Venous and glymphatic drainage of the brain: Brief history of the International Society for Neurovascular Disease

Ewart Mark Haacke, Meiyun Wang, Xiaoyue Ma, David Utriainen
1Wayne State University, Detroit, MI, USA; 2The Magnetic Resonance Imaging Institute for Biomedical Research, Detroit, MI, USA; 3Magnetic Resonance Innovations, Inc., Detroit, MI, USA; 4Spin tech, Inc., Detroit, MI, USA; 5Henan Provincial Peoples’ Hospital, Zhenzhou, Henan Province, China

Abstract

The International Society of Neurovascular Diseases is an International, Interdisciplinary Scientific Organization (ISNVD: www.isnvd.org) devoted to the study of intracranial and extracranial vasculature. Different from other scientific societies, ISNVD is interested also in the investigation of the cerebral drainage, including the venous and glymphatic systems. Moreover, ISNVD promotes studies on: stroke, carotid surgery, neurovascular aspects of neurodegeneration, models of circulation, vasoactive peptides, and basic science. This review summarizes the contribution of the society to the fields above, as well as the history of the annual meetings and the major impact papers promoted by ISNVD.

Introduction

The foundation of the ISNVD had its history in the first meeting held on chronic venous hypertension by Dr. Paolo Zamboni in Bologna, Italy in 2009. His pioneering work on iron and vascular effects in multiple sclerosis (MS) opened the door to a more intensive international effort to study the vascular sources of neurodegenerative disease. The story really began with his seminal paper on iron: The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. After the Bologna meeting, it became clear that there was not a major focus on venous effects in neurodegenerative disease and even the role of the arterial system was under-represented. This spurred a group of leading scientists to meet in 2010 at the house of Sal Sclafani, M.D. (one of the past Presidents of the Society). At that meeting it was decided to go ahead and form a 501(c)3 Non-Profit Society which was then centered in Detroit, Michigan for the first 3 years. Subsequently the office moved to Buffalo for the next 3 years with Robert Zivadinov, M.D., Ph.D. (also one of the past Presidents of the Society) and then to Shreveport for two years with Steve Alexander (also one of the past Presidents of the Society) and then back to Detroit in 2017 with Mark Haacke Ph.D. (the current past president).

Highlights of the past eight meetings

Bologna, Italy 2011; President and Annual Meeting Chair Paolo Zamboni

The ability to understand the vascular system has the potential to lead to new treatments. Dr. Berislav Zlokovic had the insight to focus on the fundamental aspects of vascular pathology including: the role of: reduced perfusion, hypoxia, tissue damage and endothelial damage. He suggested that neurodegeneration occurs secondary to vascular damage and that novel pharmaceuticals might be designed to target inflammation and endothelial pathology. Today trials are underway using activated protein C, which is a blood protease with its anti-coagulant functions turned off so that it is a multiple cell and protein therapy. This was followed by Dr. Costantino Iadecola who discussed the role of iron as a potential inflammatory agent, the role of oxidative stress and endothelial damage. He further suggested there might be a relationship with poor vascular conditions and that these could lead to the production of beta amyloid plaque. Today, along with the glymphatic system to be discussed later, this is now a very promising direction of research.

Dr. Robert Zivadinov followed with examples from imaging demonstrating reversible cerebrospinal fluid stagnation and increased iron content in MS patients, and also suggesting that these increases may correlate with the severity of the disease (Figure 1).

Orlando, Florida, USA 2012; President Robert Zivadinov, Annual Meeting Chair Mark Haacke

The keynote speech was given by Michael Chopp, Ph.D., from Henry Ford Hospital. He discussed vascular responses to neural injury and neurorestorative therapies. His work focused on using drugs such as Niaspin (niacin or vitamin B3) and sildenafil (Viagra) to help generate the formation of new micro-vessels to regenerate brain tissue.

A highlight of this workshop was the focus on providing a Consensus on Imaging & Treatment Protocols. Ultrasound, Magnetic Resonance Imaging (MRI) and balloon angioplasty groups met separately to discuss the state-of-the-art technology in each area with an eye toward creating a white paper. The outcome of this effort was a paper published in 2014 in JVIR, 2014, 25, 1785.

The Gold Medal was given to Franz Schelling for his pioneering contributions to understanding the role of the venous vasculature in MS. Dr. Schelling then gave an overview of some of the history and where he thought we still needed to forge ahead to clearly addresses the role of abnormal venous vasculature in MS.

