Dano Cerebral Associado a Urticária Crónica
Espontânea Lembrando Síndroma de Kounis

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RESUMO – A síndrome de Kounis caracteriza-se por um síndrome coronário agudo devido a vasoespasmo arterial que ocorre em reacções alérgicas imediatas ou na urticária crónica espontânea. Recentemente foi reportado a nível da vasculatura cerebral. Apresentamos três pacientes observadas entre Janeiro de 2016 e Dezembro de 2018 com acidente vascular cerebral agudo ou transitório durante exacerbações de urticária crónica espontânea, incluindo uma doente com episódios neurológicos recorrentes coincidentes com as crises de urticária. Foram detectadas alterações isquémicas cerebrais em duas doentes, mas não foram encontrados factores de risco cardiovascular ou anormalidades da coagulação que explicassem os sintomas neurológicos. A urticária crónica espontânea, através da activação e libertação de mediadores por parte dos mastócitos, poderá induzir dano a nível da vasculatura cerebral. Os autores enfatizam esta possível associação e a necessidade do controlo das crises de urticária de forma a prevenir manifestações de dano vascular.

PALAVRAS-CHAVE – Doença da Artéria Coronária/complicações; Hipersensibilidade; Lesões Cerebrais; Urticária.

Brain Injury Associated with Chronic Spontaneous Urticaria: a Kounis-Like Syndrome?

ABSTRACT – ‘Kounis Syndrome’ is an acute coronary artery event due to an artery spasm occurring during immediate hypersensitivity reactions or chronic spontaneous urticaria. Recently it has been reported in other systems, including the cerebral vasculature. We present a case series of three patients observed between January 2016 and December 2018 with acute and transient brain injury associated with concomitant exacerbation of chronic spontaneous urticaria, including one patient with multiple recurrences of neurologic symptoms during exacerbations of urticaria. Minor imaging defects were observed in two patients, but there were no apparent vascular risk factors or coagulation abnormalities that might explain neurologic symptoms. Chronic spontaneous urticaria, through activation of mast cells and mediator release, seems capable of inducing cerebral arterial aggression. The authors want to call the attention to this possible association, reinforcing the need to keep urticaria under control to prevent neurological manifestations.

KEYWORDS – Coronary Artery Disease/complications ; Brain Injuries; Hypersensitivity; Urticaria.

INTRODUCTION

‘Kounis syndrome’ (KS), described in 1991 as the syndrome of allergic angina, is defined as the concomitant occurrence of an immediate allergic or hypersensitivity reaction and acute coronary events in patients with normal coronary arteries with or without predisposing factors, and in patients with stent thrombosis (type I, II or III variants, respectively).1 Mast cell (MC) activation and release of their mediators during anaphylaxis or the hypersensitivity reaction are the key events underlying coronary artery spasm.2 There are several factors and diseases that may induce KS, including venoms, food allergens, drugs, stings by ants and jellyfishes, various conditions (angioedema/urticaria, asthma, exercise induced allergy, mastocytosis and serum sickness) and a variety of environmental exposures (poison ivy, latex contact, limpet ingestion).3 In recent years, KS has also

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been associated with exacerbation of physical\textsuperscript{4-6} or chronic spontaneous urticaria\textsuperscript{7} (CSU). In CSU, type I and IIb autoimmune mechanisms (respectively with cross-linking of autoreactive IgE by autologous or with IgG autoantibodies binding to FcγRI or IgE), cause activation and degranulation of skin mast cells and basophils.\textsuperscript{8} Both preformed granule-associated mediators such as histamine, neutral proteases, cytokines, chemokines and proteoglycans and the lipid mediators rapidly synthesised from endogenous arachidonic acid, such as prostaglandin D\textsubscript{2}, leukotriene B\textsubscript{4} and LTC\textsubscript{4}, have been associated with arterial spasm or rupture of atheromatous plaques in the heart.\textsuperscript{2,3}

More rarely, Kounis-syndromes had been reported in other systems, including one case of transient cerebral vasospasm occurring in chronic urticaria.\textsuperscript{9}

**CLINICAL CASES**

We report three patients from our urticaria center observed between January 2016 and December 2018 who developed acute and transient cerebral injury coincident with CSU exacerbations without any other apparent cause, concomitant disease, previous vascular risk or coagulation abnormalities that might explain neurologic symptoms. Apart from brain computed tomography (CT) and/or magnetic resonance imaging (MRI) performed by all patients at the emergency and after neurologic recovery, the following tests performed immediately after the acute episode were normal: electroencephalography (EEG) (except case 3), carotid Doppler ultrasound, echocardiogram and blood tests, that included complete blood count and differential, basic metabolic panel, thyroid hormones, coagulation parameters and tests for thrombophilia, homocysteine, antinuclear, anti-ds-DNA and ANCA antibodies, anti-neuronal antibodies (Hu, Ri, Yo, amphiphysin, recoverin, titin, Mo2, CV2 and Sox1), complement factors, immunoglobulins, serum protein electrophoresis, serologies for HIV, syphilis, *Borrelia burgdorferi*, *Toxoplasma gondii*, Rubella, Epstein-Barr, Herpes simplex and Cytomegalovirus.

