

Dorsal expansion-related manual disability in verrucae vulgaris patients treated with cryotherapy: A longitudinal study via big data



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ABSTRACT

Background: Common warts frequently occur over the hands and may overlie critical structures, including the extensor expansion of the digits, for which cryotherapy can lead to manual disability. **Aims and Objectives:** We aim to implement big data to infer knowledge on the interest of web users regarding the dorsal expansion-related manual disability in verrucae vulgaris patients managed with cryotherapy. **Materials and Methods:** We mapped the interest of users of the surface web in connection with five topics: cryosurgery, extensor digitorum muscle, human papillomavirus, manual disability, and verruca vulgaris. We retrieved longitudinal data [2004-2019] concerning the spatio-temporal variations of interest in these topics, using Google Trends. We are also reporting a case of interest while analyzing it using the Bradford Hill criteria. **Results:** Sixty-four nations contributed to the spatial (geographic) map, including ten countries from the Middle East and the north of Africa (15.63%). There was high temporal variability concerning cryosurgery 29.61 (+/- 0.94), extensor digitorum muscle 64.43 (+/- 0.86), human papillomavirus 0.01 (+/- 0.01), manual disability 2.89 (+/- 0.13), and verruca vulgaris 9.39 (+/- 0.20). Conjoint inference, via Post-Hoc testing and neural networks [machine learning], assigned the highest synaptic weight [effect size] to "cryosurgery" and "extensor digitorum muscle", thus indicating that these topics are of prime interest for web users, including anatomists and dermatologists. **Conclusion:** We are conveying two messages: 1) Dermatologists are encouraged to collaborate with data scientists to realize the importance of big data for evidence-based dermatology. 2) Physicians should exercise extra caution in managing patients with verrucae vulgaris using cryotherapy.

Key words: Cryotherapy; Disability Studies; Extensor Expansion; Human Papillomavirus; Machine Learning

INTRODUCTION

The extensor expansion, also known as the dorsal aponeurosis, is a specialized connective attachment by which the extensor tendons, principally the extensor digitorum muscle, insert into the phalanges.¹ Dermatologists use cryotherapy for benign lesions, including viral warts, but with some precautions in

dark-skinned individuals, on the face and intertriginous areas, in children, and on delicate sites overlying a tendon or neurovascular bundle.¹⁻⁴ Common warts, also known as verruca vulgaris, are small cutaneous growths that frequently occur over the hands and fingers, which is associated with Human papillomavirus (HPV) type-2, while patients with acquired immunodeficiency syndrome, other types of the virus can coexist, such

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as HPV type-57.⁵⁻⁹ Common wart can overlies critical structures of the hand, including extensor tendons and the extensor expansion.¹⁰ This peculiar topography can interfere with specific therapeutic modalities, including cryotherapies.^{2,11} Data scientists computationally analyze big data to reveal patterns, and associations, especially relating to biological life systems.^{12,13} The implementation of those analytics and machine learning in Dermatology is lagging.¹⁴ Big data applies to the digital epidemiology of inborn errors of metabolism, congenital anomalies, sociology, dentistry, anatomical sciences, neuroscience, addiction studies, and behavioral psychology.¹⁵⁻³³ Real-time and predictive analytics can potentiate big data towards a near-perfect mathematical precision in describing an epidemiological or digital epidemiological phenomenon in Dermatology, including Dermoscopy.¹⁴ The “March of Progress” towards evidence-based dermatology is necessary, in analogy with evidence-based medicine.³⁴ The combined implementation of big data and machine learning with top-tier studies, including randomized controlled trials, systematic reviews, and meta-analytics, will revolutionize Dermatology in the 21st century.^{35,36}

The primary objective of the current study is to implement big data, using the Google search engine, to infer data on the interest of web users regarding the dorsal expansion-related manual disability in verrucae vulgaris patients treated with cryotherapy. We are also reporting a case of interest in an elderly patient with a renal transplant with common warts.

