



# Herpes Simplex Virus (HSV) Infection in the Acute Presentation of Fibromuscular Dysplasia (FMD)

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## ABSTRACT:

Fibromuscular dysplasia (FMD) is typically monophasic, and a non-atherosclerotic, non-inflammatory arterial disease that affects primarily medium-sized cerebral and systemic vessels in women of childbearing age resulting in dissection, arterial stenosis, occlusion, and aneurysm. FMD is diagnosed by its clinical presentation, and its radiographic findings, which can be mimicked in other disease states. The etiology of FMD is unknown and has been attributed to genetic, hormonal and viral factors. Likely viral causes of FMD include the alphaherpesvirus Herpes Simplex Virus (HSV) which is latent in >90% of the population. Also, (1) similar vascular abnormalities seen in FMD are also seen in alphaherpesvirus infected arteries; (2) virus can infects arteries in skip areas paralleling the skip areas seen in some cases of FMD, and (3) hormonal changes in women of childbearing age can contribute to virus reactivation.

Herein, we describe five patients with a recent diagnosis of FMD and concurrent infection with Herpes Simplex Virus, supported by the presence of herpes labialis in all and the presence of anti-HSV antibodies.

32, F	FMD, Dissection x 3	HSV IgM +
32, F	FMD, Dissection x 2,	HSV IgM +
43, F	FMD, Dissection, Aneurysm	HSV IgG + 2 year later
22, F	FMD, Dissection	HSV IgM +
40, F	FMD, Incidental	Not done

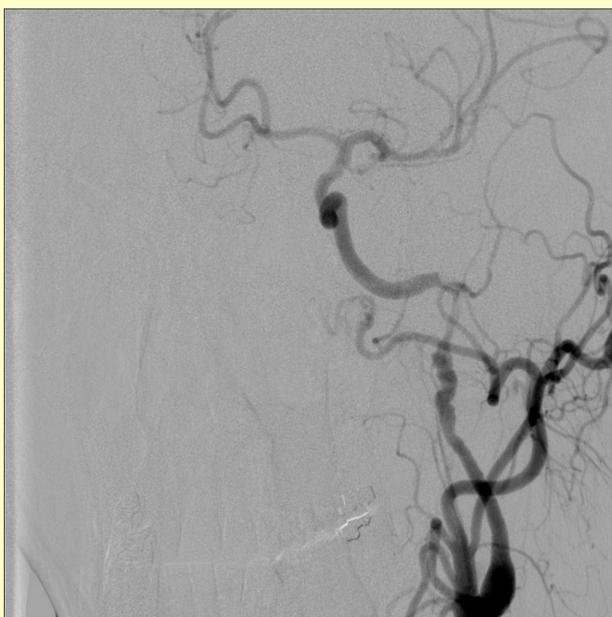
Assessing for concurrent alphaherpesvirus infection during the time of FMD presentation may lead to a better understanding of the direct or indirect role of virus infection in the development of FMD and may lead to potential antiviral therapy.

## Introduction:

•Recent evidence demonstrating Varicella-Zoster Virus is the likely etiology of Giant Cell arteritis has encouraged researchers to look for viral causes of unusual vascular syndromes. VZV has been indentified in many vascular syndromes when tissue is available for direct testing, including Primary Angiitis of the CNS (PACNS)..

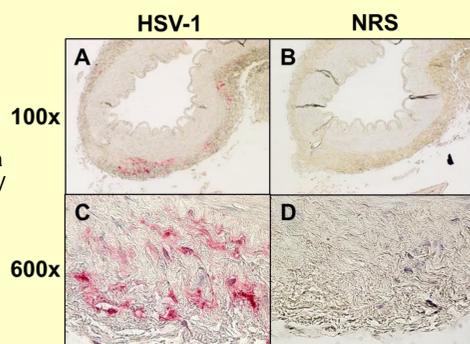
•Herpes Simplex Virus, like VZV an Alpha Herpes Virus Group agent, is a latent virus, similar to VZV, with early life infection as children in the vast majority of the population and then characteristic reactivation throughout life.

