD: standard deviation; IQR = interquartile range, CEH = cervicogenic headache; m: male; f: female; ONS = occipital nerve stimulation; SPG: Sphenopalatine Ganglion Stimulation; PBCS: Percutaneous Bioelectric Current Stimulation; GON: Greater Occipital Nerve; nVNS: Non-invasive vagus nerve stimulations; PS =Philipp Schröder, CG=Dr. Charly Gaul, AD = Dr. Attyla Drabik, AM=Prof. Albrecht Molsberger.

Declarations

Ethics approval and consent to participate

The data was collected anonymously. For this reason, according to the Ethics Committee of the North Rhine Medical Association, Düsseldorf, Germany (application 272/2015), no ethics vote was necessary, and the study was therefore exempt from oversight.

Within the survey, patients gave us online consent to process their data.

Consent

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing interests

Philipp Schröder is shareholder of the medical device company “Columbus Health Products GmbH”, Germany.

Within the past three years, Charly Gaul has received honoraria from Allergan, TEVA-Ratiopharm, Boehringer Ingelheim, Lilly, Novartis, Desitin Arzneimittel, Cerbotec, Bayer Vital, Hormosan, Grunenthal, Reckitt Benckiser. He has no stocks or ownership interests in any pharmaceutical or medical device companies.

Albrecht Molsberger is CEO and shareholder of the medical device company “Columbus Health Products GmbH”, Germany.

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Authors' contributions

PS conducted the data analysis, interpretation and visualization of the data. The questionnaire was developed by PS, AM and CG. AD contributed to the statistical analysis. AM and CG supervised the survey. All authors were involved in survey development, and in discussing, writing and approving the final version.