Krakow, Poland, 2013; President and Annual Meeting Chair Marian Simka

At this meeting the venue of presentations continued to expand and covered a number of new concepts including the work of Jaap Valk from Amsterdam. He presented the results of a prospective study on patients with chronic intractable headache and other concurrent symptoms such as vertigo, dizziness, tinnitus and visual disturbances. The patients were examined by the use of magnetic resonance venography.
Often the patients were found to have intracranial abnormalities such as persistent occipital sinus with loop formation or thrombosis of the intracranial sinuses. He concluded that venous intracranial pathology is prevalent in patients presenting with neurological symptoms and that MRI would play a key role in diagnosing these patients.

San Francisco, California, USA 2014; President and Annual Meeting Chair Mike Dake

Reflecting the expanding interest and collaborations within the society, a special focus on traumatic brain injury (TBI) was the theme of the 2014 meeting. Dr. Diaz-Arrastia discussed treatment of patients with TBI.\textsuperscript{25-29} He presented several different treatment options including: sildenafil, erythropoietin, statins, G-CSF, VEGF, pioglitazone, exercise, enriched endothelia progenitor cells, from cord blood or bone marrow, and low level laser light therapy. His findings in humans were similar to the keynote lecture in 2012 by Dr. Michael Chopp.

Naples, Italy, 2015; President Ziv Haskal, Annual Meeting Chair Marcello Mancini

Research into new therapeutic approaches for human neuro-degenerative disorders is part of the effort by Dr. Jacques De Keyser and his group from Brussels, Belgium.\textsuperscript{29,31} They demonstrated the reversibility of the reduction in cerebral blood flow observed in MS patients by using antagonists of endothelin-1 (ET-1), a vasoactive peptide which is also over-expressed in Alzheimer’s Disease (AD) and other disorders associated with chronic brain hypoperfusion.\textsuperscript{32}

The role of vessel wall began taking on importance at this meeting. The effects of ET-1 and other markers of endothelial dysfunction of the autoregulation of cerebral vessels and cerebral circulation time in MS patients were quantitatively demonstrated by Serena Monti, M.S. from Siena, Italy using digital subtraction angiography.\textsuperscript{33}

Zamboni for his pioneering contributions to understanding the role of the venous vasculature in chronic cerebral spinal venous insufficiency (CCSVI).\textsuperscript{34} Paolo continues to be a leader in this field not only constantly probing the effects of venous hypertension but also developing new means by which to monitor these vascular abnormalities.\textsuperscript{35}

New York City, New York, USA 2016; President and Annual Meeting Chair Sal Sclafani

A new area of interest sprang up this year that continues to be an important topic today. The session on Vascular Function, Lymphatic System and New Drug Approaches gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists gave presentations with more than 40 well-known radiologists and neurologists.
ly participating. The speakers were able to give their presentations in both Chinese and English as simultaneous interpretation was provided through special headsets. This ensured easy understanding of the speeches and a fluent exchange of information throughout the meeting. The meeting was formally hosted by Henan Provincial People’s Hospital in Zhengzhou, Henan, China, which is one of the largest hospitals in China with a history of more than 114. Please visit our website at www.isnvd.org for more information about the ISNVD or e-mail info@isnvd.org.

The opening ceremony welcomed everyone with a video of the history and culture of Henan Province, the Henan Provincial People’s Hospital and the ISNVD. Dr. Meiyun Wang gave a welcome speech and introduced the other invited guests including: Dr. Longde Wang, an academician of the Chinese Academy of Engineering, Honorary President of the ISNVD 2018 Annual Meeting and President of the Chinese Preventive Medicine Association from Stroke Prevention and Control Project Committee, National Health Commission; Dr. Jianping Dai, a foreign academician of the American Academy of Medical Sciences, Past Vice-President of the Chinese Medical Association; Prof. Lawrence L. Wald, President-Elect of the Chinese Preventive Medicine Project Committee, National Health Commission; Prof. E. Mark Haacke, 2017/2018 President of the Chinese Preventive Medicine Project Committee, National Health Commission; Dr. Meiyun Wang talked about chemical exchange saturation transfer (CEST) imaging in stroke. She introduced two CEST concepts: 1) amide proton transfer (APT) and length and 2) offset varied saturation (LOVARS). She and her team have pioneered the application of these methods to demonstrate that they can be used to detect stroke and distinctly differentiate hyperacute intracranial hemorrhage from cerebral ischemia thereby opening the door for a rapid single scan evaluation of stroke.52-53

