Application of artificial neural network analysis in the evaluation of cardiovascular risk in primary Sjögren's syndrome: a novel pathogenetic scenario?

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Received on July 2, 2019; accepted in revised form on July 22, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 118): S133-139.

Key words: Sjögren's syndrome, artificial neural network, cardiovascular risk

Competing interests: none declared.

ABSTRACT

Objective. *The aim of the present study was to verify whether artificial neural networks (ANNs) might help to elucidate the mechanisms underlying the increased prevalence of cardiovascular events (CV) in primary Sjögren's syndrome (pSS).*

Methods. *408 pSS patients (395 F: 13 M), with a mean age of 61 (±14) years and mean disease duration of 8.8 (±7.8) years were retrospectively included. CV risk factors and events were analysed and correlated with the other pSS clinical and serological manifestations by using both a traditional statistical approach (i.e. Agglomerative Hierarchical Clustering (AHC)) and Auto-CM, a data mining tool based on ANNs.*

Results. *Five percent of pSS patients experienced one or more CV events, including heart failure (8/408), transient ischaemic attack (6/408), stroke (4/408), angina (4/408), myocardial infarction (3/408) and peripheral obliterative arteriopathy (2/408). The AHC provided a dendrogram with at least three clusters that did not allow us to infer specific differential associations among variables (i.e. CV comorbidity and pSS manifestations). On the other hand, Auto-CM identified two different patterns of distributions in CV risk factors, pSS-related features, and CV events. The first pattern, centered on "non-ischaemic CV events/generic condition of HF", was characterised by the presence of traditional CV risk factors and by a closer link with pSS glandular features rather than to pSS extra-glandular manifestations. The second pattern included "ischaemic neurological, cardiac events and peripheral obliterative arteriopathy" and appeared to be strictly associated with extra-glandular disease activity and longer disease duration.*

Conclusion. *This study represents the first application of ANNs to the analysis of factors contributing to CV events in pSS. When compared to AHC, ANNs had the advantage of better stratifying CV risk in pSS, opening new avenues for planning specific interventions to prevent long-term CV complications in pSS patients.*

Introduction

Primary Sjögren's syndrome (pSS) is a complex disease characterised by a heterogeneous spectrum of clinical features (1-3). The disease course is generally considered benign and life-threatening systemic extra-glandular manifestations are observed only in the 15–20% of patients (4). Traditionally, pSS-related morbidity and mortality have been associated with lymphoproliferation rather than with other systemic complications (4-7). Recently, however, a number of papers have highlighted that, when compared to general population, pSS patients also present an increased risk for cardiovascular (CV) events (8-13). Particularly, pSS has been associated with nearly one and a half-fold increased risk of both cardiac and cerebrovascular events in comparison to control subjects (8, 14).

Similar to other autoimmune diseases, several interacting mechanisms have been demonstrated to contribute to CV damage and accelerated atherosclerosis in pSS (15). First, according to the recent literature, the prevalence of traditional CV risk factors (*i.e.* hypertension and dyslipidaemia) is higher in pSS patients than in general population. Second, inflammatory mediators and disease-related immune factors seem to cooperate with traditional CV risk factors in the pathogenesis of endothelial dysfunction and in favouring organic

damage of arterial wall and plaque formation (15). However, the actual contribution of each of these factors to the pathogenesis of atherosclerosis and to CV events in pSS is still under investigation. More specifically, how and to what extent traditional CV risk factors, chronic inflammation, autoimmune factors and disease activity interact in contributing to atherosclerosis in pSS is still to be investigated. Indeed, in the era of precision medicine, to individualise preventive strategies and to target therapeutic approaches a better definition of disease subsets at higher CV risk is urgently needed as well as a better awareness of the independent role of traditional and immunological factors in influencing the overall CV risk.

