CLAE CONNECTIONS

MARCH 31, 2014; VOLUME 2: ISSUE 1

Canadian League Against Epilepsy

MESSAGE FROM THE PRESIDENT

INSIDE THIS ISSUE:

There is one quality common to all successful organizations - harnessing the strengths and individual attributes of its grass root membership. Our Canadian League is very fortunate to have close to 200 best minds in the field of epilepsy, all under one umbrella. It is now high time that each of us takes an active role in making our organization more successful. Other than networking during national and international conferences, I invite all of you to consider sharing your research and research ideas through the CLAE Newsletter. This newsletter as well as our website can provide a robust platform for collaboration between our basic scientists and clinicians to foster the best of projects from bench to bedside.

As most of you already know the upcoming biennial CLAE Meeting will be held in London Ontario from October 17 to 19, 2014. Dr Burneo and the Education committee has done a fantastic job in the organization and structuring of the Scientific Program. This would not have been possible without the outstanding submissions from our members. On a separate note the adjudication process for the fellowship award has now been completed, and Dr Burneo - our education director will soon announce the name of the successful candidate. I am grateful to UCB pharmaceuticals for providing the funding and support.

Any member interested in participating in epilepsy advocacy, fund raising or working on guideline development can feel free to contact me through email. I wish you all the best for 2014.

S Nizam Ahmed, MD, FRCPC

RISING STARS

In this issue we introduce Colin Josephson, MD, FRCPC

Dr. Colin Josephson is a Clinical Epilepsy Research Fellow and Master of Epidemiology student at the University of Calgary. Dr. Josephson received his B.Sc. (Hons) from Queen's University in 2000, his M.Sc. in Physiology from McGill University in 2003, and his M.D. at Dalhousie University in 2006. He began his residency in Neurology at Dalhousie University in 2006 but took a two-year leave of absence to pursue additional research training as a Clinical Research Fellow in Stroke at the University of Edinburgh between 2009-2011. His research area was focused on seizures and epilepsy outcomes in patients with intracranial vascular malformations of the brain. He subsequently returned and completed his residency with FRCP(C) certification in 2013.

He has been the recipient of many national and international awards. He received a 2010 European Stroke Conference Young Investigator of the Year for his work on the prospective 5 -year risk of seizures and epilepsy in patients with arteriovenous and cavernous malformations of the brain and the 2013 CLAE Mary Ann Lee Award for his systematic review and meta-analysis of selective amygdalohippocampectomy versus standard anterior temporal lobe surgery. He was the recipient of the inaugural 2013 Canadian Society of Clinical Neurophysiologists (CSCN) National Clinical Fellowship in Epilepsy and Electroencephalography and a 2013 Canadian Institutes of Health Research (CIHR) Fellowship. He was further selected as the recipient of the 2014 American Academy of Neurology/ American Epilepsy Society/American Brain Foundation/ Epilepsy Foundation Susan S. Spencer Clinical Research Fellowship in Epilepsy. To date, Dr. Josephson has published widely in journals such as JAMA, Lancet Neurology, BMJ, Neurology, and PLoS Medicine.

Dr. Josephson's major research interests are in evidence-based outcome studies and the methodology of clinical decision-making. He still retains interest in intracranial vascular malformations of the brain and continues to collaborate with his colleagues at the University of Edinburgh. Dr. Josephson's current research in Calgary, however, is focused on harnessing the potential of 'big data' for epilepsy. Under the supervision of Drs. Nathalie Jette and Samuel Wiebe, and in conjunction with Dr. Jordan Engbers and Mr. Mark Lowerison, data scientists and computational and bioinformatic specialists at the University of Calgary's Clinical Research Unit, Dr. Josephson's thesis work is dedicated to systematically developing methods of evaluating big data for the purposes of developing clinical decision rules (CDRs) for epilepsy.

