Original Article

Infodemiology of antiphospholipid syndrome: Merging informatics and epidemiology

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Abstract

Objective: To investigate trends in Internet search volumes linked to Antiphospholipid Syndrome (APS), using Big Data monitoring and data mining.

Methods: Based on the large amount of data generated by Google Trends and scientific search tools (SCOPUS, Medline/Pubmed, and ClinicalTrails.gov), we performed a longitudinal analysis based on the term "antiphospholipid" in a 5-year web-based research.

Results: Google Trends captured that APS-related digital interest was generally steady in the study period (Relative Search Volume [RSV] mean value 71.1±9.3% [95%CI 55.6-89.4], median 72.0), with no significant peak based on different seasons (e.g. winter vs. summer time). When comparing the APS-related digital interest with search volumes generated in the same time period for Inherited Thrombophilias (IT) and Systemic Lupus Erythematosus (SLE), we found a digital interest 35-times higher for APS than for IT (RSV mean value 71.1±9.3% [95%CI 55.6-89.4] vs. 2±3.2% [95%CI 0.7-7.4]). When compared to SLE, APS reached a similar RSV, showing a comparable digital interest (RSV mean value 71.1±9.3% [95%CI 55.6-89.4] vs. 87±11.8% [95%CI 60.7-107.9]). When adjusting for relative search volumes of Google Trends, we found a relative prevalence of search volumes of 35.5% in Europe, 12.3% in the United States, 11.5% in South America, 11.2% in Australia, 9.2% in Canada, 9.2% in Japan, and 5.1% in India. We observed an overall similar distribution of search volumes from Google Trends compared to results from Medline/Pubmed, SCOPUS, and ClinicalTrials.gov. In brief, the United States and Europe (mainly Italy, the United Kingdom, Spain, France, and Germany) presented the higher RSV. Similarly, these countries showed a higher number of research publications and on-going trials in the field of APS.

Conclusion: In this study, we demonstrated that the interest in APS is not equally distributed globally. Thus, geopolitical differences might represent a challenge when attempting to estimate the prevalence of APS or designing worldwide investigations in APS. Combining the expanding framework of infodemiology with scientific networking collaborative efforts, such as AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION), will help better define the syndrome in terms of prevalence, event occurrence ratios, and thrombosis risk assessment.

Keywords: APS, infodemiology, epidemiology, thrombosis, antiphospholipid antibodies, antiphospholipid syndrome

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Introduction

The incidence and prevalence of Antiphospholipid Syndrome (APS) in the general population are not well known. Some reports estimate the incidence as 5 cases per 100,000 persons per year, and the prevalence as 40-50 cases per 100,000 persons (1, 2). Recently, several studies have attempted to estimate the prevalence of antiphospholipid antibodies in different cohorts, such as young patients with stroke and patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis (3, 4).

Investigating the prevalence and the features of rare conditions requires multicentre efforts. However, the low prevalence of rare diseases makes funding arduous and, for similar reasons, randomized controlled trials difficult to conduct. In the "world wide web era" new tools are available for researchers and clinicians, especially to study sub-groups of low prevalence populations. By extrapolating relative search data, one can obtain relative information on how patients navigate the web and how the spread of information on rare conditions is affecting clinicians and patients in different areas of the globe. "Infodemiology" is a recent term, first described by Eysenbach, based on Big Data monitoring and data mining, used to define this new approach in public health (5).

Infodemiology data can be collected and analyzed in near real time and are relatively costless. The applications of this new approach have already been widely applied, including to the disease outbreaks prediction analysis using Internet search volumes, e.g., influenza, monitoring people's status updates on social networks for syndromic surveillance, and to tracking the effectiveness of health marketing campaigns. More recently, it has been applied to investigate autoimmune diseases, and more specifically the seasonability and flares of autoimmune conditions, such as systemic lupus erythematosus (SLE) (6-8).

Google Trends (GT) has recently made available the large amount of trend data generated by the number of Google searches in a geographic region over time (http://www.google.com/trends). GT is a feature that allows users to graph the frequency of searches for a term, a string of multiple terms, or a phrase. The data used to generate these graphs are scaled to the average search traffic for the selected term and are also normalized on a relative, rather than absolute, basis.

Analyzing how patients, researchers, and physicians search and navigate the Internet for health-related information, as well as how they communicate and share this information, can provide valuable insights into the health-related behavior of populations, especially in the setting of rare diseases (5).

In the study, using this new approach, we investigate possible trends of Internet search volumes linked to APS and on-going research developments associated with the disease, and compare APS-related digital interest with those for inherited thrombophilia (IT) and SLE.

Methods

We analyzed the large amount of data generated by GT, based on the search term "antiphospholipid" in a 5-year worldwide web-based research (from January 2012 to January 2017). Search terms, considered on Google Trends separately, were: "antiphospholipid" (requiring the exact phrase to be present in the search field) (http://www.google.com/trends) with the following filters: "Worldwide," in "All Categories" and for "Web Searches").