In recent years, progress has been made in data mining technology, which has emerged as an additional strategy for constructing risk assessment models. In this setting, artificial neural networks (ANN) represent an interesting data mining computational approach inspired by the structure and functions of biological neural networks (16, 17). Recent applications of ANN in CV medicine have been promising and have provided interesting preliminary results in risk stratification, diagnosis, treatment and prognosis of CVD (18). To date, no studies have investigated the ability of ANNs in evaluating the interplay of traditional CV risk factors with pSS descriptors complexity and the contribution of traditional CV risk factors and disease-related inflammatory and autoimmune features in influencing the CV risk. Therefore, the aims of the present study were: 1. to investigate in a large cohort of SS patients the relationship between traditional CV risk factors and pSS-related features by using traditional and ANNs approaches in order to better identify patients at increased CV risk and, 2. to analyse the association between traditional CV risk factors, pSS-related immunological abnormalities and CV event occurrence during the disease course.

Patients and methods

We retrospectively included a cohort of 408 pSS patients fulfilling the revised classification criteria proposed by the American-European Consensus Group (AECG) in 2002 (19). Disease clinical and laboratory data were systematically collected from patient medical records. Briefly, clinical data included: age at diagnosis and inclusion, xerophthalmia, xerostomia, recurrent parotid enlargement, extra-glandular manifestations as defined in the ESSDAI (20) and Raynaud's phenomenon. Disease-specific laboratory markers included: cytopenia, low C3 and C4 complement levels, hypergammaglobulinaemia, rheumatoid factor by nephelometry, antinuclear antibodies by indirect immunofluorescence on HEp-2 cells, anti-SSA/Ro and anti-SSB/La antibodies by enzyme-linked immunosorbent assay and cryoglobulins. Finally, ongoing and previous therapies, including symptomatic therapy, glucocorticoids (GC, prednisone or equivalent ≤7.5 mg/day), hydroxychloroquine (HCQ) and immunosuppressants (IS) were registered.

In addition, the following CV risk factors were recorded: smoking (defined as previous/current use of ≥1 cigarette/day); hypertension (defined as a physician diagnosis and/or prior/ongoing anti-hypertensive therapy); hypercholesterolaemia (total serum cholesterol level >240 mg/dl on ≥3 assays); hypertriglyceridaemia (serum triglyceride level >150 mg/dl on ≥3 assays); high-density lipoprotein cholesterol (HDL-c) level (reduced <40 mg/dl, normal 40–60 mg/dl, increased >60 mg/dl on ≥3 assays); low-density lipoprotein cholesterol (LDL-c) level (reduced <130 mg/dl, normal 130–160 mg/dl, increased >160 mg/dl on ≥3 assays); diabetes mellitus (DM) (defined as ongoing treatment with insulin or oral hypoglycaemic agents and/or ≥2 fasting glycaemia >126 mg/dl); obesity (according to body mass index). Finally, prevalence of CV events was evaluated. Namely, CV events included a generic category "heart failure" defined as a complex condition derived from different causes such as ischaemic heart disease, hypertension, primary or toxic cardiomyopathy, valvular or congenital lesions, right ventricular dysfunction caused by lung disease, and arrhythmia. We also distinguished separately, ischaemic heart events (myocardial infarction and angina), cerebrovascular events and peripheral obliterative arteriopathy. CV events were recorded only if the diagnosis was confirmed by hospital discharge and/or available specific laboratory and instrumental exams. The study received the local ethics committee approval and was conducted according to the Declaration of Helsinki.

Statistical analysis

In this paper we used two different statistical approaches: Auto-CM and Agglomerative Hierarchical Clustering (AHC).

Auto-CM, a data mining tool based on fourth-generation artificial neural networks (ANNs) developed at Semeion Research Centre, Italy, was used to compute the natural association scheme of the variables on study and the strength of the emerging associations in terms of many-to-many rather than dyadic. The architecture and mathematics of Auto-CM are described elsewhere (17). Association strength across all variables were visualised by the concept of "closeness". In other words, variables whose connection weights are higher, get relatively nearer and vice versa. By applying a minimum spanning tree to the matrix of distances, a graph, named "semantic connectivity map (SCM)," was generated, allowing a visual mapping of the complex web of connection schemes among variables.

