June, 2016

From the President 1
Visions of Disease 2
Therapeutic Hypothermia in Stroke Management 3
The Heart and the Brain, CNU Edition 7
Vascular Dementia 8
Etanercept: An Alternative Treatment for Stroke 9
Letter From the Editor 10

FROM THE PRESIDENT:

To the Neurites—Cheers to a successful first year of the CNU-COM Student Interest Group in Neurology. These newsletters, our inaugural Brain Day and all the articles and studies we have swapped since the group’s inception are a testament to your dedication to our interest in neuroscience and the school’s reputation in the broader medical community and our own. I sincerely thank you all.

I would now like to invite our readers to enjoy our last newsletter of the school year, before our SIGN parts ways for two months to enjoy the proverbial “last summer” of medical school. Because we are in the cardiology block, the theme of this issue is on the cerebrovasculature. As a PhD student in the lab of a neurosurgeon who specialized in treating skull-base aneurysms (areas of weakness within the wall of an artery leading to a ballooning effect and making the artery more prone to serious rupture), I came to appreciate the complexity of this system. He would famously remark, at least to my awe-inspired ears, that I could take the cerebrovasculature from Loma Linda to San Francisco—all 500 miles of it. Well, here I am—pretty close, so thank you Dr. Wolff Kirsch. He also suggested to me that the smooth muscle cells that make up the walls of the arterial system of the brain are probably smarter than the neurons that do our thinking and that when those smooth muscle cells are destroyed, the brain—and its neurons—shrink under the crushing pressure of dementia. Fittingly then, Salil Babbar has provided you with an article on the specifics of Vascular dementia—an entity similar to and at one time compared to Alzheimer’s disease. Mohammad Aziz has additionally contributed an article on the controversial effects of hypothermia treatment on stroke outcomes with commentary by Dr. Forshing Lui. Lastly, Nancy Li has graced you again with a humorous “neurocomic”,

Page 1
“Vascular dementia is easily preventable if detected and diagnosed early on, so it’s essential for clinicians to be able to recognize all the various signs and symptoms of the disease.”

this time featuring The Heart, and Arleen Grewal has written a beautiful poem for your reading enjoyment.

To close, I would like to thank Trevor Tsay for taking the time to format these newsletters—it could not be done without his efforts. Additionally, thank you to our Faculty Advisor, Dr. Forshing Lui for his support and contributions. Finally, a special thanks goes out to our readers and supporters outside of the SIGN. We hope you enjoyed the first iteration of this epic journey we as medical students have started. Starting in the fall of 2016, we will introduce to you a new crop of budding neurites with our upcoming class of 2020. For now, please enjoy this issue of The Newsletter, courtesy of the CNUCOM SIGN.

-Matthew Zabel
President, CNU SIGN

VISIONS OF DISEASE

An x-ray, culture, CT, even MRI,
All of these hint to where, how, and what went awry.
Is it his nose, the left ear, or was it mid-thigh?
No no, it was Trachoma that left him one-eyed.

But what if I claimed a simple painting by you,
Could unveil the wicked plights of your vision too?
You see, the canvas may mirror your tainted view,
And thereby, oh so niftily offer a clue.

A French impressionist, Claude Monet was his name.
Sublime depictions of light gave birth to his fame.
In his late seventh decade, not-so-good news came:
“Bilateral cataracts,” the doctor claimed.

Far less vibrant, his pieces muted in color.
He then wrote “[I] see a complete fog,” as it were.
Cataracts absorb light and today we infer,
They stain the world with yellows and reds in a blur.

From blue-green to red-yellow, his palette shifted.
Reds posed as muddy pinks, he could not resist it.
Next envision your sight and mind, too, have drifted.
That when Doctor said “Alzheimer’s,” your heart twisted.

That was the fate of one American artist.
William Utermohlen, though not a narcist,
Offered a peak into his mind at its darkest,
By painting self-portraits that slowly lost sharpness.

-Matthew Zabel
MS1, CNUCOM
President, CNU SIGN
Diagnosed in ’95, at age 61.
Demise of Will’s perception of depth had begun.
He painted for four years, lounging under our sun.
In his last seven it could no longer be done.

