Bee Sting-Induced Acute Ischemic Stroke: A New Manifestation of Kounis Syndrome?

In the very interesting report published in *Annals of Indian Academy of Neurology,*[1] a 41-year-old man developed a fatal right middle cerebral artery territory stroke following an attack by more than 50 bees. The authors speculating on the causality of stroke attributed this to either anaphylactic hypotension and reduced cerebral perfusion or to thromboxane and phospholipase induced platelet aggregation and hypercoagulant state and carotid

spasm from retrograde stimulation of the superior cervical ganglion.

Indeed, the honey bee sting venom named also *Apitoxin* (from Latin apis = bee and Greek toxikon = poison) can induce allergic, cardiovascular, and neurotoxic events.[2] Whereas honeybees are one of our planet's most important and hardest working creatures, their sting venom can induce a variety of actions including vasoconstriction of the cerebral arteries. It contains peptides such mast cell degranulating peptide, and melittin, as well as a variety of enzymes such as phospholipase A2, hyaluronidase, phosphomonoesterase acid esterase, α-D-glucosidase, lysophospholipase, α-galactosidase, α-acetylamino-deosiglucosidase, and arylamidase.[3] The mast cell degranulating peptide is a direct mast cell degranulator that triggers mast cells to release various cytokines and chemokines and in particular histamine and enzymes such as tryptase, chymase, and cathepsin-D and arachidonic acid products. Histamine via H1 coronary receptors and chymase together with cathepsin-D by converting of angiotensin I to angiotensin II, which is a major vasoconstricting substance, can induce artery spasm in individuals with even normal arteries. Furthermore, arachidonic acid products including thromboxane can induce platelet activation, with consequent vasospasm and thrombosis.[4]

We agree with the authors' pathophysiological explanation. However, in our opinion, all above substances participate in the pathophysiology of the allergy and anaphylaxis associated acute coronary syndrome, the so-called Kounis syndrome. Three variants of this syndrome have been described so far, namely, coronary spasm with normal or nearly normal arteries, artery thrombosis, and stent thrombosis.[4] This syndrome is caused by a variety of allergens, including drugs, several conditions, and environmental exposures such as bee stings on several occasions.[5]

Symptoms involving organs other than the heart might also occur in patients with conditions characterized by acute mast cell mediator release, as in systemic mastocytosis and mast cell activation disorders.

We have come across 2 patients, with mast cell-related disorders, who developed transient cerebral ischemic attacks[6] while they had the previous history of chest pain and Kounis syndrome. The first developed transient hemiparesis with decreased sensation and muscular weakness of the face and the second developed episodes of sudden transient paresis and numbness of his right arm following strenuous work that was redeveloped during hospitalization.

Recently, we have treated a patient with Kounis syndrome type-I variant caused by wasp sting who developed irreversible diffuse hypoxic-ischemic encephalopathy and he is still, for 6 months, in a vegetative state.[7] Another patient with Kounis syndrome type-II variant caused by an allergic reaction to amoxicillin-clavulanic acid under general anesthesia was complicated with severe, irreversible, and subsequently fatal encephalopathy of ischemic origin resulting from low blood pressure or direct proinflammatory and/or vasoconstrictive mediator action in the cerebral arterial system.[8]

All of the above show that Kounis syndrome is a pan-arterial hypersensitivity-associated disorder that affects not only the coronary arteries but also the cerebral arteries.[9] The latter can be affected via the same mechanism as the coronary arteries through the action of anaphylactic mediators that can induce vasoconstriction, hypo-perfusion, and thrombosis. Physicians should be aware of the various manifestations of this disorder in order to apply prompt and appropriate therapeutic measures.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Nicholas G. Kounis, Ioanna Koniari[1], Panagiotis Plotas, Andreas Argyriou[3], George D. Soufras[2], Grigorios Tsigkas, Periklis Davlouros, George Hahalis

Department of Cardiology, University of Patras Medical School, Patras, Greece, [1]Department of Electrophysiology and Device, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK, [2]Departments of Cardiology, [3]Department of Neurology, "Saint Andrews" State General Hospital, Patras, Greece

Address for correspondence: Dr. Nicholas G. Kounis, Department of Cardiology, University of Patras Medical School, Queen Olgas Square, 7 Aratou Street, Patras 26221, Greece.
E-mail: ngkounis@otenet.gr

References

1. Elavarasi A, Haq TM, Thahira T, Bineesh C, Kancharla LB. Acute ischemic stroke due to multiple bee Stings_A delayed complication. Ann Indian Acad Neurol 2020;23:135-6. doi:10.4103/aian.AIAN_118_19.
2. Katsanou K, Tsiafoutis I, Kounis NG. Timeo apis mellifera and dona ferens: Bee sting-induced Kounis syndrome. Clin Chem Lab Med 2018;56:e197-200. doi:10.1515/cclm-2018-0002.
3. Kounis NG, Koniari I, Velissaris D, Tzanis G, Hahalis G. Kounis syndrome—not a single-organ arterial disorder but a multisystem and multidisciplinary disease. Balkan Med J 2019;36:212-21. doi:10.4274/balkanmedj.galenos.2019.2019.5.62.
4. Kounis NG, Kouni SN, Kounis GN, Kounis SA. Intravenous tissue plasminogen activator, ischemic stroke, and the risk of Kounis syndrome. Ann Indian Acad Neurol 2011;14:223-4. doi:10.4103/0972-2327.85913.
5. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? Int J Cardiol 2006;110:7-14. doi:10.1016/j.ijcard.2005.08.007.
6. González-de-Olano D, Alvarez-Twose I, Matito A, Sánchez-Muñoz L, Kounis NG, Escribano L. Mast cell activation disorders presenting with cerebral vasospasm-related symptoms: A "Kounis-like" syndrome? Int J Cardiol 2011;150:210-1. doi:10.1016/j.ijcard.2011.05.007.
7. Anastogiannis H, Litsardopoulos P, Anastopoulou GG, Petsas A, Tsigkas G, Kounis NG, *et al*. Irreversible diffuse hypoxic-ischemic encephalopathy, secondary to type I Kounis syndrome [published online ahead of print, 2019 Dec 12]. Int J Neurosci 2019:1-3. doi:10.1080/00207454.2019.1702541.
8. Peláez-Pérez JM, Sánchez Casado M, Álvarez-Twose I, Kounis NG.

Amoxicillin-clavulanic acid-induced type II Kounis syndrome during general anaesthesia complicated with hypoxic-ischaemic encephalopathy [published online ahead of print, 2019 Aug 7]. Rev Esp Anestesiol Reanim 2019;S0034-9356 (19) 30123-9. doi: 10.1016/j.redar.2019.06.002.

9. Soufras GD, Kounis GN, Kounis NG. Brain injury due to anaphylactic shock: Broadening manifestations of Kounis syndrome. Int Endod J 2014;47:309-13. doi:10.1111/iej.12152.

Submitted: 26-Jan-2020 **Revised:** 12-Feb-2020 **Accepted:** 21-Feb-2020
Published: 16-Feb-2021

DOI: 10.4103/aian.AIAN_54_20