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Figures

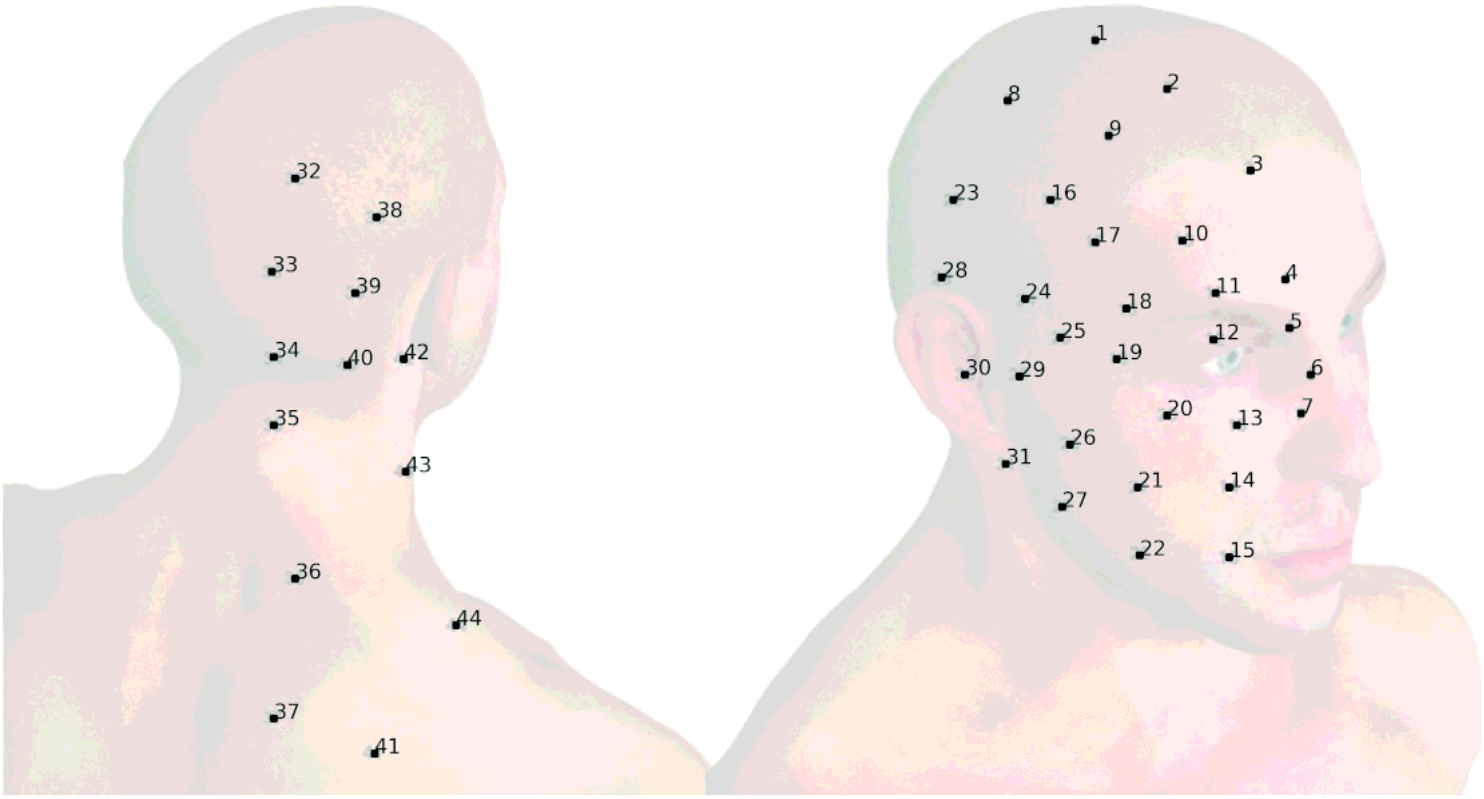

Figure 1

Pain locations 1-44 mapped to anatomic image for indication of pain location. Source: Image courtesy of Complete Anatomy