MATERIALS AND METHODS

Using big data from the Google search engine, specifically Google Trends, we mapped the interest of users of the surface web in connection with five topics: extensor digitorum muscle, cryosurgery, human papillomavirus, manual disability, and verruca vulgaris. We shall deduct the spatio-temporal patterns while implementing advanced polynomial regression analytics, Post-hoc testing following univariate analysis, and neural networks [machine learning]. We implemented the Statistical Package for the Social Sciences [IBM-SPSS version 24] and Excel [Microsoft Office 2016] with integrated Data Analysis ToolPak add-in. The authors carried out the work described in this article following the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, EU Directive (210/63/EU) on the protection of animals used for scientific purposes, Uniform Requirements for manuscripts submitted to biomedical journals and the ethical principles defined

in the Farmington Consensus of 1997. We evaluated the level-of-evidence according to the Oxford Centre for Evidence-based Medicine [University of Oxford, 2016].³⁴ According to the Oxford Centre for Evidence-based Medicine (OCEBM), our study represents observational data analytics.³⁴ It also represents an amalgam of an internet snapshot and a case report (Grade C), and longitudinal analyses via the database of literature and trends (Grade D).^{34,35} Accordingly, we cannot categorize the level-of-evidence for this study in correspondence with the existing categorization scheme imposed by the OCEBM in 2016.

RESULTS

Big data analytics

We retrieved longitudinal data [2004-2019] concerning the spatio-temporal variations of interest of surface web users in these topics (Figures 1 and 2). Sixty-four nations contributed to the spatial (geographic) map. The top 20 countries included: Australia, Spain, Bolivia, United States, South Korea, Sri Lanka, Jordan, Belgium, Tunisia, Norway, Belarus, Israel, Algeria, Morocco, France, Colombia, Zambia, Paraguay, Brazil, and Russia (Figure 1). Data signals from the Middle East and the north of Africa represented 15.63% of the holistic geographic map, including Jordan, Tunisia, Israel, Algeria, Morocco, Egypt, Saudi Arabia, Iran, Turkey, and the United Arab Emirates. On a percentile scale, the interest of surface web users revealed fluctuations with time concerning cryosurgery 29.61 (+/- 0.94), extensor digitorum muscle 64.43 (+/- 0.86), human papillomavirus 0.01 (+/- 0.01), manual disability 2.89 (+/- 0.13), and verruca vulgaris 9.39 (+/- 0.20) (Table 1 and Figure 2). Surface web users were most interested in cryosurgery and extensor digitorum muscle, and least interested in manual disability and human papillomavirus, while being moderately interested in verruca vulgaris.

Statistical inference, implementing the Univariate Analysis of Variance, confirmed a statistically significant model for web-based interest (df=4; F=2127.665; p-value<0.001; Partial

Table 1: Keywords-based interest of web users: univariate analysis and post-hoc testing

Descriptive statistics			
Dependent variable: interest			
Keyword	Mean	Std. deviation	N
cryosurgery	29.61	13.076	192
extensor digitorum muscle	64.43	11.855	192
human papilloma virus	.01	.072	192
manual disability	2.89	1.869	192
verruca vulgaris	9.39	2.824	192
Total	21.26	25.251	960

Tests of Between-subjects effects						
Dependent variable: Interest						
Source	Type III sum of squares	df	Mean square	F	Sig.	Partial eta squared
Corrected model	549769.465 ^a	4	137442.366	2127.665	.000	.899
Intercept	434052.676	1	434052.676	6719.315	.000	.876
Keyword	549769.465	4	137442.366	2127.665	.000	.899
Error	61690.859	955	64.598			
Total	1045513.000	960				
Corrected Total	611460.324	959				

a. R Squared = .899 (Adjusted R Squared = .899)

Tukey HSD Post hoc tests				
Dependent variable: Interest				
(I) Keyword	(J) Keyword	Mean Difference (I-J)	Std. Error	Sig.
cryosurgery	extensor digitorum muscle	-34.82*	.820	.000
	human papilloma virus	29.60*	.820	.000
	manual disability	26.72*	.820	.000
	verruca vulgaris	20.22*	.820	.000
extensor digitorum muscle	cryosurgery	34.82*	.820	.000
	human papilloma virus	64.42*	.820	.000
	manual disability	61.54*	.820	.000
	verruca vulgaris	55.04*	.820	.000
human papilloma virus	cryosurgery	-29.60*	.820	.000
	extensor digitorum muscle	-64.42*	.820	.000
	manual disability	-2.88*	.820	.004
	verruca vulgaris	-9.39*	.820	.000
manual disability	cryosurgery	-26.72*	.820	.000
	extensor digitorum muscle	-61.54*	.820	.000
	human papilloma virus	2.88*	.820	.004
	verruca vulgaris	-6.51*	.820	.000
verruca vulgaris	cryosurgery	-20.22*	.820	.000
	extensor digitorum muscle	-55.04*	.820	.000
	human papilloma virus	9.39*	.820	.000
	manual disability	6.51*	.820	.000

