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Conditions and Factors Associated with Spontaneous Coronary Artery Dissection (From a National Population-Based Cohort Study)

Running Title: Conditions and Factors Associated with SCAD

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ABSTRACT

The pathophysiology of spontaneous coronary artery dissection (SCAD) is heterogeneous, associated with systemic arteriopathies and inflammatory diseases, and often compounded by environmental precipitants, genetics, or stressors. However, the frequency of these associated conditions with SCAD on a population level remains unknown. Therefore, the objective of this analysis was to evaluate heterogeneous phenotypes of SCAD in the United States using data from the Nationwide Inpatient Sample (NIS) from January 1, 2004, to September 31, 2015. Among 66,360 patients diagnosed with SCAD, the mean age was 63.1 ± 13.2 years and 44.2% were women. A total of 3,415 (5.14%) had depression, 670 (1.0%) had rheumatoid arthritis, 640 (0.96%) had anxiety, 545 (0.82%) had a migraine disorder, 440 (0.66%) had steroid use, 385 (0.58%) had malignant hypertension, 280 (0.42%) had systemic lupus erythematosus, 250 (0.38%) had cocaine abuse, 215 (0.32%) had hypertensive heart or renal disease, 130 (0.19%) had coronary spasm, 105 (0.16%) had fibromuscular dysplasia, 85 (0.13%) had Crohn's disease, 75 (0.11%) had celiac disease, 60 (0.09%) had adult autosomal dominant polycystic kidney disease, 60 (0.09%) had hormone replacement therapy, 55 (0.08%) had sarcoidosis, 55 (0.08%) had amphetamine abuse, 15 (0.02%) had granulomatosis polyangiitis, 10 (0.02%) had α1-antitrypsin deficiency, 10 (0.02%) had Marfan syndrome, 10 (0.02%) had Ehlers-Danlos syndrome, 10 (0.02%) had Kawasaki disease, 10 (0.02%) had polyarteritis nodosa, 5 (0.01%) had multiparity. In conclusion, most cases of SCAD had no apparent concomitant arteriopathy, inflammatory disorder, or evident risk factor.

Keywords: Spontaneous coronary artery dissection; Pathophysiology**;** Nationwide Inpatient Sample

Introduction

Spontaneous coronary artery dissection (SCAD), a heterogeneous clinical syndrome, associated with systemic arteriopathies and inflammatory diseases and illicit drug use, is frequently seen in males and females presenting with acute coronary syndrome (ACS).[1] Despite advances in diagnosis using angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT), the pathogenesis of SCAD remains unknown. Interestingly, SCAD patients tend not to have typical risk factors for ACS such as diabetes mellitus, smoking, dyslipidemia, or obesity. In fact, the pathophysiology of SCAD appears heterogeneous, including possible inherited or acquired arteriopathies, prothrombotic states, genetic predisposing factors, hormonal influences, or systemic inflammatory diseases.[2, 3] SCAD has also been described in relation with Crohn's disease,[4] systemic lupus erythematosus (SLE),[5, 6] Marfan syndrome[7], Ehler-Danlos,[8] fibromuscular dysplasia (FMD),[9] cocaine abuse,[10] amphetamine abuse,[11] steroid use,[12-14] and migraine.[15] In addition, SCAD has been frequently described with coexisting depression or anxiety.[16, 17] An analysis of large database such as NIS could potentially shed light on the diagnosis and treatment of heterogeneous clinical syndromes such as SCAD. We hypothesized that using a large population database may identify phenotypes of SCAD and could potentially classify and guide prognosis and treatment.