The Auto-CM and the self-organising maps are systems for unsupervised data mining. However, it should be noted that the self-organising maps are mainly directing the clustering individuals rather than variables. To handle a benchmarking analysis the AHC was carried out with XLSTAT package 2019. AHC is one of the most popular clustering methods which seeks to build a hierarchy of clusters with a "bottom-up" approach: each observation starts in its own cluster, and pairs of clusters are merged as one moves up the hierarchy. The agglomerative clustering is the most common type of hierarchical clustering used to group objects in clusters based on their similarity. The algorithm starts by treating each object as a singleton cluster. Next, pairs of clusters are successively merged until all clusters have been merged into

one big cluster containing all objects. The result is a tree-based representation of the objects, named dendrogram. It is then possible to gain an idea of a suitable number of classes into which the data can be grouped. Results of this benchmarking analysis allowed us to compare findings from the Auto-CM approach with findings from the traditional statistical approach.

Results

Patients' demographic clinical and serological features

Table I illustrates the clinical and serologic features of patients enrolled in the study. The whole cohort included 408 pSS patients with a mean age of 61 (±14) years and mean disease duration of 8.8 (±7.8) years. Xerophthalmia and xerostomia were the most prevalent disease manifestations, being reported in 97% and 95% of patients, respectively, followed by articular involvement (58%). About one third of patients were characterised by concomitant fibromyalgia. As far as serologic features were concerned, anti-Ro/SSA were detected in 77% and anti-La/SSB in 36% of patients. About 60% of patients were characterised by rheumatoid factor positivity. Lymphoproliferative complication was registered in about 6% of patients. The majority of patients received symptomatic therapy only, although up to 40% of patients were treated with low glucocorticoid dose and hydroxychloroquine while immunosuppressant therapies, including biologic drugs, were employed in 10% of cases.

Table I. Patients' clinical and serological features.

	All (408)	pSS-CV (22)	pSS-no CV (386)	*p*-value
Age (SD), yrs	60.7 (14.2)	68.4 (12.8)	60.3 (14.2)	*0.002*
Disease duration (SD), yrs	8.8 (7.8)	6.5 (7.1)	8.9 (7.8)	ns
Male	13 (3.2%)	1 (4.5%)	12 (3.1%)	ns
Xerostomia	387 (94.9%)	21 (95.5%)	366 (94.8%)	ns
Xerophthalmia	394 (96.6%)	22 (100%)	372 (96.4%)	ns
Ocular tests	384 (94.1%)	22 (100%)	362 (93.8%)	ns
SGE	146 (35.8%)	6 (27.3%)	140 (36.3%)	ns
Articular	237 (58.1%)	11 (50%)	237 (58.1%)	ns
Purpura	37 (9.1%)	3 (13.6%)	34 (8.8%)	ns
Raynaud's phenomenon	111 (27.2%)	7 (31.8%)	104 (26.9%)	ns
Fibromyalgia	145 (35.5%)	13 (59.1%)	132 (34.2%)	ns
Leukopenia	97 (23.8%)	7 (31.8%)	90 (23.3%)	ns
NHL	22 (5.4%)	1 (4.5%)	21 (5.4%)	ns
Low C3	69 (16.9%)	4 (18.2%)	65 (16.8%)	ns
Low C4	52 (12.7%)	4 (18.2%)	48 (12.4%)	ns
Hyper-gamma	212 (52%)	13 (59.1%)	199 (51.6%)	ns
Anti-Ro/SSA	316 (77.5%)	17 (77.3%)	229 (77.5%)	ns
Anti-La/SSB	147 (36%)	5 (22.7%)	142 (36.8%)	ns
Rheumatoid factors	244 (58.9%)	16 (72.7%)	228 (59.1%)	ns
Cryoglobulins	11 (2.7%)	1 (4.5%)	10 (2.6%)	ns
Anticardiolipin antibodies	8 (2%)	1 (4.5%)	7 (1.8%)	ns
Only symptomatic	212 (52%)	7 (31.8%)	205 (53.1%)	ns
Low GC	157 (38.5%)	12 (54.5%)	145 (37.6%)	ns
HCQ	188 (46.1%)	13 (59.1%)	175 (45.3%)	ns
DMARDs	40 (9.8%)	2 (9.1%)	38 (9.8%9	ns

pSS-CV: patients with primary Sjögren's syndrome and cardiovascular events; pSS-no CV: patients with primary Sjögren's syndrome and no cardiovascular events; yrs: years; NHL: non-Hodgkin's lymphoma; GC: glucocorticoids; HCQ: hydroxychloroquine; DMARDs: disease modifying anti-rheumatic drugs.