Born in the 1830s in Paris one night
Was Edgar Degas, who lost defined, central sight.
A scotoma, little by little gained in might.
Age and drusen stole his macula in cold spite.

A remarkable painter, he learned to adapt—
Replaced oil paints with pastels to feel less trapped.
Though not a Michelangelo, I, too, in fact
House ophthalmic maladies and a cataract.

At age 17, my right eye nearly went blind.
But enough about me, fast forward to real time.
To how exquisitely 60 lives intertwine,
Like tree roots drawing close together in sunshine.

Thank the colors and lines and shapes that you can see.
And CNU, our home, where we’re humbled to be.
Reflecting on our good grace each day is key.
For these people, places, and life won’t always be.

-Written by: Arleen Grewal

Arleen Grewal
MS1, CNUCOM

Claude Monet painted “Waterlily Pond,” in 1899. His vision problems with cataracts didn’t begin until 1912.

Current photograph of the same bridge, blurred as it might appear to someone with a moderate cataract.

Details from William Utermohlen’s self-portraits, the first, made in 1967, the rest from 1996 the year following his diagnosis of Alzheimer’s disease, to 2000, charting his decline. Courtesy of the artist’s estate and GVArt Gallery, London

Pastels; Ballet Dancers in the Wings, 1900 by Edgar Degas.

Oil paint; Dance Class at the Opera, 1872 by Edgar Degas.
Stroke is the fifth leading cause of death in the United States accounting for one in every 20 deaths. The vast majority of strokes are ischemic (87%) and their management ranges from thrombolytic therapy to symptomatic management. Therapy is directed at reducing neuron death due to ischemia or subsequent reperfusion. A newer approach to combatting neuronal loss is therapeutic hypothermia. Therapeutic hypothermia has been implemented into the standard of care for cardiac arrest patients by the American Heart Association, however, its use in stroke management remains much more controversial.

Cardiac arrest results in global cerebral ischemia and chances of reperfusion injury are implicated in neurological decline. Two randomized controlled trials published in the New England Journal of Medicine in 2002 showed neuroprotective effects of therapeutic hypothermia (32-34°C) in comatose patients after out-of-hospital ventricular fibrillation cardiac arrest within 2 hours of return of spontaneous circulation and maintained for 12-24 hours (Kirkman et al., 2014). Conversely, acute ischemic stroke does not always result in global cerebral ischemia. Localized brain infarcts may benefit from therapeutic hypothermia at the risk of compromising metabolism in competent regions. Furthermore, return of circulation following cardiac arrest is typically associated with accompanying cerebral reperfusion. In stroke, the affected vessel may remain occluded for days, or indefinitely, which enhances the side effects of cooling on other parts of the body. Lastly, unlike cardiac arrest patients, those undergoing acute ischemic stroke are not usually comatose or endotracheally intubated and risk of shivering and other discomfort presents another challenge for treatment (Midori et al., 2010). Given these trade-offs, current clinical application takes advantage of therapeutic hypothermia in symptomatic management to lower intracranial pressure and hypertension while clinical trials are geared at optimizing protocols to extract the most therapeutic benefit.

The mechanisms underlying the neuroprotective effects of therapeutic hypothermia in stroke management, as well as its associated complications and proposed methods of accomplishing optimum therapy will be discussed herein.

**Injury Following an ischemic event**

Adequate blood flow delivers oxygen and glucose to the brain in order to maintain its normal function. Normal function requires the integrity of ionic gradients maintained by transmembrane channels. Following an acute ischemic event, ionic homeostasis is disrupted, which leads to an influx of calcium and the excitatory neurotransmitter, glutamate. Glutamate induced excitotoxicity leads to generation of reactive oxygen species (ROS) and nitric oxide (NO) that induce apoptosis by damaging cell structures. Progressive cell damage leads to dissipation of ion gradients established across the cell membrane, which further contributes to osmotic changes that result in cerebral edema.
Neuroprotective Effects, A Multi-pronged Approach:

1) Decreasing cerebral metabolic demand
2) Modulatory on Glutamate
3) Inhibit Mitochondrial Apoptosis
4) Decrease Reperfusion Injury

Cerebral edema can progress to increased intracranial pressure (ICP) which threatens to compress vital structures and eventually herniate. In addition, anoxia causes metabolic alterations with elevated lactate leading to acidosis. The location and extent of these changes are dependent on the nature of ischemia which includes location, metabolic demand and level of collateral blood supply.