Methods

We performed the analysis using the National Inpatient Sample (NIS) database, a part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). It aggregates yearly data from over 8 million hospital stays involving over 1,000 hospitals and provides nationwide information on hospital utilization,

charges, and quality of care (http://www.hcup-us.ahrq.gov/db/nation/nis/nisrelatedreports.jsp). Data were extracted from the NIS using ICD-9 codes from January 1, 2004, to September 31, 2015. SCAD diagnosis using ICD-9 codes from the NIS has been previously described.[1] Conditions and factors associated with SCAD including rheumatoid arthritis (RA), migraine disorder, SLE, FMD, adult autosomal dominant polycystic kidney disease (ADPKD), celiac disease, sarcoidosis, granulomatosis polyangiitis (GPA or Wegener's granulomatosis), α1-antitrypsin deficiency, Marfan syndrome, Ehlers-Danlos syndrome, Kawasaki disease, malignant hypertension, cocaine abuse, amphetamine abuse, steroid use, depression, anxiety, and multiparity were evaluated using their specific ICD-9-CM codes. (online supplementary table 1) We used the methodological standards that complied with the AHRQ's recommendations (online supplementary table 2).[18] We conducted descriptive analysis by using R 3.4.0 and Stata version 14.2. Percentages and means ± standard deviations were computed for categorical and continuous variables, respectively. Categorical variables were compared using the Chi-square test or Fisher's exact tests, when appropriate. All p-values were two-sided, and statistical significance was determined at the level of $p<0.05$.

Results

A total of 66,360 of patients were diagnosed with SCAD. The mean age was 63.1 ± 13.2 years and 44.2% were women. SCAD and its associated conditions are presented in Figure 1. SCAD was associated with less than 1% each of coronary spasm, cocaine abuse, amphetamine abuse, migraine, rheumatoid arthritis (RA), Ehlers-Danlos syndrome, Marfan syndrome, α1-antitrypsin deficiency, adult polycystic kidney disease (ADPKD), polyarteritis nodosa (PAN),

Kawasaki disease, celiac disease, GPA), steroid use, and sarcoidosis. Table 1 demonstrated associated conditions by comparing between SCAD and non SCAD ACS patients.

Discussion

To the best of our knowledge, this is the first study about conditions related to SCAD using a national database. There were 2 main findings. First, consistent with previously published case reports, we demonstrated that SCAD was associated with a variety of heterogeneous conditions, many of which are not associated with traditional ACS.[4, 5, 10, 12] Second, our study highlighted the use of a large database potentially to characterize an uncommon disease such as SCAD.

Although SCAD is mainly thought to be associated with non-atherosclerotic dissection, the underlying etiology seems to be multifactorial. Two potential mechanisms for SCAD have been proposed: (1) intimal tear leading to separation of the arterial wall; and (2) spontaneous rupture from increased density of the vasa vasorum, leading to medial hemorrhage.[19] Identifying phenotypes of SCAD is crucial because it can lead to better prognostication and appropriate management. For example, while statins have been shown to reduce cardiovascular mortality in ACS,[20] some studies have suggested that they can increase risk for recurrent SCAD.[21] The use of heparin and dual antiplatelet therapy in SCAD remains controversial.[22] Although beta-blockers are recommended in SCAD patients, the role of beta-blockers in SCAD related to cocaine abuse and the role of ACE-inhibitors in SCAD have largely remained unexplored.[23, 24] Most studies of SCAD are case reports and studies from single centers that cannot be generalized. The incidence of SCAD and its associated conditions using a large population

database could potentially yield the mechanisms of heterogeneity and allow for future study of more appropriate therapy.

Although, in some case reports and small studies, SCAD has been previously reported with several conditions such as psychological stress, autoimmune and inflammatory conditions,[2, 25] or cocaine and amphetamine use, our results did not show those associated conditions were higher in SCAD than non-SCAD ACS patients. However, our results are consistent with previous reports that SCAD is associated with genetic arteriopathies, FMD, both anabolic steroid and corticosteroid use, migraines, and some autoimmune and inflammatory conditions (Table 1).

We classified potential associations with SCAD into the following. First, SCAD could be associated with genetic arteriopathies such as Marfan and Ehlers-Danlos syndromes. Although these connective tissue conditions are uncommon (1% to 2%),[2, 25] SCAD has been associated with a number of these syndromes, and predisposing connective tissue disorders could potentially be a factor related to SCAD. However, studies of genetic testing in SCAD are rare.