Relative search volumes (RSV) data for APS were compared to those for IT and SLE (search terms included ́Systemic Lupus Erythematosus ́ and ́Inherited Thrombophilia ́ in a a 5-year worldwide web-based research). Search volumes generated by GT are expressed as percentages calculated by worldwide RSV. For those countries where English is not the

first language, additional analyses were conducted by including search terms in the local language. Generalized linear models were employed to assess possible differences in relative search volumes for "APS," "IT" and "SLE," and results are presented as rate ratio (adjusted on the median) and 95% CIs.

We compared results with data from scientific search tools (SCOPUS, Medline/Pubmed) and with a global registry of publicly and privately supported human clinical studies (ClinicalTrials. gov). For scientific search tools, only original research was considered and data are presented as relative percentages of scientific contribution.

All statistical analyses were performed using SPSS version 19.0 (IBM Corp.; Armonk, NY, USA).

Results

Antiphospholipid Syndrome-related digital interest, expressed as search volumes, compared with SLE and IT is shown in Figure 1. Google Trends captured APS-related digital interest, was generally steady in the study period (RSV mean value 71.1±9.3% [95%CI 55.6-89.4], median 72.0), with no significant peak based on different seasons (e.g. winter vs. summer time). When comparing the APS-related digital interest with search volumes generated in the same time period for IT and SLE, we found a digital interest 35-times higher for APS than for IT (RSV mean value 71.1±9.3% [95%CI 55.6-89.4] vs. 2±3.2% [95%CI 0.7-7.4]). When compared to SLE, APS reached a similar RSV, showing a comparable digital interest (RSV mean value 71.1±9.3% [95%CI 55.6-89.4] vs. 87±11.8% [95%CI 60.7-107.9]).

The geo-infodemiology for search volumes for APS-related terms, related search topics and on-going research developments are shown in Figure 2 and Figure 3.
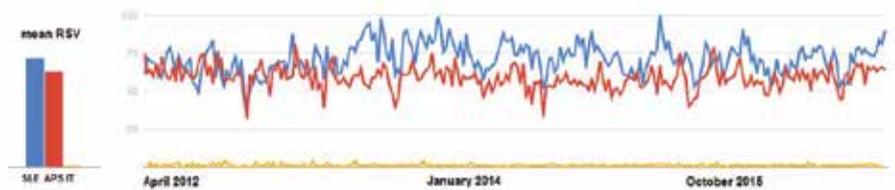

Figure 1. APS-related digital interest expressed as search volumes compared with SLE and IT
RSV: relative search volume; APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; IT: inherited thrombophilias
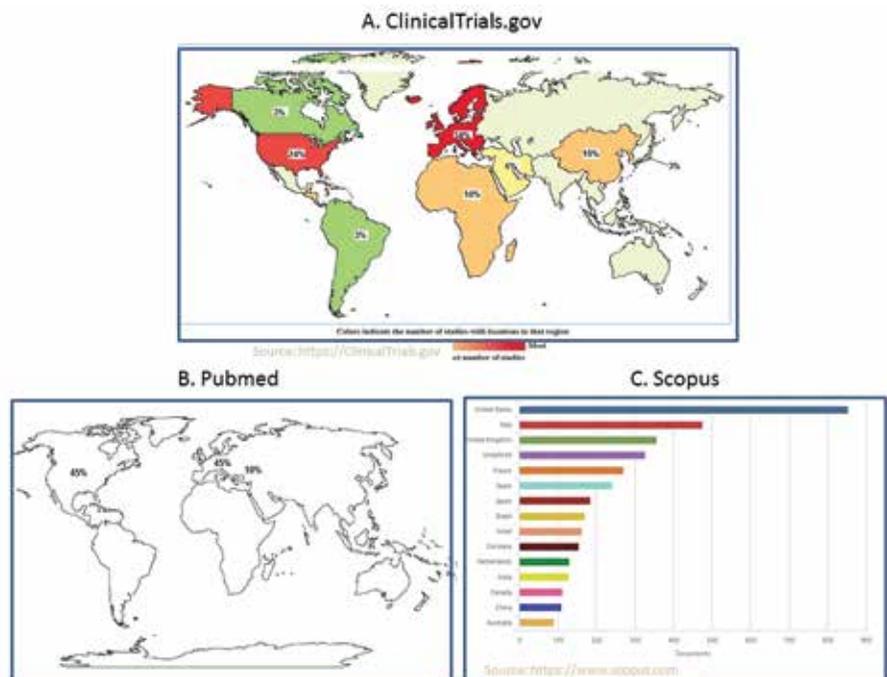