**Neuroprotective effects of Hypothermia**

Cerebral metabolic rate is dependent on temperature. A 1° C drop in body temperature translates into a 6%-7% reduction in cerebral metabolic rate (Polderman, 2009). Decreasing cerebral metabolic rate reduces utilization of oxygen and glucose. This lessens the extent of anoxic injury from metabolic acidosis and less excitotoxicity by lowering metabolic demand. In addition to its effects in the immediate stages of acute stroke, therapeutic hypothermia can lower the risk of reperfusion injury by decreasing inflammation caused by the resurgence in blood flow.

In early glutamate induced excitotoxicity, there is a protective function served by nearby astrocytes which uptake glutamate via the GLT-1 transporter. In prolonged ischemia, however, this function reverses as injury to astrocytes becomes more pronounced. The regurgitation of glutamate unleashes a heavy burden on the neuron resulting in a potent inflammatory response with more ROS release. One laboratory study showed a reduction in NMDA receptor phosphorylation and increase in GLT-1 transporter in astrocytes in newborn piglets with induced hypoxic-ischemic injury followed by therapeutic hypothermia (Wang et al., 2013).

Therapeutic hypothermia has also been shown to inhibit intrinsic (mitochondrial based) apoptosis by lowering pro-apoptotic BCL-2 family members such as BCL-2 associated X (BAX) and upregulating anti-apoptotic protein Bcl-2, inhibiting cytochrome c release and caspase activation (Fukuda et al., 2001, Phanithi et al., 2000, Yenari et al., 2002 and Zhang et al., 2001). Furthermore, the therapy can prevent endoplasmic reticulum stress apoptosis through suppressing C-EBP-homologous protein (CHOP) (Liu et al., 2013).

Reperfusion mediates injury through providing oxygen for pro-oxidant enzymes such as NADPH oxidase to churn out more ROS (Tang et al., 2011). This leads to disruptions in the blood brain barrier which can lead to hemorrhage. Hypothermia can reduce this inflammation and lower the risk of hemorrhage.

There are other mechanisms of neuroprotection mediated by therapeutic hypothermia that aid neuronal recovery post ischemia. These largely stem from the preservation of neuronal function during the initial ischemic insult by pacifying the inflammatory response and limiting damage to the brain infrastructure.

**Complications**

There are consequences to depressing the body’s natural inflammatory response; mainly a propensity for developing infection. Up to one third of ischemic stroke patients develop infection (Emsley and...
“There are consequences to depressing the body’s natural inflammatory response; mainly a propensity for developing infection. Up to one third of ischemic stroke patients develop infection.”

Hopkins, 2008 and Meisel et al., 2005). As body temperature is lowered to 32°C, heart rate is lowered to 40-45 beats/min (Bernard and Buist, 2003, De Georgia et al., 2004 and Staikou et al., 2011). Cardiac complications due to decreased heart rate include lowered mean arterial pressure and cardiac output, arrhythmias and myocardial infarction. Hematologically, the coagulation cascade is induced in temperatures less than 35°C (Polderman, 2009). This is challenging considering stroke itself is a coagulation-fibrinolysis disorder. Other complications include electrolyte disorder, hyperglycemia, insulin resistance, cold diuresis, and bowel disorders (Zipling et al., 2015).

Methods of Inducing hypothermia

Unlike therapeutic hypothermia for cardiac arrest, there are no set guidelines for its use in the management of acute stroke. Implementation is case-dependent and clinical outcomes have not been consistent. Much consideration is needed to determine the temperature at which to induce hypothermia and the duration of therapy. Early hypothermia with a longer course is typically associated with better outcomes. Most interventions hover in the neighborhood of 32°C-35°C (Zipling et al., 2015). Rewarming is performed slowly, paying close attention to markers like intracranial pressure. In terms of location, therapy can be localized to the brain or the entire body. Options are available for intra-arterial cooling and pharmacological cooling as well.