The first genetic study of SCAD by Goel et al.[26] found that family history of SCAD was relatively uncommon in SCAD patients (1.2%) while a study by Kaadan et al.[27] reported that among 44 patients from a prospective SCAD registry, 6 patients had a pathogenic variant and 3 patients had a deleterious variant in COL3A1, the gene believed to cause vascular Ehlers–Danlos syndrome. Additionally, studies have shown minor morphological alterations of the connective tissue structure from skin biopsies despite no clinical signs of a known connective tissue disorder in patients with cervical artery dissection.[28, 29] Further characterization of SCAD using genetic markers (i.e., SCAD- COL3A1 or SCAD-SNP related to connective tissue) is needed. In addition, previous studies and case reports demonstrated that SCAD is associated with FMD.[2,19]

Interestingly, our study showed that 0.16% of SCAD cases had FMD.[2, 21] Potentially, genetic screening in FMD patients or FMD screening in SCAD patients may help in risk stratification.

Second, both SCAD and non-SCAD ACS could be associated with psychological stress. A few case reports have demonstrated the association between SCAD and emotional stress.[30-33] A previous study demonstrated high rates of depression and anxiety after SCAD.[16] Previous studies found 12.5% to 48.3% of patients reported extreme emotion prior to or after SCAD.[23, 34] The mechanism between emotional stress and SCAD is unclear. Many case reports have suggested that SCAD can be present with Takotsubo cardiomyopathy.[35, 36] Indeed, both SCAD and non-SCAD ACS might share some of the same mechanisms as Takotsubo cardiomyopathy. For example, increased sympathetic stimulation leading to elevated catecholamines could potentially cause an intimal tear or rupture of the vasa vasorum.[37]

Third, both anabolic steroid and corticosteroid use could be related to one of the SCAD phenotypes. Steroid use could result in weakness of the arterial wall, increased atheroma in the coronary wall, and arterial reactivity.[38-40] Steroids are atherogenic, and atherosclerotic plaques may be ruptured by severe hypertension during weight lifting. There are case reports about SCAD and anabolic steroid use and corticosteroid steroid use.[12, 13] One proposed explanation is steroid-induced vasospasm, perhaps superimposed on a pro-atherogenic state.[41]

Fourth, SCAD may be associated with autoimmune and inflammatory conditions due to the cellular immune response. One of the proposed mechanisms of SCAD is eosinophilic infiltration of the vessel followed by the release of lytic enzymes, causing dissection.[42]

There are limitations to this study. First, we could not find codes for specific connective tissue diseases such as Loeys-Dietz syndrome. Second, despite a national cohort, SCAD and its

associated conditions are relatively infrequent and lack statistical power to estimate mortality. Third, the NIS database did not provide discharge medications or some known risk factors for SCAD (e.g., extreme physical activity) which may be important predictors of mortality among SCAD patients.

In conclusion, most cases of SCAD had no apparent concomitant arteriopathy, inflammatory disorder, or evident risk factor.

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FIGURE LEGEND

Figure 1: The prevalence in conditions and factors associated with SCAD.

Abbreviations: PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; ADPKD, adult autosomal dominant polycystic kidney disease; GPA, granulomatosis polyangiitis; FMD, fibromuscular dysplasia