Prof. Paolo Zamboni talked about Eagle jugular syndrome. He said that the jugular variant of the Eagle syndrome is a distinct

Highlights of the 2018 meeting

Dr. Longde Wang gave a lecture entitled Exploration on the prevention and control of stroke in China. He elaborated the major challenges, preliminary achievements and future plans in stroke prevention in China.51

This was followed by a speech on Imaging techniques of cerebral ischemia by Dr. Jianping Dai.52 He said new therapies of recanalization of cerebral ischemia may improve patient outcome and that early diagnosis by imaging is significant for choosing a suitable treatment. He noted that precision medicine requires the combination of P4 medicine, integrated imaging, artificial intelligence (AI) and molecular medicine but that despite advances in this era of precision medicine, challenges remain.

Prof. Lawrence L. Wald gave the second keynote speech titled MRI unchained; removing hardware constraints to make faster, portable and motion tolerant images. From the insight of biomedical imaging and bioengineering, Prof. Wald gave an excellent talk on several advanced technologies, mainly about MR image reconstruction (based on modeling the structure of interest rather than using Fourier Transform), the portable brain MRI, accelerated imaging and removing motion artifacts.53 He said, “If you can measure a systematic error, you can fix the systematic error”. Many in the audience were excited about this new technology and its implications in the field of medical imaging.

Prof. E. Mark Haacke spoke about a rapid multi-contrast MRI method using strategically acquired gradient echo (STAGE) imaging.54,55 He noted that STAGE provides a rapid standardized imaging approach of the entire brain in less than 5 (7) minutes that can be used for all 3T (1.5T) manufacturer systems.57-61

Dr. Meiyun Wang talked about chemical exchange saturation transfer (CEST) imaging in stroke. She introduced two CEST concepts: 1) amide proton transfer (APT) and length and 2) offset varied saturation (LOVARS). She and her team have pioneered the application of these methods to demonstrate that they can be used to detect stroke and distinctly differentiate hyperacute intracranial hemorrhage from cerebral ischemia thereby opening the door for a rapid single scan evaluation of stroke.52-53

Prof. Paolo Zamboni talked about Eagle jugular syndrome. He said that the jugular variant of the Eagle syndrome is a distinct

Figure 2. Gold medal winners Franz Schelling (2012), Mark Haacke (2016), Robert Zividinov (2018) and Paolo Zamboni (2015).

Figure 3. Presidium and invited speakers. All the invited speakers and honorary guests were present for this picture.
clinical entity with respect to both classic and carotid variants, and it seems to be a factor which potentially increases the susceptibility to subarachnoid hemorrhage (SAH). 36 Prof. Bruno’s talk was called "Venous lesions in patients with Meniere’s Disease (MD): Results of a multicentric Italian study and guidelines for an international project." His research found that the prevalence of CSVSI in Meniere’s disease is high and PTA has a significant curative effect on MD. 37 He believed that the venous stasis of the head and neck veins may be considered a further etiopathogenetic mechanism which adds to many other already known mechanisms that still define MD as a multifactorial disease.

Prof. Paolo Zamboni also discussed the Brave Dreams trial. 38,39 He believed CSVSI contributed to a better understanding of the function and role of the extracranial venous system. He then suggested, "Rather than rejecting this accumulated new knowledge, we should use it more appropriately for future endeavors". Prof. Robert Zivadinov discussed the role of cardiovascular (CV) comorbidities in the pathogenesis of neurological disorders. 40 He pointed out that CV comorbidities are associated with higher susceptibility to neurodegenerative disorders and disease progression, there is a stronger link between CSA of neck vessels and CV risk factors, and that the heart-brain axis should be better investigated in diseases such as MS, AD and PD. Prof. Salvatore Scalfani discussed Carotid arteri-al trauma and minimally invasive treatments. He believed that treating carotid injury surgically is challenging and endovascular options are essential for survival. 41 The 2019 meeting will be held in Ferrara, Italy, bringing us back to our roots. The ISNVD is a non-profit organization registered in the United State of America. To become a member, please go to www.isnvd.org.

References


[page 6] [Veins and Lymphatics 2019; 8:7839]