Conclusion

Therapeutic Hypothermia is a controversial intervention in the management of acute ischemic stroke. Laboratory studies with animals have produced much more promising results than clinical application. Currently, it has been used in conjunction with other tactics like thrombolytics, mechanical thrombectomy, hemicranietomy, and other pharmacological therapy to limit brain injury. Going forward, research is increasingly directed towards clinical practice in order to attain the greatest efficacy of treatment.

-Mohammad Aziz

References


Matthew A. Kirkman, Martin Smith, Therapeutic hypothermia and acute brain injury, Anaesthesia & Intensive Care Medicine, Volume 15, Issue 4, April 2014, Pages 171-175, ISSN 1472-0299, http://dx.doi.org/10.1016/j.mpac.2014.01.021.


All other citations provided are from this review article:

THE HEART &
THE BRAIN
CNU EDITION

- Nancy Li
MS1, CNUCOM
When people hear the word “dementia” they usually think about Alzheimer’s Disease (AD). However, vascular dementia still remains the second most common cause of dementia amongst elderly in the US and Europe, and the most common form of dementia in some parts of Asia. The prevalence rate in Western countries is about 1.5% and it accounts for about 20% of dementia cases in the US. In patients with dementia who have had a stroke, the increase in mortality is profound. The 5-year survival rate is 39% for patients with vascular dementia compared with 75% for age-matched controls. Vascular dementia is easily preventable if detected and diagnosed early on, so it’s essential for clinicians to be able to recognize all the various signs and symptoms of the disease.

Currently, many subtypes of vascular dementia have been identified. These forms include mild vascular cognitive impairment, multi-infarct dementia, vascular dementia due to a strategic single infarct, vascular dementia due to lacunar lesions, vascular dementia due to hemorrhagic lesions, subcortical vascular dementia, and mixed dementia (combination of AD and vascular dementia). Vascular dementia, which is the result of multiple arterial infarcts and/or chronic ischemia, is the step-wise decline in cognitive ability with late-onset memory impairment. Injuries accumulate in a stepwise manner with every minor stroke that occurs. Most infarcts are due to the formation of a thrombus at the particular site of injury or a thromboembolism moving to the site of injury from a different location. An MRI or CT of a person with vascular dementia will show multiple cortical and/or subcortical infarcts, so performing an MRI or CT is essential to confirm the diagnosis.

In addition to cognitive decline, patients with vascular dementia may have accompanying motor or sensory symptoms, depending on where the infarct occurs in the brain. Most of the time these infarcts occur in the parietal lobe, cingulate gyrus, and other areas of the brain supplied by the anterior cerebral artery. Damage to the cingulate gyrus results in changes in emotional state, long-term memory formation, olfaction, behavior, and autonomic nervous system function. Anterior cerebral artery strokes often result in contralateral paralysis and sensory loss of the lower limbs as it supplies the lower limb sections of the primary motor cortex (frontal lobe) and primary somatosensory cortex (parietal lobe). Vascular dementia can also be triggered by cerebral amyloid angiopathy, which involves the accumulation of beta amyloid plaques in the walls of the cerebral arteries, leading to the breakdown and rupture of these arteries.

Ischemic damage is often permanent, so prevention of future strokes is very important for patients at risk for vascular dementia. The best way to avoid a stroke is by lowering hypertension, hyperlipidemia, atrial fibrillation, and maintaining blood glucose levels in patients with diabetes mellitus, all of which are major risk factors for stroke. All of these factors are major risk factors for stroke. When it comes to medication, aspirin and other antiplatelet agents like ticlopidine and clopidogrel are useful in prevent the formation of new thrombi and emboli. For patients with atrial fibrillation, which is an abnormal heart rhythm characterized by

Salil Babbar
MS1, CNUCOM
Vascular dementia is easily preventable if detected and diagnosed early on, so it’s essential for clinicians to be able to recognize all the various signs and symptoms of the disease.