Distribution of traditional cardio-vascular and disease-related risk factors in pSS patients with or without cardiovascular events

As illustrated in Table I, during the disease course 5% of patients experienced one or more major CV events including heart failure (8/408), transient ischaemic attack (6/408), stroke (4/408), angina (4/408), myocardial infarction (3/408) and peripheral obliterative arteriopathy (2/408). We subdivided our pSS cohort in two groups according to occurrence of CV events and we defined two subsets: patients who have presented at least one CV events of any kind since pSS diagnosis (*i.e.* pSS-CV) and patients without CV events (pSS-no CV). Patients with previous CV events were significantly older in comparison to patients who did not experience CV events (68±13 *vs.* 60±14 mean years, respectively). No differences between the two groups were detected with respect to all other parameters analysed except for a trend in a higher prevalence of symptomatic therapy use in patients not reporting CV events (p=0.07).

When we focused on traditional CV risk factors, we found that hypertension was the most prevalent traditional CV risk factor in the entire pSS cohort, followed by dyslipidaemia. Interestingly, patients presenting at least of one CV event displayed a significant higher prevalence of hypertension in comparison to patients free from CV comorbidity (Table II).

Auto-CM analysis and semantic connectivity map: role of traditional CV risk factors and pSS-related features in cardiovascular event occurrence

Figures 1 and 2 show a "semantic connectivity map" (SCM) performed by Auto-CM analysis for all the variables analysed reporting significant correlations between pSS clinical and demographic manifestations, serological features, traditional CV risk factors and CV events. CV event were analysed all together (*i.e.* defined as at least one, of any kind) as a single variable in Figure 1 and considered separately in Figure 2, distinguishing the generic definition of "heart failure" from "ischaemic heart events". Figure 2 also considered individually the other CV events, in particular neurological events and peripheral arterial disease. Both the maps showed that the vast majority of traditional CV risk factors (*i.e.* hypertension, dyslipidaemia, BMI |25) with the exception of smoking, appeared associated one to each other and placed in the connectivity map closer to pSS ocular and oral manifestations and to the demographic feature "age older than 65 years" and relatively far from systemic extra-glandular disease manifestations. As illustrated in Figure 1, when cardiovascular events were considered as a whole, they resulted

Table II. Prevalence of cardiovascular risk factors in patients with and without CV events.

	All (408)	pSS-CV (22)	pSS-no CV (386)	*p*-value
Smoking	44 (10.8%)	2 (9.1%)	42 (10.9%)	ns
Obesity	51 (12.5%)	1 (4.5%)	50 (13%)	ns
Hypertension	152 (37.3%)	17 (77.3%)	135 (355)	*0.001*
Diabetes	21 (5.1%)	None	21 (5.1%)	ns
Dyslipidaemia	148 (36.3%)	9 (40.9%)	139 (36%)	ns

pSS-CV: patients with primary Sjögren's syndrome and cardiovascular events; pSS-no CV: patients with primary Sjögren's syndrome and no cardiovascular events.

more strongly associated with the traditional CV risk factors than with pSS-related features. On the other hand, when CV events were considered separately (Fig. 2) focusing on "ischaemic heart events", "ischaemic neurological events" and "peripheral obliterative arteriopathy", a closer association was observed between them and pSS systemic extra-glandular "vasculitic manifestations" (purpura, leukopenia, low complement, cryoglobulins), disease duration and previous/current use of glucocorticoids/DMARDs. Smoking resulted the only traditional CV risk factor clearly connected with CV ischaemic events. The generic condition "heart failure" remained closely connected with hypertension and the other traditional CV risk factors.

Agglomerative hierarchical clustering of CV risk factors and events

The AHC provided a dendrogram in which at least three variable cluster appeared (blue, red and green in Fig. 3). One of the three clusters, marked in green, is very large and does not allow to infer specific differential association behaviours among variables.

In particular, with regards to the CV risk factors, hypertension, dyslipidaemia and diabetes are part of the same cluster and are separated from smoking as in SCM. At variance with SCM, in AHC angina, transient ischaemic attack, myocardial infarction and peripheral obliterative arteriopathy, are far away from extra-glandular involvement. Other important features are missed with AHC.