CDRs have been empirically demonstrated to enhance provision of resources and prevent unnecessary exposure to risk. Current CDRs are developed using prospective datasets amalgamated for the express purpose of developing the specific rule. This can be cumbersome, resource intensive, and ultimately time-prohibitive. Using 'big data' is a means of mitigating these limitations. Big data are large existing datasets collected during the course of routine clinical care that are of a sufficient volume and variety to permit the discovery of new insights in an expedited fashion that cannot be appreciated from smaller datasets. A classic example is tracking and predicting geographical flu outbreaks in real-time using search terms entered into Google; a rapid, accurate, and efficient approach contrasted with conventional disease surveillance systems that have a 1-2 week delay. It is expected that large healthcare databases represent an even greater potential and are poised to revolutionise fields such as epilepsy that are chronically plagued by low statistical power.

If we can extract representative, population-based epilepsy cohorts from these datasets, and can demonstrate that subsequent analyses yield accurate and reliable information, then the potential exists to revolutionise care. Methods for developing CDRs from large pre-existing sources of data have yet to be explored. Once available, these techniques can be exploited to conduct concurrent derivation and validation studies to develop high quality, cost-effective CDRs designed to immediately improve care for patients with epilepsy.

Dr. Josephson is committed to pursuing a career as an epileptologist and clinician-scientist with a special interest in research methodology and, in particular, the evidence-based approach to developing clinical decision rules for the diagnosis and treatment of epilepsy. It is his desire to remain in Canada where he aims to improve the quality of life for those with epilepsy through daily clinical contact with patients and robust research collaborations with members of the CLAE. The CLAE, in particular, is a vibrant and integral network that will be key to consolidating this form of research. The CLAE is crucial to our work; the invaluable input of our colleagues will ensure optimal implementation of CDRs that have the widest impact and clinical acceptance both on a national and global scale.

'SUDEP Aware': A GLOBAL LEADER IN ADVOCACY

TAMZIN JEFFS

A global call for openness on sudden unexpected death in epilepsy (SUDEP) was declared at last summer's 30th International Epilepsy Congress in Montreal. Led by SUDEP Action UK, it was supported by epilepsy experts and organizations around the world. One such advocacy group is the Toronto-based non-profit, SUDEP Aware, co-founded by Tamzin Jeffs and Dr Elizabeth Donner to spearhead and promote the discussion of SUDEP in North America.

Dr Donner is a pediatric neurologist, specializing in epilepsy, at the Hospital for Sick Children in Toronto. Tamzin has lived with epilepsy for 13 years and lost her sister to SUDEP in 2007. Over the past six years the two have pooled their experience and knowledge to help facilitate the difficult, but highly necessary, conversation about SUDEP between doctors and families. The majority of people living with epilepsy are unaware of the possibility of SUDEP and the risk of it happening to them. They are also unaware that, despite its unknown cause, there are ways they can reduce their own risk – and that the first step begins with an open and frank conversation with their doctor.

To assist with this and encourage discussion, SUDEP Aware makes SUDEP information brochures freely available for download and distribution from its website, www.sudepaware.org. These are targeted towards different audiences, currently: people with epilepsy, teens and young adults, caregivers of children, people bereaved by epilepsy and healthcare providers. French and Spanish translations are also available.

Another helpful resource, SUDEP – continuing the Global Conversation (2011) is also freely available online. Evolving from an editorial partnership between SUDEP Action UK (formerly Epilepsy Bereaved), Epilepsy Australia and SUDEP Aware, it is an all-encompassing book that blends scientific research and family stories about SUDEP.

By way of its own example, SUDEP Aware strongly supports doctors and families working together to combat SUDEP risk. In 2012, in collaboration with seven other North American organizations, it co-founded a first-of-its-kind Partners Against Mortality in Epilepsy (PAME) conference. This three-day event brought together more than 250 clinicians, researchers and families for knowledge share and learning. Its success and value to all parties encouraged a second PAME, scheduled for this summer (June 19-22, 2014) in Minneapolis, Minnesota. Registration is available now, online, with early bird rates until April 3rd. To assist family attendance, SUDEP Aware provides a limited number of travel awards for bereaved families from Canada. Further information and the application form may be obtained through the contact details below.

