European Journal of Cardio-Thoracic Surgery 58 (2020) 1109–1110
doi:10.1093/ejcts/ezaa367 Advance Access publication 24 October 2020

Cite this article as: Boyle EC, Haverich A. Microvasculature dysfunction as the common thread between atherosclerosis, Kawasaki disease, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated multi-system inflammatory syndrome in children. Eur J Cardiothorac Surg 2020;58:1109–10.

Microvasculature dysfunction as the common thread between atherosclerosis, Kawasaki disease, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated multi-system inflammatory syndrome in children

Erin C. Boyle and Axel Haverich*

Department of Cardiothoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Hannover, Germany

* Corresponding author. Department of Cardiothoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Carl-Neuberg Strasse 1, 30625 Hannover, Germany. Tel: +49-511-5326581; fax: +49-511-5325404; e-mail: haverich.axel@mh-hannover.de (A. Haverich).

Keywords: Severe acute respiratory syndrome coronavirus 2 • Coronavirus disease 19 • Kawasaki disease • Multi-system inflammatory syndrome in children • Microvasculature

Having first been described in Italy and England [1, 2], there are increasing reports of a Kawasaki-like disease in connection to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of children. This illness has now been termed multi-system inflammatory syndrome in children (MIS-C).

Kawasaki disease is a rare, acute, self-limited vasculitis primarily affecting infants and young children under the age of 5. Treatment of Kawasaki disease involves the administration of immunoglobulins and is often successful if diagnosed early; however, 10–20% of patients show resistance to this therapy [3]. Its main complications involve coronary artery stenosis and/or aneurysm formation. In contrast to Kawasaki disease, MIS-C seems to affect older children, is resistant to intravenous immunoglobulins, and can have relatively severe respiratory, gastrointestinal, meningeal and cardiovascular involvement.

Pathophysiologically, there are similarities between Kawasaki disease and atherosclerosis. Kawasaki disease vasculitis can cause two manifestations of adult atherosclerosis, namely, stenosing and calcifying sclerosis and aneurysm. There is accumulating evidence that both Kawasaki disease and atherosclerosis are initiated in the vasa vasorum—blood microvessels that supply the walls of medium and large arteries and veins with nutrients and oxygen [4]. When blood vessels are small, oxygenation of vessel walls occurs through diffusion alone. However, at a critical thickness, diffusion from the lumen becomes insufficient. As children age and the blood vessel walls thicken due to increased pressure load, hypoxic conditions in the outer media and adventitia trigger angiogenic processes that result in vasa vasorum development in other more distant areas of the arterial tree. Because vasa vasorum are functional endarteries, no collateral flow from neighbouring microvessels occurs if they become compromised. There is abundant evidence that vasa vasorum dysfunction, via obstruction or leakiness, can initiate atherosclerotic disease in the parent vessel [4]. Similar to atherosclerosic disease development, in the animal model of Kawasaki disease, the disease also appears to progress in an outside-in manner, beginning in the adventitial vasa vasorum and advancing inward towards the lumen [4, 5]. We suspect that the aortic root and proximal sections of the epicardial coronary arteries are specifically affected in Kawasaki disease as these are the only arteries in young children that possess vasa vasorum.

Despite decades of research, the underlying mechanisms of Kawasaki disease and atherosclerosis disease development are still unknown, however, infectious agents have been implicated in both cases. The concentration of seasonal, wind-borne fungal toxins correlates with several outbreaks of Kawasaki disease in Japan implicating *Candida albicans* as the aetiological agent of Kawasaki disease [6]. In animal models of Kawasaki disease, an immunological reaction in response to administration of non-infectious fungal (from *C. albicans*) or bacterial wall products is sufficient to precipitate vasa vasorum dysfunction leading to coronary artery arteritis with pathological features resembling human Kawasaki disease [5].