Discussion

By using a novel unsupervised ANN method, our study allowed us to depict the interplay between autoimmunity and CV comorbidity in pSS, analysing concomitantly the burden of traditional and immunological risk factors on CV events.

In details, we identified two different patterns of distributions in CV risk factors, pSS-related features, and CV events in a relatively large cohort of pSS patients. The first pattern was centered on "non-ischaemic CV events/generic condition of HF" whereas the second pattern was focused on "ischaemic events". The first one was characterised by the presence of traditional CV risk factors that appeared strictly interconnected one to each other and more

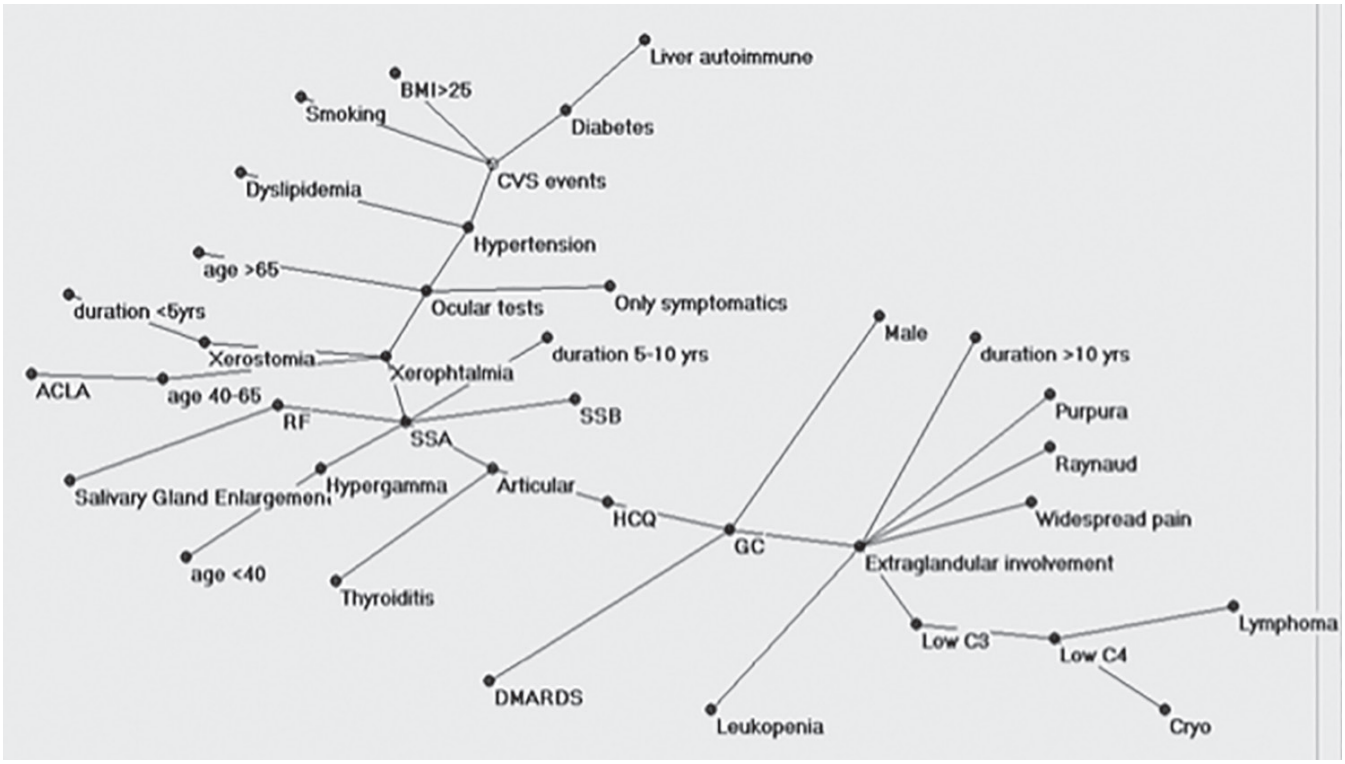

Fig. 1. "Semantic connectivity map" (SCM) performed by Auto-CM analysis reporting significant correlations between clinical and demographic manifestations of pSS, serological features, traditional CV risk factors and CV events analysed all together.
CVs: cardiovascular events; BMI: body mass index; ACLA: anti-cardiolipin antibodies; HCQ: hydroxychloroquine, GC: glucocorticoids; DMARDs: disease modifying anti-rheumatic drugs; RF: rheumatoid factor; SSA: anti-Ro/SSA; SSB: anti-La/SSB; Cryo: cryoglobulins.