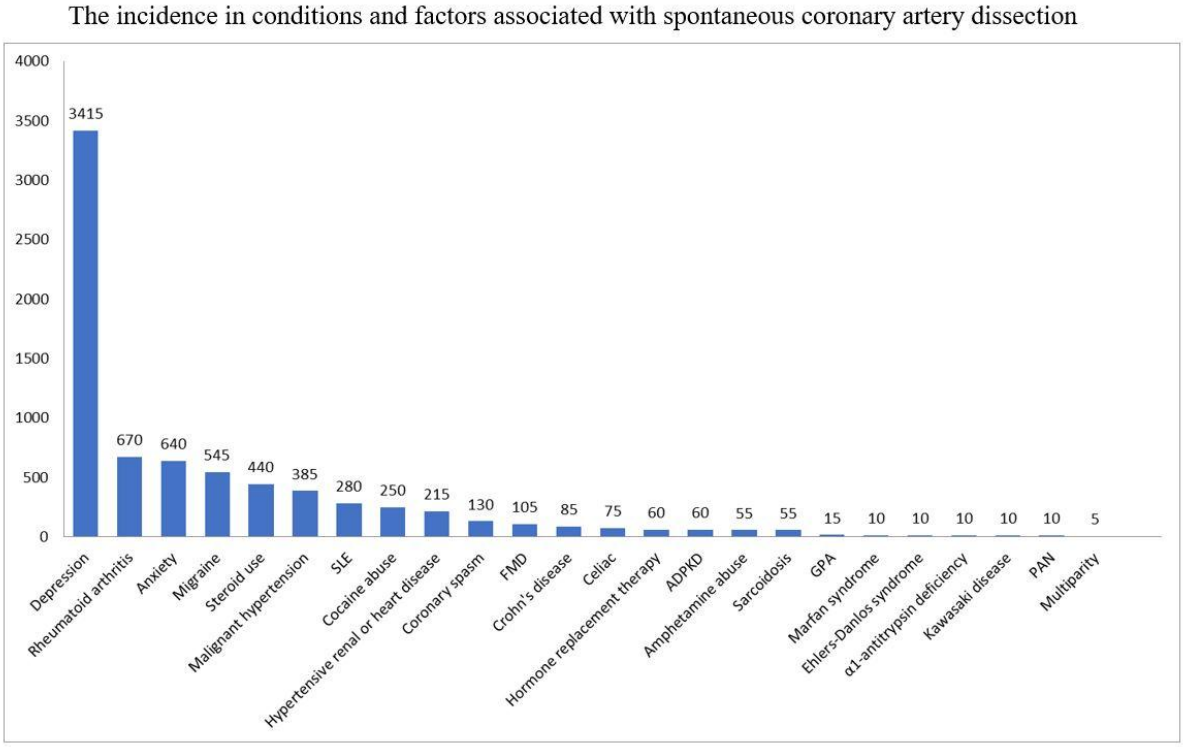

Table 1: A comparison between SCAD and Non-SCAD ACS patients and associated conditions

	SCAD (%)	**Non-SCAD ACS (%)**	**p-values**
Cocaine abuse	0.377	0.748	<0.001
Amphetamine abuse	0.083	0.173	<0.001
Migraine	0.821	0.487	<0.001
Crohn's disease	0.128	0.157	<0.001
Rheumatoid arthritis	1.010	1.209	<0.001
Systemic lupus erythematosus	0.422	0.378	<0.001
α1-antitrypsin deficiency	0.015	0.007	<0.001
Polycystic kidney disease	0.090	0.067	<0.001
Ehlers-Danlos syndrome	0.015	0.004	<0.001
Marfan syndrome	0.015	0.006	<0.001
Coronary spasm	0.196	0.091	<0.001
Hormone replacement therapy	0.090	0.032	<0.001
Steroid use	0.663	0.641	<0.001
Celiac disease	0.113	0.051	<0.001
Kawasaki disease	0.015	0.004	<0.001
Granulomatosis with polyangiitis	0.023	0.029	<0.001
Sarcoidosis	0.083	0.154	<0.001
Polyarteritis nodosa	0.015	0.009	<0.001
Depression	5.146	5.475	<0.001
Anxiety	0.964	1.269	<0.001
Multiparity	0.008	0.0001	0.663
Malignant hypertensive heart/kidney disease	0.324	0.522	<0.001
Malignant hypertension	0.580	0.692	<0.001
Fibromuscular dysplasia	0.163	0.006	<0.001