*. The mean difference is significant at the .05 level

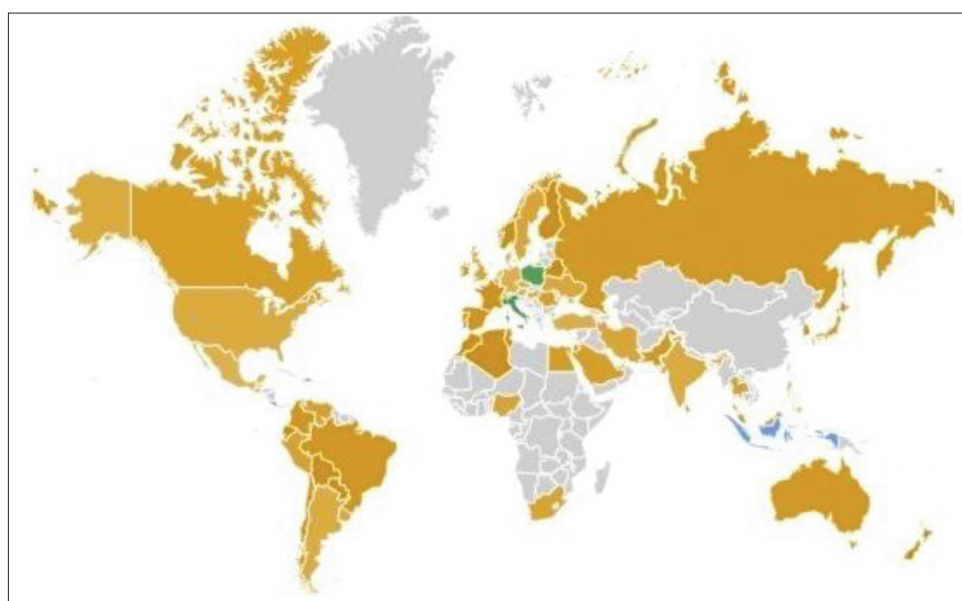


Figure 1: Geographic mapping of the trends database [Timestamp: 01.01.2004 — 01.01.2020]: Color-Coding: Brown [extensor digitorum muscle]; Green [cryosurgery]; Blue [verruca vulgaris]

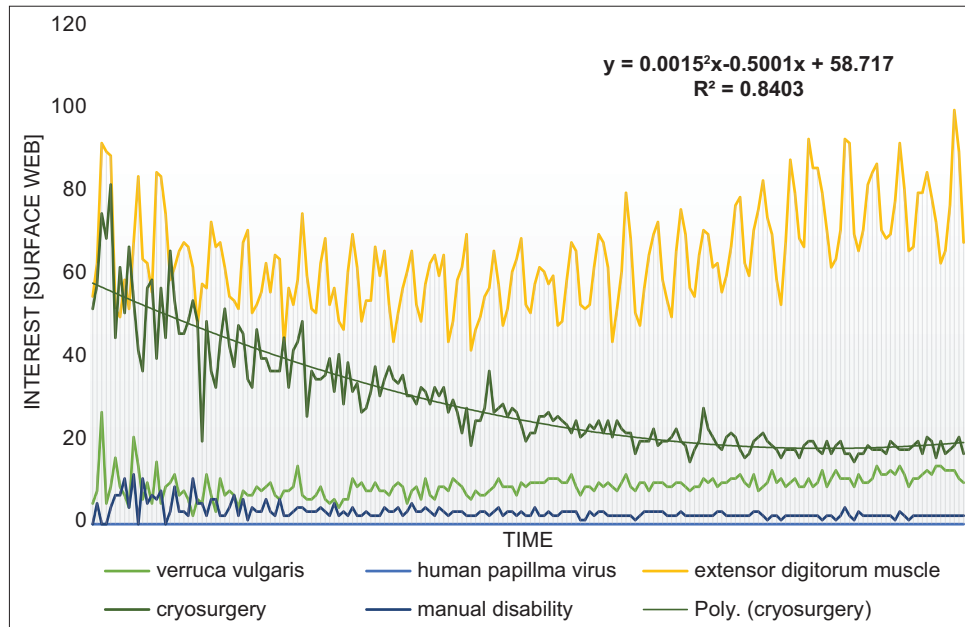


Figure 2: Temporal variation of interest [Surface Web]: Interest of Surface Web Users [Google Trends: 01.01.2004 — 01.01.2020]