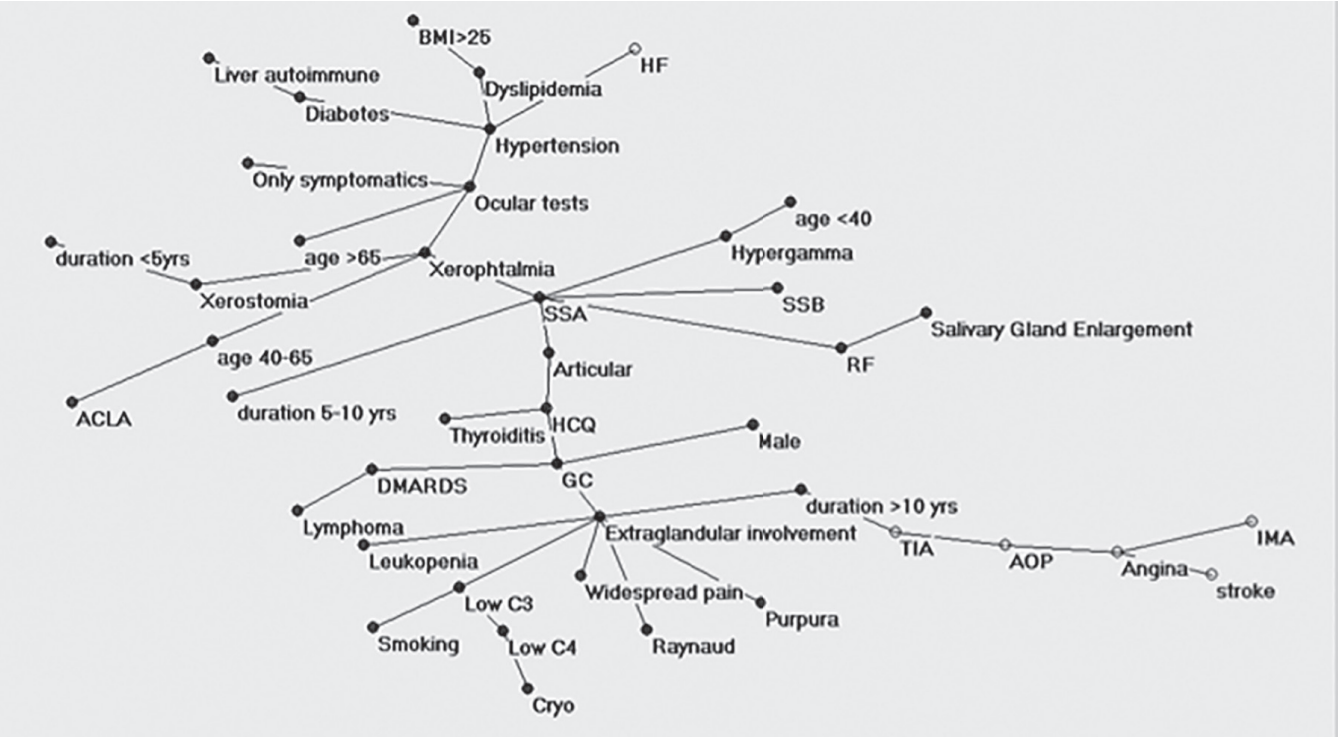

Fig. 2. "Semantic connectivity map" (SCM) performed by Auto-CM analysis reporting significant correlations between clinical and demographic manifestations of pSS, serological features, traditional CV risk factors and CV events analysed separately.
CVs: cardiovascular events; HF: heart failure; TIA: transient ischaemic attack; AOP: peripheral obliterative arteriopathy; IMA: myocardial infarction; BMI: body mass index; ACLA: anti-cardiolipin antibodies; HCQ: hydroxychloroquine, GC: glucocorticoids; DMARDs: disease modifying anti-rheumatic drugs; RF: rheumatoid factor; SSA: anti-Ro/SSA; SSB: anti-La/SSB; Cryo: cryoglobulins.