While it seems quite clear that MIS-C has an infectious cause, patients' swabs often test negative for SARS-CoV-2. However, patients with MIS-C have high titres of IgG and IgM against SARS-CoV-2 suggesting the disease occurs in a later phase of viral infection likely due to an adaptive immune response [2]. Recent adult autopsy studies found that SARS-CoV-2 affects the blood microvasculature through microthrombosis and endotheliitis, not only affecting pulmonary vessels but often leading to systemic impaired microcirculatory function in different vascular beds [7, 8]. The systemic effects of SARS-CoV-2 infection are likely due to the expression of the virus receptor angiotensin-converting enzyme 2 in cells within the lungs, arteries, heart, kidney and intestinal tract. The involvement of the large vessels during coronavirus disease 19 (COVID-19) in both children and adults is likely due to dysfunction of their vasa vasorum, however, to our

knowledge, this has not yet been specifically investigated. SARS-CoV-2-induced microthrombosis of vasa vasorum would lead to hypoxic conditions in the adventitia, prompting neoangiogenesis. Neovessels, in general, are inherently immature, fragile and leaky. In addition to endotheliitis affecting the vasa vasorum, and there is a high probability of lipoproteins, inflammatory cells and red blood cells infiltrating blood vessel walls via vasa vasorum. Accordingly, it will be important to track post-COVID-19 patients to determine whether they have an increased risk of cardiovascular or cerebrovascular disease. A comparison between individuals that had symptomatic infections with asymptomatic carriers would be very interesting. We speculate that damage incurred to vasa vasorum during a symptomatic SARS-CoV-2 infection would predispose these large vessels to future atherosclerosis development.

We strongly believe the unifying observation of malfunctioning microvasculature in all three disease entities (atherosclerosis, Kawasaki disease and MIS-C) cannot be overlooked. We would like to highlight the potentially important role of a newly recognized thrombotic component in all three diseases—neutrophil extracellular traps (NETs). NETs are highly condensed DNA structures released by neutrophils that both trap and—due to a high concentration of antimicrobial peptides—kill pathogens. While an important innate immune response, NETs also have prothrombotic consequences. Microthrombi triggered by NETs are implicated in atherosclerotic plaque formation [4], have been recently observed to be elevated in patients with Kawasaki disease [9], and are now hypothesized to play an important role in the pathology of COVID-19 [10]. There are several drugs being clinically tested that either degrade or prevent NET formation, with at least six COVID-19-related trials registered on https://clinicaltrials.gov to date. These new therapeutic approaches administered to SARS-CoV-2 patients may illuminate novel strategies to treat Kawasaki disease patients—especially for those resistant to immunoglobulin therapy. Until viable therapies are validated to tackle SARS-CoV-2 replication, treatment of adult and paediatric COVID-19 should focus on maintaining microvascular integrity using a combination of anti-oxidative, anti-inflammatory and antithrombotic strategies.

Conflict of interest: Both authors declare no conflict of interest.

REFERENCES

[1] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8.

[2] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395:1771–8.

[3] McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M *et al.*; On behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99.

[4] Haverich A, Boyle EC. Incriminating evidence for the role of the microvasculature in atherosclerosis. In: Atherosclerosis Pathogenesis and Microvascular Dysfunction. Cham: Springer, 2019, 55–74.

[5] Hamaoka-Okamoto A, Suzuki C, Yahata T, Ikeda K, Nagi-Miura N, Ohno N *et al.* The involvement of the vasa vasorum in the development of vasculitis in animal model of Kawasaki disease. Pediatr Rheumatol 2014;12: 12.

[6] Rodó X, Curcoll R, Robinson M, Ballester J, Burns JC, Cayan DR *et al.* Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci USA 2014; 111:7952–7.

[7] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–8.

[8] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS *et al.* Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–18.

[9] Yoshida Y, Takeshita S, Kawamura Y, Kanai T, Tsujita Y, Nonoyama S. Enhanced formation of neutrophil extracellular traps in Kawasaki disease. Pediatr Res 2020;87:998–1004.

[10] Thierry AR. Does the newly observed inflammatory syndrome in children demonstrate a link between uncontrolled neutrophil extracellular traps formation and COVID-19? Pediatr Res 2020;3:1–2.