Eta Squared=0.899; Adjusted R Squared=0.899) (Table 1). The interest peaked in October 2019 (100%) as well as in February 2017 (93%) and October 2017 (93%). Statistical outliers existed in six consecutive years: 2004 (February-December), 2005 (January-July, November, and December), 2006 (January, March, April, August, and October), 2007 (March and June), 2008 (June), and 2009 (November). It appears the temporal variations of web-based interest in cryosurgery is following a polynomial regression, i.e., a curvilinear pattern with time (R^2 score = 0.840; Coefficient of Correlation = 0.917; $y = 0.0015x^2 - 0.5001x + 58.717$) (Figure 2). The polynomial curve estimation is useful for predictive analytics with some margin of error. Tukey's HSD Post-Hoc testing indicated a statistically significant difference between all five topics: cryosurgery, extensor digitorum muscle, human papillomavirus, manual disability, and verruca vulgaris (p -value<0.005) (Table 1). The strongest effect size was for extensor digitorum muscle versus human papillomavirus (Cohen's $d=7.685$; p -value<0.001) and extensor digitorum muscle versus manual disability (Cohen's $d=7.252$; p -value<0.001). Machine learning analytics, via the implementation of neural networks, yielded affirmative collateral evidence on the effect size that goes in line with our results from Post-Hoc testing. Multilayer perceptron, while deploying default SPSS allocation of 70% versus 30% data input [training versus testing] and a gradient descent algorithm, assigned the highest synaptic weight, i.e., an effect size to "cryosurgery" and "extensor digitorum muscle".

Case report

A sixty-seven years old male, by the pseudonym "Satoshi Nakamoto" who had a renal transplant for 25 years. The

patient is on the long-term treatment of Azathioprine. He is of type-2 Fitzpatrick skin that tends to burn quickly upon exposure to sunlight without tanning. Mr Nakamoto started developing skin dermatoses within ten years following his successful kidney transplant. He had nearly a dozen surgical excisions for cutaneous pre-neoplastic and neoplastic lesions, including multiple basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Those lesions are distributed over sun-exposed areas, including the head, neck, scalp, ear, behind the ear, and the hands. The worst and most significant lesion, a rapidly growing cauliflower-like biopsy-proved SCC over the scalp, was surgically removed, and followed by skin grafting approximately 6 cm in diameter over the left parietal-temporal region. Unfortunately, Mr Sataoshi had a poor prognosis due to SCC metastases to the lung, as confirmed using MRI and PET scan.

Now, the patient presented with other non-melanocytic skin lesions, including one over the right temple that existed for four weeks, in addition to multiple solar (actinic) keratoses all over the scalp and the hands. The patient also had numerous common warts (verrucae vulgaris) over the extensor and lateral surfaces of his fingers, some of which are 1-1.5 cm centimetres in diameter (Figure 3). Those warts existed for years and following his renal transplant. Mr Nakamoto had no other types of warts in different regions of the body, including genital warts and plantar warts. Nakamoto declared that he always worked indoor and did not have any sunny holidays or sunbathing. There is no family history of melanocytic or non-melanocytic cutaneous neoplasms. Upon clinical examination, the patient had multiple plane wart over the

face, a superficial BCC around the left temporomandibular joint, as well as some purpuric and limited ecchymotic lesions over the extensor aspect of his forearm, perhaps as a consequence of long-term immunosuppressive therapy for his transplant. Over the dorsum of the hand, he had multiple solar keratoses and several common warts over the dorsum of the digits and the knuckles. A noticeable semi-flexion deformity existed, affecting his right ring finger. The patient confirmed that he had a prior cryotherapy session for warts that have grown over the extensor surface of that digit. We postulate that this deformity results from an underlying cryotherapy-induced trauma to the dorsal (extensor) expansion.

DISCUSSION

The literature

During January 2020, we conducted a systematic review of the medical and paramedical databases of the



Figure 3: An elderly patient with verrucae vulgaris on the extensor surfaces of the digits

peer-reviewed literature, in an aim to detect publications of interest concerning our presented case. We searched the Cochrane Library [the Cochrane Database of Systematic Reviews], PubMed [the United States National Library of Medicine], and Embase [Elsevier Database]. We deployed a composite of MeSH-based keywords and generic terms, as well as truncations, and shuffling those using Boolean operators. We included keywords related to five main themes, including “Cryotherapy”, “HPV Wart”, “Anatomy”, “Disability”, and “the Hand”. The review strategy generated a total count of 2,936,933 papers distributed to the Cochrane Library [20,811 (0.71%)], the United States National Library of Medicine [2,741,596 (93.35%)], and Embase [174,526 (5.94%)]. Based on the combination of all themes of keywords, the total number of publications was 59,366, allocated to the Cochrane Library [19 (0.03%)], United States NLM [0 (0.00%)], and Embase [59,347 (99.97%)] (Figure 4). At the moment the snapshot was taken, it is evident that the indexed search volume in PubMed database, is assuming a logarithmic pattern (R^2 score = 0.956; Coefficient of Correlation = 0.978; $y = -8E+05\ln(x) + 1E+06$), while most of the relevant publications are indexed in PubMed database and the Cochrane Library. Embase represented much statistical noise, i.e., publications that were not relevant to our keywords-based search strategy. After retrieving the full-text articles from the Cochrane Library ($n=19$) and scanning through the titles and abstracts, we found only one top-tier level-of-evidence study, a systematic review with meta-analyses by Kwok and coworkers (2012). The systematic review is by the title: “Topical treatments for cutaneous warts”.¹¹