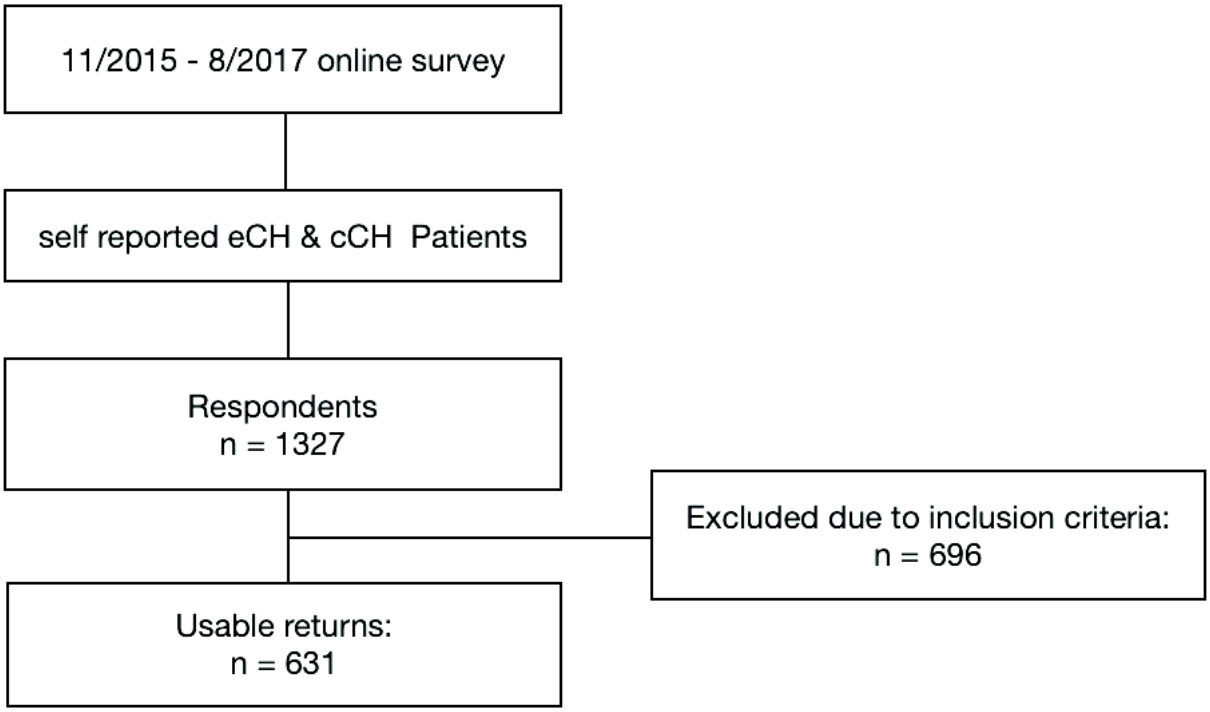

Figure 2

Survey flowchart

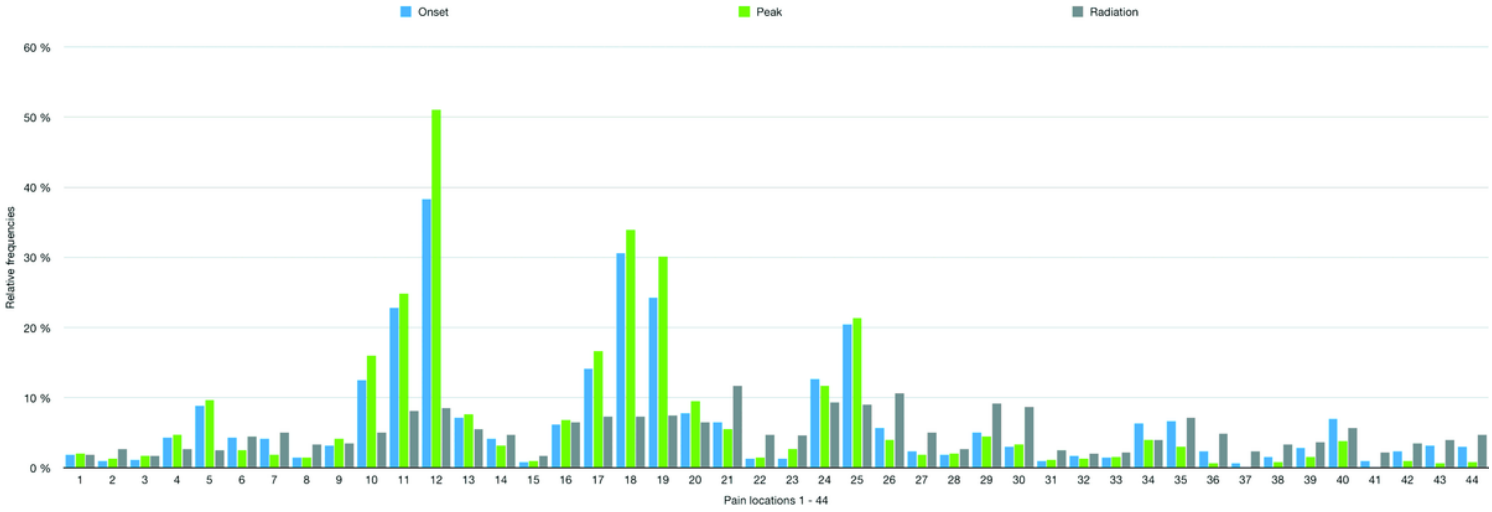

Figure 3

Reported frequencies per point for onset, peak and radiation pain

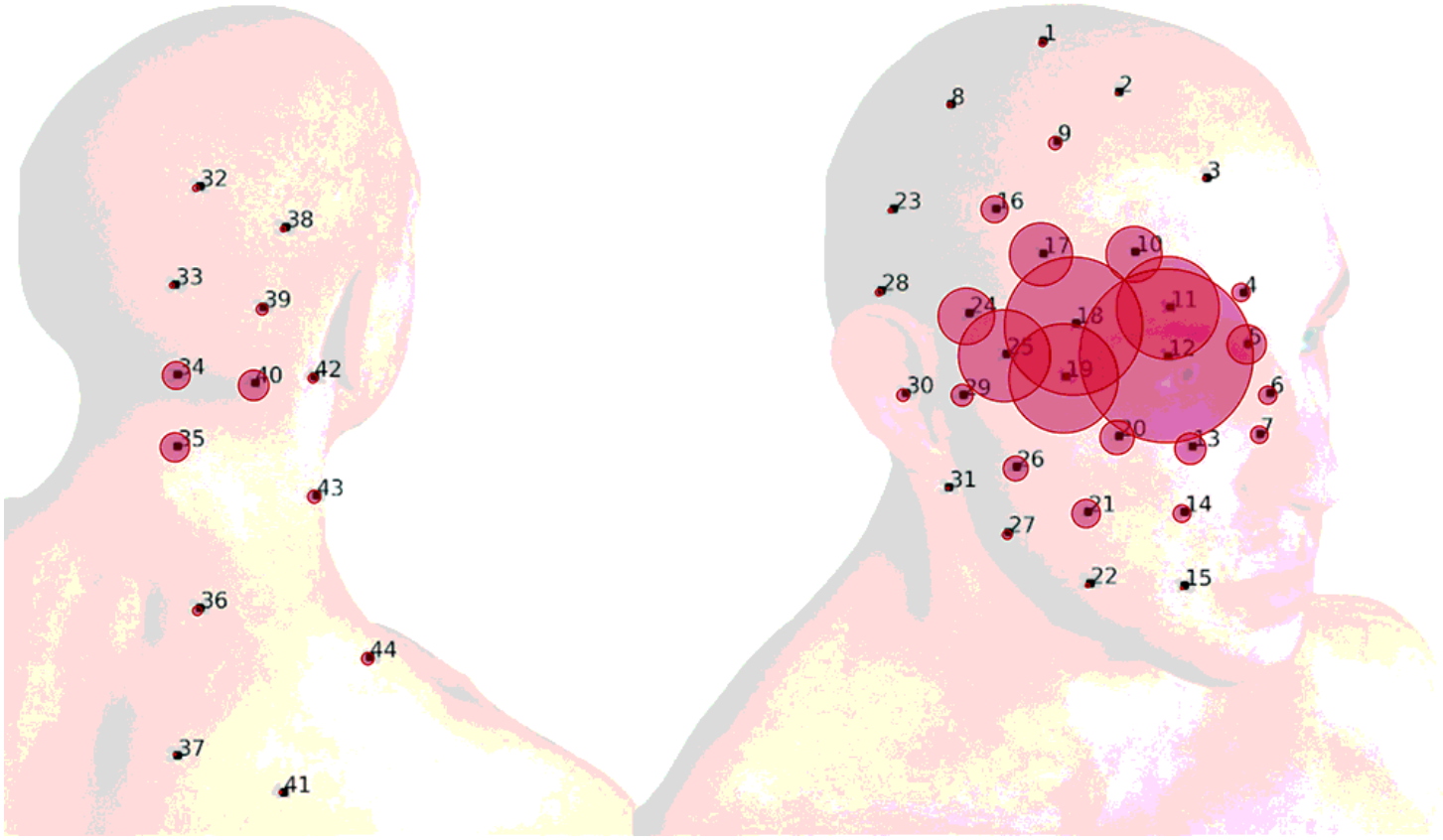

Figure 4

Bubble chart for onset-pain location frequencies. Points 1-44 are mapped to X,Y coordinates of the chart. Size of bubble = Z-value: diameter of bubble corresponds to pain location frequency [percentage, Table

1]. Bubbles are sized proportionally.