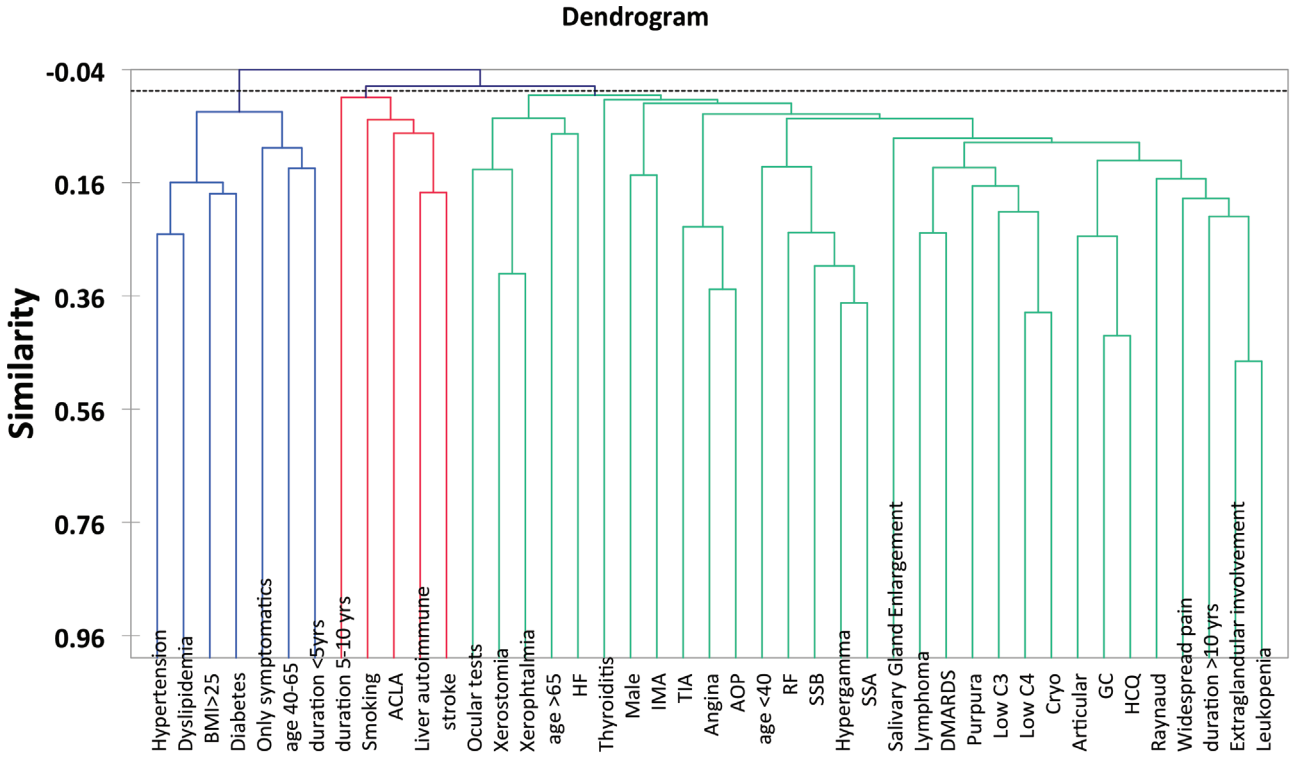

Fig. 3. Agglomerative hierarchical clustering (AHC). There are three clusters of variables marked in red, blue and green. In the ordinate axis the degree of similarity is gradually decreasing, going up. In the blue cluster, hypertension, dyslipidaemia, BMI>25 and diabetes form a sub-cluster; the same is true for ocular test positivity, xerostomia and xerophthalmia in the green large cluster. Male gender, TIA, angina, AMI and AOP are together in a sub-cluster of green area. At variance with the map obtained with Auto-CM depicted in Figure 2. these variables are far away from extra-glandular involvement. See text for further comments.

closely linked to pSS glandular features rather than to pSS extra-glandular manifestations. These findings apparently suggest a direct involvement of traditional CV risk factors in the occurrence of pSS-associated CV events, with hypertension clearly acting as central factor as observed in the general population. Hypertension directly linked to all other traditional CV risk factors except smoking and with the generic condition of HF. This may reinforce literature data that have described a higher prevalence of hypertension in pSS patients and the hypothesis that traditional CV risk factors represent a main comorbidity in pSS patients also in those patients with a more benign disease phenotype (8, 9, 21-23). Interestingly, from this perspective our analysis showed that traditional risk factors were apparently associated with pSS patients older age but not with extra-glandular disease activity, cumulative use of steroids or immunosuppressive drugs.

