NEW INSIGHTS INTO SUSAC SYNDROME

Ilka Kleffner1, Urvashi Bhatia1, Marius Ringelstein2, Jan Dörr2, Heinz Wiendl1, Thomas Duning1, Catharina Groß1

1Department of Neurology, University Hospital Münster, Germany
2Department of Neurology, Medical Faculty, Heinrich-Heine-University, Germany
3NeuroCure Clinical Research Center, Charité - Universitätsmedizin Berlin, Germany

Introduction
Susac syndrome (SuS) is a rare disease characterized by the clinical triad of sensorineural hearing loss, branch retinal artery occlusion, and encephalopathy. It usually affects young people with a female preponderance. Since its first description in the seventies, almost 400 cases have been published. The diagnosis and differential diagnosis has improved by the help of new techniques such as optical coherence tomography (OCT), special magnetic resonance imaging and a higher awareness of physicians dealing with these patients. Treatment strategies consist of aggressive immunosuppression, intravenous immunoglobulines and plasma exchange, with widely variable success. The response to immune therapy, the finding of anti-endothelial cell antibodies, inflammatory changes in brain biopsies, cerebrospinal fluid (CSF), fluorescein angiography and magnetic resonance imaging strongly suggest an underlying autoimmune pathogenesis of the disease, but the role of the immune system is still poorly understood. Here, we present a pathway for the diagnosis, new findings on the pathogenesis of SuS and treatment recommendations.

Methods
To determine the role of the immune system, 16 patients with clinically SuS, 71 patients with multiple sclerosis (MS), and 24 healthy individuals were included. MS represents the most common differential diagnosis of SuS. Multi-parameter flow cytometry of immune-cells derived from the peripheral blood (PB) and CSF was performed to identify disease specific patterns in the peripheral and intrathecal immune cell profile, respectively. Possible SuS-related alterations in the T-cell receptor (TCR) repertoire of peripheral CD4+ and CD8+ T cells were analyzed by complementarity-determining region 3 (CDR3) spectratyping. A potentially related defect in immune regulatory function was specified in T cell suppression assays.

Results
We present a diagnostic pathway developed by a team of neurologists, neuroradiologists, otorhinolaryngologists, and ophthalmologists with long time experience in the care of SuS patients united in the European Susac Consortium (EuSac).

The examination of the blood and CSF revealed that the cytotoxic CD8+ T cell subset seems to be crucial in both systemic and intrathecal pathology of SuS. The intrathecal CD4/CD8 ratio was significantly decreased in SuS patients compared to MS patients and patients with somatoform disorders. The proportions of HLA-DR expressing activated CD8+ T cells were significantly enhanced in both the PB and in the CSF of SuS patients. CD8+ T cells derived from SuS patients expressed higher levels of granzyme B and perforin in their cytolytic granules and exhibited a higher cytolytic activity upon TCR triggering. With regard to the TCR repertoire, SuS patients showed a much higher degree of alterations in the TCR repertoire of CD8+ T cells when compared to healthy individuals, but more importantly also to MS patients, whereas changes in the CD4 TCR were more pronounced in MS patients than in SuS patients. In accordance with these findings, CD8+, but not CD4+, T effector cells derived from SuS patients were resistant to regulatory T cell mediated suppression.

Based on these findings, our clinical experience and new case reports and series, we present treatment strategies for SuS.

Conclusions
In the last years, the diagnosis of SuS has improved by new techniques and a wider knowledge of the clinical presentation. Based on these developments, we propose a pathway to facilitate the diagnosis for both experts and physicians unfamiliar with the disease. The results of the immune system examination strongly support the hypothesis that the immune system plays a crucial role in the pathogenesis of SuS. Particular cytotoxic CD8 T cells seem to be the key in both systemic and intrathecal pathogenesis of this disease. A better diagnosis and knowledge on the pathogenesis will help to improve the treatment of patients with SuS.