Immunological mechanisms in multiple spontaneous cervical artery dissection: An illustrative case and review of the literature

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ABSTRACT

Dissection of the cervical arteries is the leading cause of stroke in young adults, yet the aetiology and pathogenesis of this event remain unclear. However, a growing number of data in the literature support the potential implications of immunological mechanisms in the pathogenesis. Several large patient groups and multicentre cohorts have reported significant associations with recent infections and elevated inflammatory markers. There are also several case reports and case series suggesting an association with various autoimmune disorders and viral infections. Some case reports have also detailed cervical artery dissections linked to the use of biological therapies for other pathologies. In the present case, a 38-year-old female patient with triple spontaneous cervical artery dissection presented multiple potential trigger factors as recent infection, autoimmune thyroid disease, primary thrombophilia and hyperhomocysteinemia. This report sought first presents this case, and then reviews the existing relevant literature data regarding the potential immunological mechanisms implicated in the pathogenesis of cervical artery dissection.

Keywords: multiple spontaneous cervical artery dissection, immunological mechanisms, autoimmune thyroid disease

INTRODUCTION

Spontaneous dissection of the cervical arteries (SCAD) is an important cause of stroke in young adults, although it can occur at any age and is frequently neglected in elderly stroke patients. The pathological hallmark of SCAD is the separation of the arterial wall layers and the formation of mural haematoma. Haemorrhage may come from an intimal tear or rupture in the vasa vasorum. SCAD most frequently affects the internal carotid arteries distal to the bifurcation but can also impact the vertebral arteries. Due to the large availability of modern imagistic methods, cases of SCAD are becoming increasingly recognised (1).

The two main entities under the umbrella of SCAD are traumatic and spontaneous dissections, respectively. The delineation between these conditions is frequently challenging because many affected patients report minor trauma in their recent history. CAD is responsible for just 1% to 2% of all instances of ischaemic stroke but, in young adults, actually accounts for 10% to 25% of cases (1).

In the most cases, the dissection affects a single artery; thus, multiple cervical artery dissections constitute a rare entity with triple and quadruple dissections found in only 2% to 4% and double dissections found in 13% to 23% of all CAD cases, respectively (2,3).
The pathogenesis of CAD is poorly understood but is thought to be linked to an underlying, genetically determined or acquired arteriopathy and an external, environmental trigger such as minor trauma or infection (4).

Minor traumas can be represented by coughing, physical activity, sudden neck movements (e.g., chiropractic manipulation) and whiplash injury. However, these minor traumas are very frequent in the population and only a minority of cases progress to CAD; therefore, it is expected that other predisposing factors must also be at play. Several authors have covered the topic of the association between CAD and a history of recent infection (5). The basis of this association is believed to be the immunological response of the host, marked by cytokine release and imbalance in the protease activity, leading to extracellular matrix degeneration and subsequent weakening of the artery vessel wall (6).

The potential role of environmental factors and, mainly, that of infections is strengthened by the observed seasonal pattern of CAD (7).

Several isolated case reports and case series have described associations between different autoimmune disorders and immunological disturbances in a manner that underlines the potential role of immunological mechanisms in the pathogenesis of CAD (8-15).

This article sought to first present a unique case of multiple cervical artery dissection in a young patient with recent infection and autoimmune thyroid disease, then review relevant literature data and discuss the potential role of the immunological mechanism in the development of CAD.

For the narrative review of the literature we performed database search with the following keywords: “multiple cervical artery dissection”, “immunological mechanisms”. The majority of the relevant articles were found in PubMed. In addition, we also performed screening of CINAHL, Cochrane Library and Embase databases. Only the articles with available full text were included in the analysis. Searches were limited to articles written in English.

CASE PRESENTATION

A 38-year-old female patient presented in October 2018 after experiencing an upper respiratory tract infection in the last two weeks characterised by severe cough, bilateral cervical pain, transient visual symptoms (e.g., scintillations, flashing lights) and a short episode of right-sided hemiparesis. Her medical history included a spontaneous abortion performed four years before, where she was diagnosed with primary hypercoagulability (factor V H1299R heterozygous mutation, MTHFR A1298C heterozygous mutation, factor XIII V34 L heterozygous mutation, PAI-1 4G/5G homozygous mutation) and autoimmune thyroiditis with a euthyroid state. The neurological examination at the time of the current admission was unremarkable.