On the other hand, when CV events were analysed separately focusing on "ischaemic events" a second more distinctive pattern emerged. This latter pattern included neurological, ischaemic cardiac events and peripheral obliterative arteriopathy, appeared to be strictly associated with extra-glandular disease activity and longer disease duration. These findings implied that inflammation and proinflammatory cytokines greatly contribute to endothelial dysfunction and atherogenesis. In line with these results, we found that ischaemic events were strictly linked to "vasculitic" manifestations, including purpura and to Raynaud's phenomenon and these features were, not surprisingly, directly associated with leukocytopenia, low complement and cryoglobulins. In this setting, it may be speculated that chronic inflammation and immune-mediated mechanisms may induce vascular damage leading to manifested CV events in SS patients. These kinds of associations would have been lost with the use of a traditional statistical approach that produced a large cluster that did not allow us to infer specific differential association behaviours among variables.

Our results largely reflect the existing literature. First of all, the prevalence of CV events in our series was comparable to that described in other series reinforcing the concept that despite relatively uncommon CV comorbidity may represent an important issue in pSS (8, 14, 23). Second, our analysis confirmed that hypertension was the most frequent and most important player in the pathogenesis of CV events in pSS (21). Third we emphasised the role of immunological dysfunction in atherosclerosis-related ischaemic events, thus suggesting the importance of proper control of disease activity to prevent long-term chronic damage in these patients (21, 23, 24).

From this perspective, Cai *et al*. (25), have recently demonstrated that pSS patients with CV involvement were significantly older and have higher rates of hypertension, diabetes, hyperlipaemia and extra-glandular involvement in comparison to patients without CV morbidity (25). In the multivariate analysis, age, hypertension, and extra-glandular organ involvement were found to be risk factors independently correlated with CV events in these patients (25). Another aspect emerging from our analysis is the importance of disease duration. In a recent study by Mofors *et al*. (26), the presence of Ro/SSA and La/SSB autoantibodies identified the subgroup of patients carrying the highest risk and, among these autoantibody-positive patients, the highest risk of cerebral infarction was seen after ≥10 years disease duration. Similarly, in a cohort of pSS untreated women, anti-Ro/SSA and anti-La/SSB were independent predictor of subclinical atherosclerotic damage, as assessed by increased carotid-intima thickness and endothelial dysfunction (27, 28). These data suggest that pSS-specific antibodies may exert a direct pathogenic role in triggering precocious endothelial damage and consequent subclinical atherosclerosis. We did not find a direct association between autoantibodies and CV events; however, anti-Ro/SSA antibodies resulted a central hub connecting on one side, a benign phenotype which included lower disease duration, traditional CV risk factors and generic HF and on the other side, a more active disease subset comprising extra-glandular involvement, longer disease duration and CV manifested events. Moreover, ANNs allowed us to reinforce the link between immunological abnormalities and inflammation and CV ischaemic events, distinguishing them from the condition of no-ischaemic HF that was strictly linked to traditional risk factor, ultimately given a broad perspective for the distribution of CV comorbidity in pSS.

This paper is not free from criticisms, especially considering the retrospective nature of the study design and the low number of CV events recorded. However, despite the fact that the number of events was low, the ANNs innovative approach allowed us to differentiate different pattern in pSS-related CV comorbidity, ultimately shading new lights on the role of autoimmunity, inflammation and traditional risk factors in accelerated atherosclerosis that could be transferred also to other rheumatic diseases. Our results are preliminary and further validation studies in larger cohorts are needed. However, from a practical point of view, ANNs appeared as a valuable tool to improve the stratification of CV risk in pSS with promising future application in health policies and in the planning of specific interventions to prevent long-term CV complications.

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