Figure 2. Profile plots for relative search volumes. Profile plots show the relative search volumes, from January 2011 to January 2016, for "antiphospholipid" using ClinicalTrials.gov (Panel A), Pubmed (Panel B) and Scopus (Panel C). Date of search: 4th October 2016.
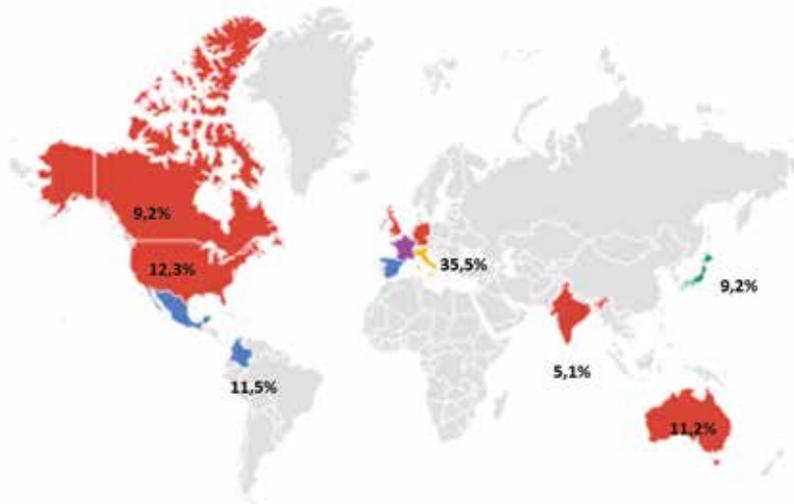
Figure 3. Profile plots for relative search volumes. Profile plots show the relative search volumes, from January 2011 to January 2016, for "antiphospholipid" using Google Trends, worldwide distribution

Table 1. The list of the top rising APS-related queries, as captured by GT and Goggle Correlate

rivaroxaban

apixaban

antiphospholipid syndrome guidelines

lupus

factor 5 Leiden

thrombophilia

heparin

livedo reticularis

Search terms, considered on Google Trends separately, were: "antiphospholipid" (requiring the exact phrase to be present in the search field) (http://www.google.com/trends) with the following filters: "Worldwide," in "All Categories" and for "Web Searches"). Google Trends automatically normalized data for the overall number of searches, and presented them as relative search volumes (on a scale from 0 to 100), in order to compare variations of different search terms across regions and periods. For those countries where English is not the first language, additional analyses were conducted by including search terms in the local language. This approach presents intrinsic limitations (e.g., limited access to the Google search tool in some areas, such as China). Therefore, a non-representative sampling bias might have occurred due to different factors, such as age, disability, income, or preferred search engine.

When adjusting for relative search volumes of GT in a worldwide search for "APS" and "antiphospholipid," we found a relative prevalence of search volumes of 35.5% in Europe, 12.3% United States, 11.5% South America, 11.2% Australia, 9.2% Canada, 9.2% Japan, and 5.1% India.

We observed an overall similar distribution of search volumes from Google Trends compared

to results from Medline/Pubmed, SCOPUS, and ClinicalTrials.gov. In brief, the United States and Europe (mainly Italy, the United Kingdom, Spain, France, and Germany) presented the higher search volumes. Similarly, these countries showed higher numbers of research publications and on-going trials in the field of APS. The list of the top rising APS-related queries, as captured by GT and Google Correlate, are shown in Table 1.

Discussion

These observations support the idea that there is a vivid and expanding research interest in the field of APS. Digital interest is higher for APS when compared to a similar group of conditions, IT, with an overall comparable epidemiology (9). Interestingly, APS presents a similar RSV distribution to SLE, a complex heterogeneous disease affecting a larger group of individuals.

The APS-related web interest as captured by GT is in line with the growing number of scientific publications in the field of APS. In fact, when stratifying for article type data from Medline/Pubmed and SCOPUS, we observed that original articles represented about 60% of publications in the field of APS.

Google Trends and Google Correlate provide an overview on related search terms and queries. Google Correlate is like GT in reverse. With GT, one can type in a query and get back a data series of activity. With Google Correlate, one can enter a data series (the target) and get back a list of queries whose data series follows a similar pattern. Since the first description of the syndrome, therapies for thrombotic APS have mainly relied on vi-

tamin K-antagonist agents and/or heparins; to date there is a growing interest in the use of direct oral anticoagulant agents (DOAC) in this setting (10). Interestingly, the top-two related search topics rising in RSV included DOAC. These observations are in line with the fact that, despite improvements in the understanding of the syndrome in the last three decades, individuals browsing the web for APS-related topic mainly focus on new therapeutic approaches.

The interest in APS is not equally distributed globally, assessed by generated search volumes from biomedical search engines and from public reliable tools. Thus, geopolitical differences might represent a challenge when attempting to estimate the prevalence of APS or designing worldwide investigations in APS.

Limitations of the study: available data are based on a sample of Google web searches, with the potential for non-representative sampling bias; the calculation of the search value index presented in the results is dependent on several mathematical assumptions and approximations in search traffic.

Combining the expanding framework of infodemiology with scientific networking collaborative efforts, such as AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking-APS ACTION will help better define the syndrome in terms of prevalence, event occurrence rates, and thrombosis risk assessment (11).

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