A duplex ultrasound examination of the cervical arteries revealed bilateral significant irregular internal carotid artery (ICA) stenosis secondary to multiple mural haematomas and the presence of mural haematoma at the V2 segment of the left vertebral artery (VA), without significant stenosis. The

FIGURE 1 a,b. Duplex mode ultrasound examination of the right ICA, revealing the hypoechoic mural hematoma (yellow lines) leading to significant irregular stenosis; c. 3D radial TOF MRI images (rotated) revealing the irregular, tapering stenosis of the right ICA (black arrows), suggestive for dissection
cervical and cerebral magnetic resonance imaging (MRI) examinations confirmed the multiple dissections in both ICAs and the left VA (Figure 1, Figure 2, Figure 3, Figure 4). Cerebral ischaemic lesions were absent.

The laboratory examinations revealed normal values for the patient’s complete blood count and biochemistry results, lipid panel, C-reactive protein (CRP) level, fibrinogen and erythrocyte sedimentation rate. Additionally, her antithyroid peroxidase antibody level was elevated to 986 UI/ml (normal values < 35 UI/ml), her homocysteine level was elevated to 17.64 μmol/l (normal range: 3.7-13.9 μmol/l) and her α1-antitrypsin concentration was normal.

The computed tomography angiography scan of the aorta and renal arteries was normal.

Anticoagulation therapy with enoxaparine was initiated, significantly decreasing the level of cervical pain. Moreover, no transient neurological symptoms were observed following the initiation of anti-
coagulation. The patient was discharged on antiplatelet therapy with aspirin.

Follow-up duplex examinations revealed the progressive regression of the intramural haematoma. During periodic follow-up visits conducted over two years, no signs of dissection recurrence have been noted.

**DISCUSSION**

A possible relationship between recent infection and the risk of cervical artery dissection has been investigated by several research teams to date. Grau et al. analyzed the prevalence of infection in the week before symptomatology onset in a cohort of 43 consecutive cases of CAD and 58 controls with ischaemic stroke of aetiology. Infections were more frequent among the patients with CAD than in the control group (58.1% vs.32.8%). During a multivariate analysis, infection remained statistically significantly associated with CAD. Mechanical factors suggesting infection such as cough, sneezing and vomiting were not associated independently with CAD (16).

In a similar study performed in 2003 by Guillon et al., 47 patients with SCAD and 52 patients ischemic stroke of another aetiology were included (5). Acute infection in the month before the vascular event was more frequently observed in the SCAD group (31.9% vs.13.5% in controls, crude odds ratio: 3.0; P = 0.032; 95% confidence interval: 1.1-8.2). The association remained significant in a logistic model adjusted for age, sex, educational level and migraine and was stronger in patients with multiple vessel dissections. These authors concluded that a recent infectious event is a risk factor for SCAD and could be also a trigger (5).

The role of environmental factors is highlighted by different studies focusing on the seasonal pattern of CAD. Schievink et al. analyzed epidemiological data from 200 consecutive cases of CAD and observed a significant seasonal variation, with 58% more patients experiencing SCAD during autumn than in other seasons (17). In particular, the peak frequency of SCAD was found in October. Possible explanations for this seasonal pattern include weather-related factors and the involvement of infections that peak during autumn (17).

Thomas et al. analyzed data from different geographical regions (i.e., the United Kingdom and Australia) related to seasonal variation in SCAD and
determined that CAD occurs more commonly in cooler months in both geographical areas. The incidence of CAD was not influenced by blood pressure or pulse pressure values. Data relating to infections in the preceding period were not available (18). This study also did not provide a response to the controversy concerning whether infection, blood pressure variations or temperature is the main determining factor for the seasonality of SCAD.