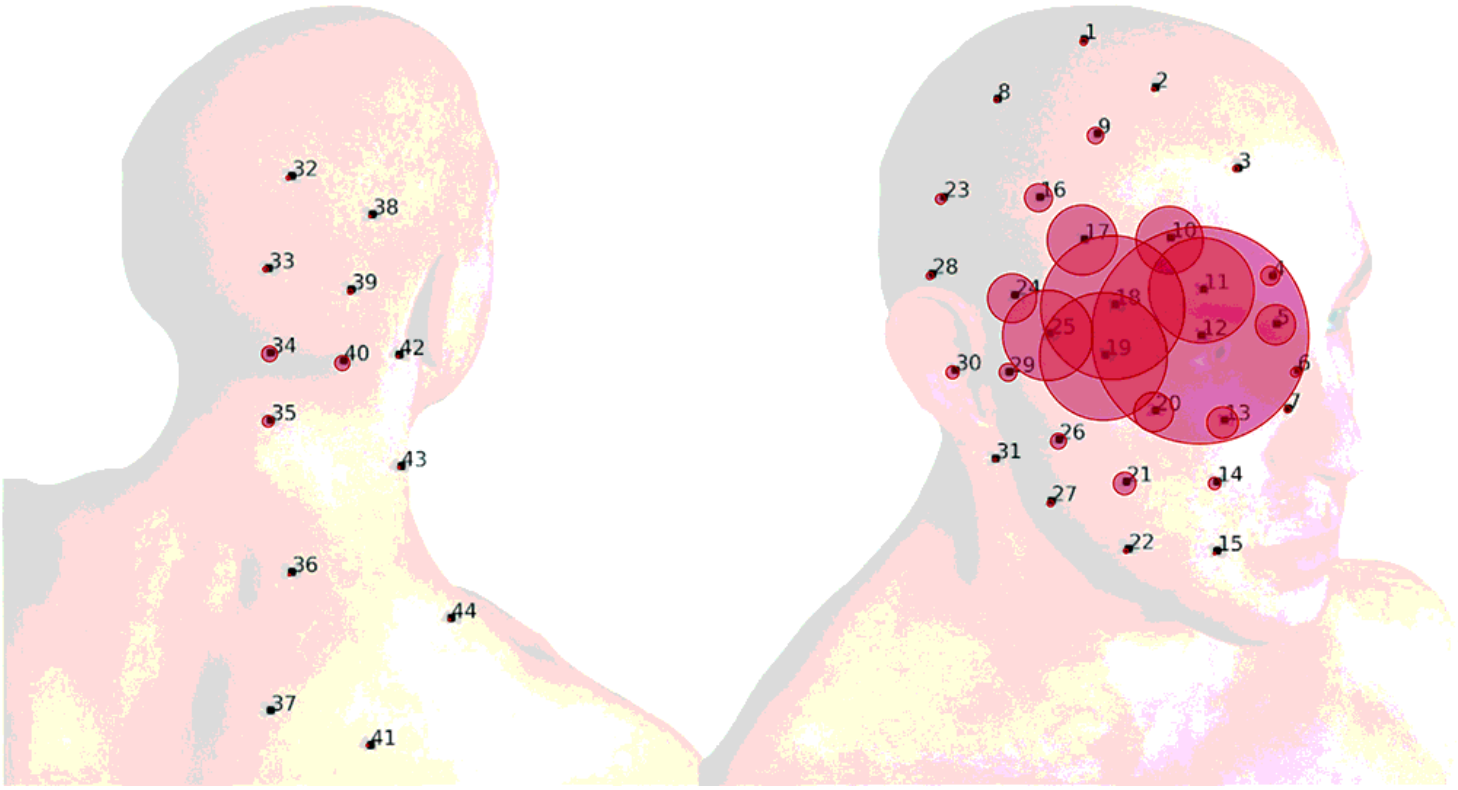

Figure 5

Bubble chart for peak-pain location frequencies. Points 1-44 are mapped to X,Y coordinates of the chart. Size of bubble = Z-value: diameter of bubble corresponds to pain location frequency [percentage, Table 1]. Bubbles are sized proportionally.