The PAME conference helps families to better understand SUDEP, to not feel so alone in their grief, to realize the extent of research that is being carried out and the importance of their contribution to that research. Families can play an invaluable role in research participation. SUDEP Aware works to connect families with researchers or studies in need of study participants. Examples of current opportunities include: the Epilepsy Death Register (an online survey completed by family members); genetics research at Baylor College of Medicine (an autopsy blood sample and/or small piece of tissue); the North American SUDEP Registry ('phone interviews with family members, collection of medical data and optional tissue donation) and Hamilton Health Sciences investigation of the optimal way to inform patients of SUDEP ('phone or one-to-one interviews with family members and patients). Participation support is provided via SUDEP Aware's North America-wide toll-free line, as well as an introduction program that connects families with one another.

The majority of bereaved families who contact SUDEP Aware are devastated by the lack of prior warning about SUDEP. Increasingly, research is showing that people with epilepsy, their families and caregivers, do want to know more about SUDEP, their risk and how to reduce it. Finding ways to raise public awareness of SUDEP, the increased risk associated with ongoing seizures and the importance of treating seizures to help reduce risk, is paramount. This starts with proactively helping to spread the word and supporting the call for openness. There is much work to be done to bring greater understanding and prevention. Together we can make sure accurate, consistent messaging is heard and that more people join in the conversation.

To keep up to date with developments in the SUDEP community, sign up for SUDEP Aware's eNewsletter. For information or questions, contact Tamzin Jeffs at tcjeffs@sudepaware.org or on toll-free: 1-855-85-SUDEP (78337).

SUDEP Aware
Suite 350, 283 Danforth Avenue
Toronto
Ontario
M4K 1N2
www.sudepaware.org

SUDEP Aware

GENETICS & EPILEPSY: FELLOWS' CORNER

Cyrus Boelman

As a trainee graduating from the SickKids epilepsy program, I have seen an explosion in the current and fast-developing role of genetic evaluation in patients with epilepsy. These evaluations routinely now yield results that improve the quality of life for patients with epilepsy and their families. I was invited to reflect on the future role of genetics in epilepsy given my experience as a clinical and research trainee.

The future is awesome. We are just scratching the surface in understanding how specific genes, gene families and gene expression influence a person's epilepsy. It was only a decade ago that all we had was expensive single-gene testing to nail down a diagnosis such as Dravet or Retts syndrome. In another decade, neurologists will have grown alongside this avalanche of genetics much like we did with the availability of MRI studies two decades ago.

It will not be long before whole exome sequencing (WES) is as commonplace in the clinic as DNA microarrays, which in 7 years went from being a $1000 out-of-country test to being a 2-week $150 in-hospital test. WES will enter the clinic in 2-3 years at the latest and the results will take 5 years to be properly embraced by clinicians. In the meantime, we already do targeted broad genetic panel screening, which uses the same next-generation sequencing technology as WES. Commercial companies charge about $4500 for these panel services to ensure good reporting of upwards of 350 epilepsy-associated genes, but the actual cost of WES today is only about $1500. Sequencing the first human genome cost $1 billion and took a decade, but whole genome sequencing (WGS) can be done now for $2500 and analyzed in a few weeks. In fact, WGS will likely supplant clinical WES within the decade.

There should not be a fear that our genotyping of epilepsy patients will get ahead of our understanding of the results. It already has. I often read genetic counseling letters from 2004 that state the microarray abnormality detected is of unclear significance and the family should re-contact the clinic in 3-5 years, as new information may be available. In fact, to understand the meaning of what we are already receiving as results, we need to be testing even more patients. We need the numbers.

My skeptical view is that genetics research that lumps more than splits patients due to a lack of robust patient characterization will get stuck. For example, it is reasonable to start with a group of cryptogenic epileptic encephalopathy patients to grab the low-hanging fruit but epilepsy is too complex a disorder to yield much more without more specific clinical phenotypes. There are 20,000 genes in our DNA so to determine which ones underlie the specific features that differentiate epilepsy syndromes will require large syndrome-specific cohorts. Consequently, more patients need to be recruited into the large genetics studies underway. With the Genome Canada project, led by Drs. Minassian, Cossette & Michaud, we hope to discover genes underlying epilepsy and genes that predict pharmacoresponsiveness by sequencing between 3000-4000 genomes.

A key point for the future of epilepsy genetics is the engagement of clinicians. Neurologists need to quarterback the results of EEGs, imaging, neuropsychological assessment, pathology and phamaracoresponsiveness, and then present cohorts of patients to genetics experts as specific phenotypes to be genotyped. How best to do this is the challenge.