Rapid and irregular beating, anticoagulation therapies such as warfarin are more effective at preventing future strokes. Patients with hypertension can take ACE inhibitors, Ca2+ channel blockers, thiazide diuretics, or β-blockers to lower their blood pressure, which would decrease their chances of forming a thromboembolism. Additionally, statins have been found to reduce the risk of stroke in patients with coronary artery disease and elevated total or low-density lipoprotein (LDL) cholesterol.

As the “baby boomer” generation gets older, the number of seniors ages 65 and older in the United States is expected to more than double from 39 million to 89 million in 2050. With this fact in mind, it’s important for all future physicians, including internists, neurologists, and cardiologists to be able to recognize the early signs and symptoms of vascular dementia in order to avoid permanent brain damage and an early death. Not only does vascular dementia impact the patient, but it has ramifications on the family members who take care of that patient. Thus, every physician needs to be able to take a thorough medical history (including family history of dementia), evaluate the patient’s daily activities, obtain input from a relative or trusted friend of the patient. While a thorough history is important, a comprehensive neurological exam is just as important in conjunction with the correct laboratory tests and brain imaging like MRI or CT scans.

-Salil Babbar

References:

ETANERCEPT: AN ALTERNATIVE TREATMENT FOR STROKE

In response to the article published in this issue by Mohammad Aziz, I have to point out that researchers have tried to study different “neuroprotective” strategies for acute stroke treatment. Many of these appeared to be promising in in-vitro and animal studies. Unfortunately none, I literally mean “none” has been shown to be beneficial in clinical practice. The best measure right now is still the “time is brain” concept. The earlier and more complete one may open a blocked artery, the better the outcome in general helped by modern and “best supportive and nursing care”.

Inflammation has been seen and may play an important role in acute ischemic stroke. TNF-alpha is the “master regulator” of the inflammatory (immune) response in many organ systems. Autoimmune
diseases are caused by an overactive immune response. Etanercept (Enbrel) has been shown and approved by FDA to treat these diseases by inhibiting TNF-alpha. These diseases include rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Some authors hypothesized that tumor necrosis factor (TNF) may play a significant role in the mediation of inflammatory changes in brain ischemia. There were actually a number of studies published showing some efficacy. The American Academy of Neurology (AAN) reviewed the evidence of the data and released a report this week.

The final conclusion is: For patients with post stroke disability, the evidence is INSUFFICIENT to support or refute a benefit of Etanercept for the treatment of post stroke disability (Class IV evidence and level U recommendation).

Personally I believe it is another neuroprotective agent for stroke that will be forgotten very quickly by stroke neurologists.

-Forshing Lui MD

References:

LETTER FROM THE EDITOR

Readers of Neuro Newsletter,

I would like to personally and sincerely thank you for your time reading the wonderful newsletter you have before you. We were glad to share with you Neuro Newsletters’ educational and entertaining content. This is our last newsletter for the inaugural 2015-2016 school year. We will be restarting the newsletter in September, 2016, and hopefully showcase pieces from our new class of 2020!

I would also like to thank the writers that have submitted an article for our newsletter. It goes without saying that none of this would have been possible without your contributions. My hope is that this experience has been both a developing adventure as well as a vehicle to display your wonderful writing ability. I firmly believe that the people who have sent in articles are well on their way to becoming talented writers, and via their stories our society will further progress to shed light on the unknown.

The year of 2016 brings with it the start of the second year of our inaugural class here at California Northstate University, College of Medicine (CNUCOM) and with it we are one step further in our personal development as physicians. Our holistic approach seeks to advance not only our medical knowledge, but also our personality, perspective, and our aptitude for life-long learning. A wonderful mentor has once told me, “If I had to name one thing that makes a good physician…it would be to have an inquisitive mind...to have an insatiable thirst for knowledge, and perpetually work to seek out answers.” I hope that we, as future physicians, can take this to heart, and Neuro Newsletter can be a small cog in the machine as we become the best citizens on earth that we can be.

-Trevor Tsay