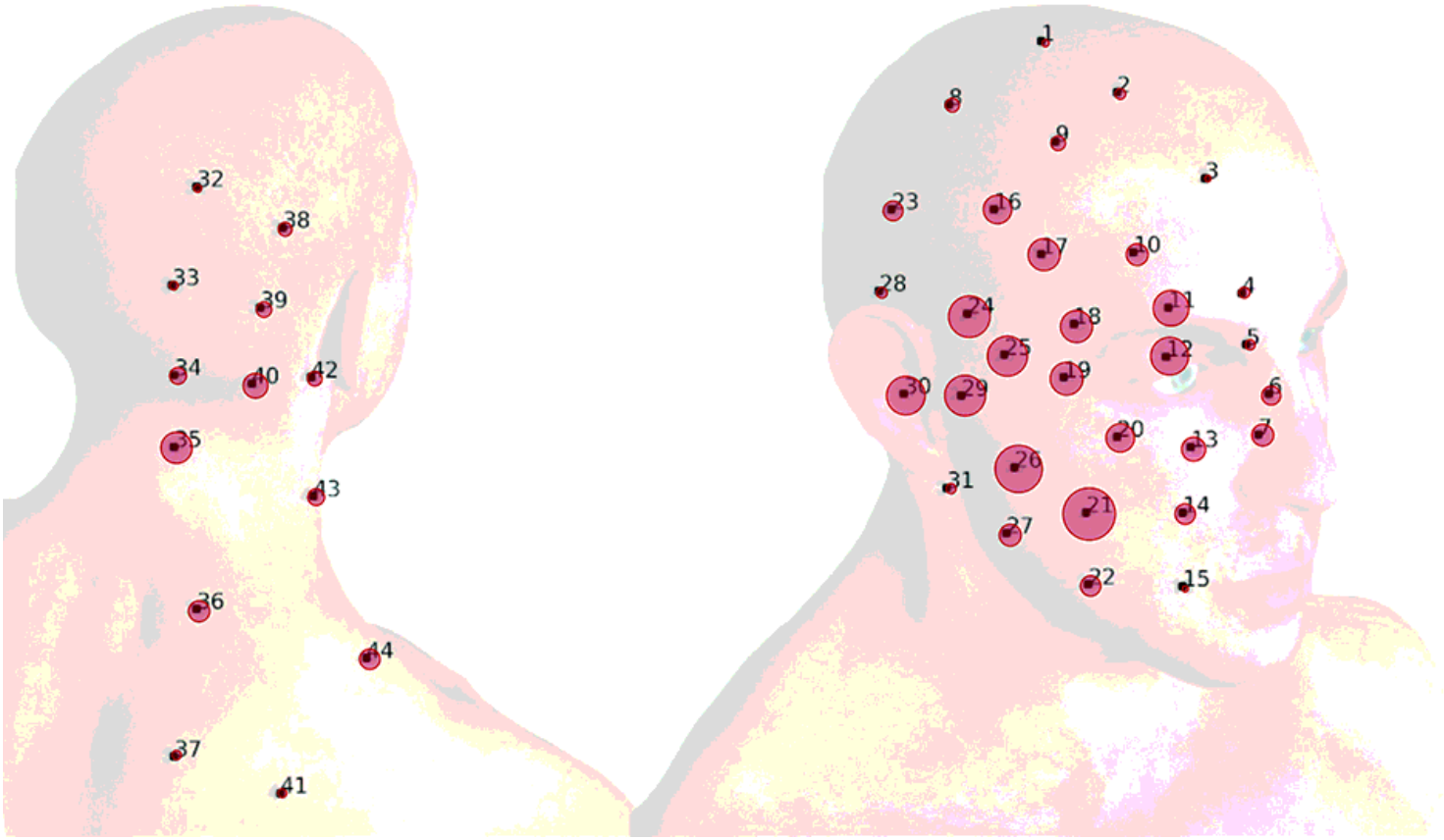

Figure 6

Bubble chart for radiation-pain location frequencies. Points 1-44 are mapped to X,Y coordinates of the chart. Size of bubble = Z-value: diameter of bubble corresponds to pain location frequency [percentage, Table 1]. Bubbles are sized proportionally.

Supplementary Files

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- additionalfile1.pdf
- additionalfile2.xlsx