P6286

Old age significantly worsens stroke outcome in old mice through a mechanism of inflamm-aging successfully countered by the tumour necrosis factor alpha antibody infliximab

N.R. Bonetti[1], L. Liberale[1], L. Pasterk[1], C. Diaz-Canestro[1], A. Akhmedov[1], S. Gobbato[1], T.F. Luescher[2], J.H. Beer[3], G.G. Camici[1]

[1]*University of Zurich, Center for Molecular Cardiology, Schlieren, Switzerland;* [2]*Royal Brompton Hospital, Cardiology, London, United Kingdom;* [3]*Cantonal Hospital of Baden, Internal Medicine, Baden, Switzerland*

Background: Stroke is the second leading cause of death and the number one cause of adult disability worldwide. As a strongly age-dependant disease, its prevalence is expected to rise along with the average age in western populations. While the epidemiological evidence linking stroke to age is non-refutable, the specific and independent effects of age on stroke remain elusive.

This presents an important missing link for developing targeted treatments tailored to the growing elderly population.

A potential mechanism pertinent to stroke outcome in the elderly is a chronic low-grade inflammatory state, coined "inflamm-aging". Such a phenomenon could not only increase the risk for stroke, but also negatively affect its outcome and thus offers both preventive and therapeutic value.

Purpose: To determine the specific effects of age on the outcome after stroke in mice and delineate culprit molecular pathways with a focus on inflammatory mediators and to assess the efficacy of specific anti-inflammatory treatment with the TNF-α antibody Infliximab in this setting.

Methods: Old (18–20 months) C57BL/6 wildtype mice were compared to young (12 weeks) controls. Baseline levels of inflammatory cytokines were assayed in plasma and brain homogenates by ELISA. Ischemic stroke was induced by transient middle cerebral artery occlusion (30 minutes/48 h). Neurological function was assessed by a Bederson based score and the RotaRod test. Anti-inflammatory treatment with Infliximab was administered to a subset of old mice via weekly intraperitoneal injections (10 mg/kg) for 4 weeks prior to stroke induction. Young and old control animals received vehicle.

Results: At baseline (prior to stroke), old animals showed significantly higher plasma levels of TNF-α compared to young (Fig. 1A), while IL-6 and IL-1β remained below detection level in both groups. In brain homogenates of healthy old and young animals, TNF-α and IL-1β did not differ, while IL-6 was below detection level.

Old mice showed significantly larger stroke sizes (Fig.1B), performed worse neurologically (Fig. 1C) and suffered from higher post-stroke mortality compared to young (Fig. 1D). Pre-treatment with the TNF-α inhibitor Infliximab significantly decreased stroke size, neurological impairment and mortality in old animals (Fig1B-D).

Conclusions: In a model lacking additional confounding factors, we demonstrate a direct adverse effect of age per se on stroke outcome and mortality. Elevated TNF-α plasma levels in old mice outline the mechanism of "inflamm-aging" as a possible culprit. This concept is strongly supported by the beneficial effect of Infliximab on stroke outcome in old animals. Further investigation of the downstream mediators of the observed effect could help in tailoring treatments to the particularly vulnerable and growing elderly population.

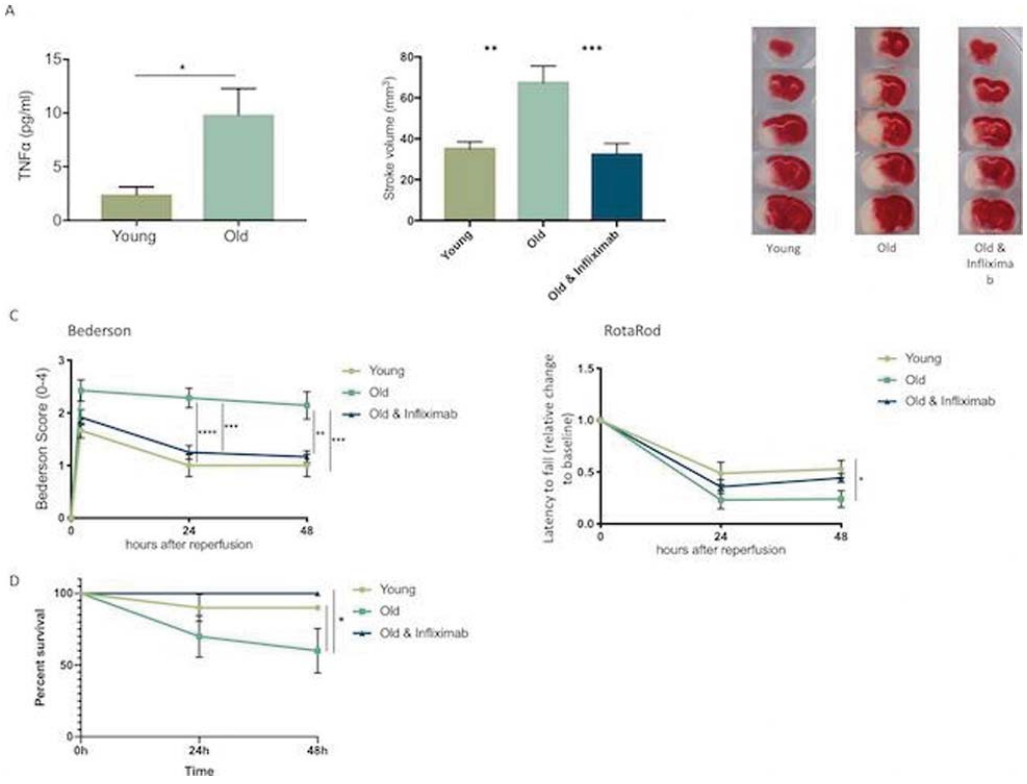

Figure 1