•Fibromuscular Dysplasia is a non-atherosclerotic, non-inflammatory disorder of unknown etiology. Genetic, Hormonal, and Viral causes have been proposed, but little to no progress has been made in identifying an cause, or set of causes, since the syndrome was first described in 1938. it is unusual to use arterial biopsy or resection in the clinical care of FMD patients.



FMD of the Internal Carotid Artery. Note the typical location of mid-artery, away from the bifurcation and intracranial portions. The typical "string of Beads" is seen here with a section of tubular stenosis.

Laboratory Model of HSV-1 in artery: Cerebral arteries can be infected by herpes simplex virus type 1 (HSV-1). Cadaveric human cerebral arteries were obtained <24 hrs postmortem and cultured *ex vivo*, then infected with HSV-1. At 2 weeks post-infection, arteries were formalin-fixed and paraffin-embedded then sectioned. Immunohistochemical analysis with a rabbit anti-HSV-1 specific antibody revealed HSV antigen predominantly in adventitia of the cerebral artery (pink color; A, C). No immunostaining was seen when normal rabbit serum was used as primary antibody on the artery.



## DISCUSSION:

A viral hypothesis in FMD must include the following features: an overall benign course with little or no progression in most, a predilection for women in their childbearing years, variable and multiple skip lesions predominantly in the mid-cervical arteries but with occasional lesions elsewhere. This includes branches of the aorta as well as SCAD (Spontaneous Coronary Artery Dissection). Genetic studies have failed to find an explanation for the occasional familial case. Hormonal changes, similarly fail to explain the male/female ratio FMD. Further, if a genetic or hormonal driver is root cause of FMD, why does this not become a typically progressive or recurrent disorder?

Traditional Vasculitis, presumed Rheumatological for many years, have increasingly been found to be caused by Virus. Varicella-Zoster Virus, like HSV-1 in the Alpha Herpes Virus group, has become well established as a model for this. The reactivation of VZV generating the typical single event of Giant Cell Arteritis, Bell's Palsy or Shingles represents and excellent hypothetical model for latent HSV-1 and FMD. Epstein-Barr Virus has similarly been suspected in Moya-Moya disease, which for the adult has similar epidemiological patterns to FMD.

Infection with HSV-1 was recently shown to be an independent stroke risk factor in the UK. Before this, many reports linking infection with stroke have appeared. This includes a 1999 report of Cervical Artery Dissection associated with recent infection. Specific mechanisms for this increased risk have been postulated, but like FMD, not well substantiated.

The small group of patients presented here with clear historical activity of virus and serological support for HSV-1, this appears to be an ideal virus from a clinical, epidemiological, and immunological point of view. A latent virus can explain the arterial pattern, occasional familial case, and clearly acquired, not inherited nature of FMD. Like VZV reactivating for shingles or Bell's Palsy, generally a single outbreak is typical. Hormonally, during the progesterone part of women's cycle, the Natural Killer Cell immunity that keeps HSV-1 in check is suppressed, providing an elegant explanation for the gender asymmetry of FMD.

In contrast to GCA and PACNS, the clinical care of FMD and Moya-Moya disease does not rely on arterial biopsy for diagnosis and treatment. This makes the need for alternative approaches to help clarify the role of HSV-1 or other viruses in FMD to allow further focused investigation from the Immunological, Hormonal, and Genetic areas to clarify their role in FMD.

## Conclusion:

FMD patients can be identified with both cutaneous and serological evidence for active HSV-1 at their presentation.

Herpes-Simplex-1 virus is an excellent candidate virus for FMD as it can cause direct arterial injury in the observed population of women in their childbearing years. A viral cause explains the lack of progression and recurrence in the vast majority of FMD patients.

The role of HSV-1 in FMD will need to be clarified as will contributions from Genetic, Hormonal, and Immunological aspects long suspected to be part of FMD.

As treatment exists for HSV-1, this could lead to a new and exciting avenue of intervention in FMD with antiviral therapy.

Emulation of the VZV and GCA link, where colleagues around the world sent pathological material to the Gilden Laboratory in Colorado, a similar effort may clarify the specific role of HSV-1 in FMD.



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