The pathophysiological mechanisms that link recent infections to an increased risk of CAD remain incompletely elucidated. One of the possible mechanisms could be the infection-induced dysregulation of protease activity involved in extracellular matrix degradation. The most frequently studied proteases are members of the matrix metalloproteinase (MMP) family, mainly the gelatinases MMP2 and MMP9. Tissue inhibitors of MMPs (TIMPs) have inhibitory effects on the proteolytic activity of MMPs. An imbalance between TIMPs and the activity of MMPs may contribute to extracellular matrix destruction and vascular wall damage (19). Separately, Guillon et al. analyzed in 2007 serum MMP9, MMP2 and elastase levels in 47 patients with SCAD and found that patients with SCAD presented with higher plasma levels of proteases, particularly MMP2. Moreover, the plasma levels were even higher in patients with multiple dissections (20).

Other pathological conditions that also imply an accentuated degradation of the extracellular matrix have been correlated with SCAD in different publications. A deficiency of α1-antitrypsin, which is an elastase inhibitor, is considered to be a predisposing condition to CAD. Among 12 patients reported by Pezzini et al., three had low serum concentrations of α1-antitrypsin (21). Similar results were also released by Vila et al. (22).

There are literature data that prove that autoimmune thyroid disease is not only an organ-specific disease but also one marked by systemic immune dysregulation (23). Pezzini et al. demonstrated in 2006 that antithyroid autoimmunity existed in nine of 29 (31%) consecutive patients with sCAD for a rate that was significantly higher than that in the control group (6.9%) consisting of non-CAD stroke cases (9). These authors concluded that an immune-mediated process may be involved in the pathogenesis of CAD (9).

Other possible proof of the involvement of immune mechanisms in the pathogenesis of CAD includes the elevated CRP level apparent in this patient group. Genius et al. analyzed the CRP serum level in the postacute phase of stroke in 21 patients with CAD, 21 with large-artery atherosclerosis and 20 with cryptogenic stroke. CRP serum levels higher than a cutoff value of 0.71 mg/l were independently associated with a history of CAD (P = 0.005) but not with that of large-artery atherosclerosis following adjustment for different risk factors. These authors concluded that inflammatory mechanisms may be involved in the pathogenesis of CAD (24).

Several cases of multiple SCAD were reported to have occurred in patients with multiple sclerosis after alemtuzumab infusion. Alemtuzumab is a humanized monoclonal antibody against CD52, an antigen found on the surface of lymphocytes that has a rapid cytolytic effect on T lymphocytes after the infusion, leading to significant cytokine release in a manner that may drive frequent infusion-related reactions. The patient reported by Durand-Dubief et al. was tested for underlying connective tissue disorders and gene mutations, with all findings being negative, suggesting that there was a potential causal relationship between the individual’s drug-induced immune response and the onset of multiple SCAD (25).

Grond-Ginsbach et al. analyzed the peripheral leukocyte count (white blood cell count; WBC) in a large group of patients (N = 172) with acute SCAD from the Cervical Artery Dissection and Ischemic Stroke Patients study (26). Further, this study also included 348 patients with non-CAD ischaemic stroke and 223 age- and sex-matched healthy controls. WBC counts were higher in both stroke groups as compared with among controls, with that in the CAD group being even higher than that in the non-CAD stroke group. Following adjustment for several potential confounders in a multiple regression model, an elevated WBC count remained significantly correlated with CAD. The authors concluded that an increased WBC count may reflect the existence of an underlying inflammatory state. This observation strengthens the purported link between CAD and inflammation (26).

Studies with imaging evidence of inflammation in the arterial wall in SCAD have also been published. Naggar et al. examined 29 consecutive patients with CAD, 18 with SCAD and 11 with traumatic CAD using high-resolution MRI, searching for periarterial oedema, which is suggestive of localised vessel wall inflammation. Ultimately, SCAD was significantly associated with periarterial oedema (odds ratio: 13.3, P = 0.005), which supports a correlation between underlying inflammation and SCAD (27). Meanwhile, Pfefferkorn et al. prospectively analyzed 37 cases with SCAD, searching for vessel wall inflammation with the aid of positron-emission tomography and high-resolution contrast-enhanced MRI. In this study, a subset of SCAD patients presented signs of inflammatory arteriopathy and multiple SCAD was significantly associated with vessel wall enhancement in high-resolution MRI (28).