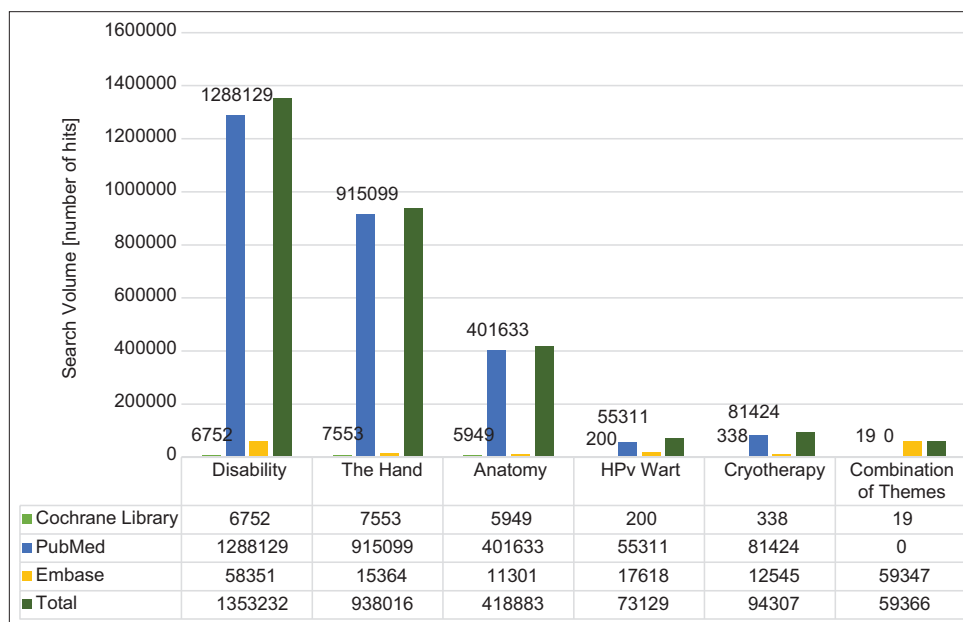


Figure 4: The literature [Timestamp: January 2, 2020]

Bradford hill's criteria: Case interpretation

In 1965, British statistician Austin Bradford Hill proposed nine-elements based criteria to provide evidence for the understanding of causality, i.e., cause and effect association for an observed outcome.^{37,38} Hill demands the analysis of the strength of association and the effect size, the reproducibility (replicability) of the results, the specificity of association, the temporality of causation, the gradient effect, i.e., a dose-response relationship, plausibility (rationality), coherence (consistency), experimental validation, and analogy.³⁷ Some authors also add reversibility to Hill's criteria as the tenth element. Our case can satisfy some items out of ten of Bradford Hill's rules, including the temporality, the gradient effect, plausibility, and analogy. Nonetheless, this individual case represents an anecdotal report in which ambiguous co-variables could have interfered.³⁸ Future studies should deploy higher-tier level-of-evidence experiments, including prospective and randomized controlled trials, meta-reviews, and meta-analyses, including meta-regression studies, to provide an externally validated inference in connection with the objectives of our study.

CONCLUSION

We highlight three key messages: 1) Clinical dermatologists, unlike anatomists, lack the detailed knowledge of the anatomy of the extensor expansion, which is critical for managing dermatological conditions affecting the fingers. 2) Dermatologists are encouraged to collaborate with data scientists to realize the importance of big data for evidence-based dermatology. 3) Dermatologists and general practitioners should exercise extra caution in managing patients with verrucae vulgaris using cryotherapy and anticipate potential complications and disabilities that may limit the quality-of-life for all age groups, including debilitated patients, and especially the elderly populations.

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Author's contribution:

AAI - collected the data, conducted data analytics, wrote the first draft of the article, and prepared the manuscript for scholarly submission; **HAD** - Contributed to developing the study design and data curation; **AAS** - Contributed to writing the first draft and developing the paper for academic presentation.

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