My hope in Canada is that centres will not just publish their cases and cohorts of different genotypes and phenotypes but that they will invest in information technology to develop a national epilepsy genome, whereby rare presentations can be brought together to make up the numbers needed to facilitate gene discovery and improve interpretation. Such national registries exist in other areas of neurology, such as stroke and multiple sclerosis, and there is a somewhat national microarray database established by cytogenetics researchers.

The first step will be to build the infrastructure for a database, for example using RedCap, a robust web-based database program championed by most research institutes. The next step is to structure it with ontological phenotyping..This means having common data elements for each area relevant to an epilepsy patient history, such as medication, EEG and MRI data. With ontology, the data can be as detailed as the person making the observation is expert to make it. For example, I might be able to identify hippocampal asymmetry but a neuroradiologist can go further to observe hippocampal malrotation.

The future of epilepsy genetics will be a flood of information. Neurologists will not control the floodgates but we will be able to channel it to improve the quality of life for our patients through collaboration. Eventually, a national epilepsy genome will provide valuable phenotype-genotype correlations that will guide management and lead to better treatments, and maybe even prevention, in our patients with epilepsy.

Dr. Cyrus Boelman is currently the chief epilepsy fellow at The Hospital for Sick Children in Toronto, where he also completed his paediatric neurology residency in 2012. His interest in epilepsy genetics has emerged from his time training with Dr. Berge Minassian in Toronto and Dr. Ingrid Scheffer in Melbourne. Currently, beyond his clinical duties, he is the Toronto site director of the national Genome Canada-funded PreGene project, based in Montreal & Toronto. He hails from Vancouver where he will return as a staff epileptologist at BC Children's Hospital in 2015.

Canadian League Against Epilepsy

The Canadian League Against Epilepsy is an organization of medical and basic sciences professionals including physicians, basic scientists, nurses, neuropsychologists, neuroradiologists, students and other healthcare professionals.

NOTE FROM YOUR EDITOR

The next issue of CLAE Newsletter (June 2014) will include meaningful and relevant information to CLAE members, including but not limited to the following:

1. CLAE Stars: A member who has received local, national or international recognition for his/her research, teaching, innovation or advocacy.

2. Innovative new programs and services (clinical, research or advocacy). These include, but are not restricted to: new major regional/ institutional or provincial clinical programs, new research themes, platforms, consortium and networks, outreach programs in vulnerable/ marginalized communities, innovative educational programs and advocacy initiatives/projects.

3. Major publications by Canadians in the field of epilepsy during the last six months.

4. Information on epilepsy meetings, and epilepsy related social events.

5. Information on recruitment of patients for research studies and opportunities for research, educational and clinical collaboration.

6. Success and success stories in major grant competitions.

7. Colleagues we recently lost /an In Memorium section.

If you are interested in contributing and providing content to the CLAE Newsletter, please contact Rajesh Ramachandran Nair (rnair@mcmaster.ca) before May 15, 2014.

Thank you.

Rajesh RamachandranNair, MD, FRCPC

Editor-in-Chief, CLAE Connections

EDITOR'S PICK: NOTABLE PUBLICATIONS FROM CANADA IN 2014

1. Is rapid withdrawal of anti-epileptic drug therapy during video EEG monitoring safe and efficacious? Rizvi SA, Hernandez-Ronquillo L, Wu A, Téllez Zenteno JF. Epilepsy Res. 2014 Feb 4. doi: 10.1016/j.eplepsyres.2014.01.022.

2. Rolandic epilepsy has little effect on adult life 30 years later: A population-based study. Camfield CS, Camfield PR. Neurology. 2014 Apr 1;82(13):1162-6.

3. Influence of seizures on stroke outcomes: A large multicenter study. Huang CW, Saposnik G, Fang J, Steven DA, Burneo JG. Neurology. 2014 Mar 4;82(9):768 -76.

UPCOMING PROGRAMS

The next CLAE Biennial Meeting will be held in London, Ontario from October 17-19, 2014. This would be a joint meeting with the Canadian Epilepsy Association. Please mark your calendars.