The role of hyperhomocysteinemia and methyltetrahydrofolate reductase (MTHFR) polymor-
phism in cervical artery dissections has been broadly discussed in the literature. The possible mechanism for this association may be the affection of elastic properties of the vessel wall. Hyperhomocysteinemia provokes oxidative stress, the accumulation of collagen in the adventitia, migration of smooth muscle cells and the formation of neointima (29-32). Luo et al. Previously published a meta-analysis concerning hyperhomocysteinemia and MTHFR mutation, including data from a total of 2,146 patients and suggested that hyperhomocysteinemia and MTHFR C677T polymorphism were significantly associated with CAD (29). Only isolated case reports currently exist in the literature regarding the possible association of MTHFR A1298C polymorphism with the risk of CAD (33). Of note, this mutation reduces MTHFR enzyme activity to a lesser extent than as seen with MTHFR C677T polymorphism (34).

In addition to inflammation, Pelz et al. also raised the issue of coagulation disturbances in patients with CAD (35). These authors monitored the WBC, CRP level, fibrinogen level, D-dimer level, activated partial thromboplastin time (aPTT) and prothrombin time in 60 consecutive patients with SCAD and compared their findings with those from a control group. Following multiple regression analysis, only the shortened aPTT time remained statistically significant. These authors concluded that inflammation-induced coagulation disorder is implicated in the pathogenesis of CAD (35).

Only isolated case reports to date have mentioned primary thrombophilia disorders in patients with SCAD. Orlandi et al. presented a case of a 50-year-old female patient with unilateral internal carotid artery dissection without any evident predisposing factor other than a heterozygous factor V Leiden mutation with secondary activated protein C resistance (36). Cardon et al. published a case of a 38-year-old female with bilateral spontaneous dissection of the internal carotid arteries without any other risk factors except smoking and mild hypercholesterolemia. Laboratory analysis revealed a heterozygotic factor V Leiden mutation (37). There is no clear pathophysiological explanation known at this time for this observation.

Infection with severe acute respiratory syndrome coronavirus 2, the virus responsible for the 2020 coronavirus disease pandemic, is known to trigger a strong inflammatory response and the phenomenon known as ‘cytokine storm’, which is responsible for several cardiovascular complications. Morassi et al. published a case of bilateral carotid artery dissection in a 58-year-old male patient without any relevant predisposing factors other than severe viral infection with this pathogen, stressing the need for awareness in this regard (38).

Multiple cervical artery dissections seem to present some distinct characteristics as compared with cases of single-vessel dissections. Béjot et al. analyzed a large patient group from the Cervical Artery Dissection and Ischemic Stroke Patients study, reporting that, among 983 patients with SCAD, 149 (15.2%) presented with multiple dissections (39). Multiple SCADs were observed more frequently in the medical history when the patient had experienced a recent infection, cervical manipulation or cervical pain at admission. Fibromuscular dysplasia and the presence of pseudoaneurysm were also more frequent findings in patients with multiple CAD (39). Arnold et al. analyzed the clinical characteristics of triple and quadruple SCADs among a total of 740 consecutive patients; in total, 11 patients (1.5%) showed three dissections and one patient (0.1%) showed four dissections, respectively. Multiple SCADs were observed more frequently in women, although none of them presented with fibromuscular dysplasia or another underlying arteriopathy and the majority of cases were actually preceded by infection or minor trauma. All cases experienced good outcomes and a benign long-term prognosis. These authors concluded that a transient vasculopathy may be the main mechanism of multiple SCADs (40).

**CONCLUSIONS**

The pathogenesis of SCAD is complex and not completely elucidated. Damage to the arterial wall through immunological mechanisms triggered by infections and autoimmune processes is plausible and is supported by several publications to date. The presence of an underlying genetically determined, monogenic connective tissue disease is rare. The association between multiple cervical artery dissections and underlying infectious and autoimmune triggers is even stronger than in the context of single-vessel dissections and the outcome is favourable in the majority of cases. From these observations, we can deduce that the onset of multiple SCADs is probably a result of an acquired, transient arteriopathy with a benign outcome. Not enough data are currently available in the literature to draw therapeutic conclusions regarding potential immunological treatment strategies in certain cases of dissection. Due to the low incidence of this condition, the feasibility of conducting randomised trials is poor. Known treatment strategies are based only on empirical data. Making an early diagnosis and offering appropriate, individualised treatment have great importance in ensuring a good outcome.
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