**Case 1:** 43-year-old woman, 13-week history of CSU under 2-fold dose of H\textsubscript{1}-antihistamines, referred three times to the emergency room: first due to intense headache, photophobia and diplopia; second (six days later) because of dysmetria and left perioral paraesthesia; third (one month later) with nausea, dizziness and ataxia. All these episodes were coincident with CSU exacerbations with exuberant left hemisyndrome during a CSU exacerbation which started 3 hours prior to admission. The patient had stopped H\textsubscript{1}-antihistamines one month before due to apparent CSU control. Brain TC and MRI showed an acute stroke involving the posterior left lenticular nucleus. CT angiography demonstrated increased regional blood flow compatible with a stroke in early reperfusion phase. The patient was admitted to the neurology service for stroke workup and poststroke care with physical and occupational therapy. For CSU the patient started 4-fold H\textsubscript{1}-antihistamines with partial control and one month later omalizumab with excellent response. She had a dramatic improvement relative to her initial presentation. At one year follow-up, she persists with a subtle decrease on right muscle strength.

**Case 2:** 44-year-old woman, with a 6-month diagnosis of CSU, presented with altered mental status and right body paresis consistent with moderate faciobrachioaxial motor hemisyndrome during a CSU exacerbation which started 3 hours prior to admission. The patient had stopped H\textsubscript{1}-antihistamines one month before due to apparent CSU control. Brain TC and MRI showed an acute stroke involving the posterior left lenticular nucleus. CT angiography demonstrated increased regional blood flow compatible with a stroke in early reperfusion phase. The patient was admitted to the neurology service for stroke workup and poststroke care with physical and occupational therapy. For CSU the patient started 4-fold H\textsubscript{1}-antihistamines with partial control and one month later omalizumab with excellent response. She had a dramatic improvement relative to her initial presentation. At one year follow-up, she persists with a subtle decrease on right muscle strength.

**Case 3:** 47-year-old woman, with CSU for 8 months under 1-fold dose of H\textsubscript{1}-antihistamines with partial control, presented with garbled speech, dizziness and transient right upper limb monoparesis that lasted 30 minutes during an angioedema episode. Brain CT performed in the emergency room and later MRI did not show abnormalities. She was diagnosed with a transient ischemic attack and started acetysalicylic acid. When questioned, the patient remembers previous transient numbness and confusion during exuberant CSU episodes. For CSU, ciclosporine was administered for 6 months and later changed to omalizumab, both with good response. No more neurologic alterations were observed in 18 month follow-up.

**DISCUSSION**

All these cases occurred in female patients without vascular risk factors or family history of brain injury. They had previous history of CSU and referred an acute exacerbation before or concomitant with the neurologic episode. Clinical symptoms, absence of abnormalities in all complementary exams and recurrence of neurologic symptoms with simultaneous CSU exacerbations (particularly in case 1) support the hypothesis that the acute release of MC mediators may be responsible for arterial vasospasm affecting the central nervous system. Although we cannot definitively prove the sequence of events, because serial evaluation of the vascular brain system and quantification of any of the MC mediators (eg. tryptase levels) in the acute episode were not performed, an association between CSU exacerbations and acute/transient vascular brain damage seems probable.

This relationship could be explained by MC activation during exacerbation of urticaria. MC are recognized as resident cells within the cerebral vasculature and can affect it either directly through their mediators (histamine, tryptase, chymase, chemotactic factors and inflammatory cytokines) or indirectly due to interaction with inflammatory cells. MC have been associated with blood-brain barrier damage, brain oedema, reduction of cerebral blood flow and induction of cerebral...
artery spasm. There is experimental and clinical evidence that anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension and this has been attributed to the early and direct action of MC mediators on cerebral vessels after massive release of MC mediators. So, it is anticipated that the primary target of MC mediators is the arterial vasculature and brain injury may, therefore, represent a manifestation of a complex pan-arterial hypersensitivity-associated disorder. The exact mechanisms of action are not well understood. For instance, histamine has been associated with ischemia-induced neuronal death in rats and increased brain-blood barrier permeability, but in recent studies, it appears to have a protective effect on cerebral ischemic injury. Further studies are necessary to elucidate these interactions and their role in stroke.

These findings suggest that CSU, through MC activation and mediator release, may induce cerebral arterial damage, similar to the transient coronary symptoms reported particularly during cold-induced urticaria episodes. Tryptase determinations should be available in emergency services in order to confirm/diagnose this relationship when suspected, although they are not routinely performed during acute episodes. The authors want to call the attention to the possibility that CSU may explain transient neurological manifestations and emphasize the need to keep CSU under control to prevent these neurological symptoms.

**REFERENCES**