Sturge-Weber syndrome through the Brain Vascular Malformation Consortium: What we have learned, future promise and how you can help

Anne Comi, MD
Associate Professor
Neurology and Pediatrics
Director
Hunter Nelson Sturge-Weber Center
Kennedy Krieger Institute
Johns Hopkins Medicine

No commercial conflicts of interest to declare.
Off-label Uses of drugs will be discussed.
Today’s Talk

- Define the Brain Vascular Malformation Consortium and its Mission
- Describe its SWS research to date and the results
- Relate the importance of these findings and some of the future work likely to build on these results
- Provide ways in which patients and families can speed the progress of research and the development of new and better treatment strategies
Acknowledgements

- **Clinical Research: Kennedy Krieger Institute and Johns Hopkins Medicine**
  - **Current**
    - Joshua Ewen
    - Balaji Lakshmanan
    - Nathan Crone
    - Doris Lin
    - Eboni Lance
  - **Hunter Nelson Sturge-Weber Center**
    - Emily Germaine-Lee – KKI Pediatric Endocrinology
    - Stacy Suskauer – KKI Pediatric Med. Rehab
    - Andy Zabel – KKI Pediatric Neuropsychology
    - Bernard Cohen – JHH Pediatric Dermatology
    - Eric Kossoff – JHH Pediatric Epilepsy
    - Henry Jampel – JHH Wilmer Eye Institute
    - Kira Lanier – KKI Research Assistant
    - Cathy Bachur – KKI Research Assistant

- **Past**
  - Laura Hatfield and Adit Sreenivasan
  - Jennifer Reeseman
  - Mihee Bay

- **Laboratory Research:**
  - Jonathan Pevsner
    - Larry Frelin
    - Matt Shirley
    - Joe Baugher
  - Comi Lab
    - Libby Shotwell
    - Tatyana Verina
  - Marsha Moses (Boston)
  - Doug Marchuk (Duke)

- **Funding from:**
  - Hunter’s Dream for a Cure
  - Private Donors
  - BVMC and National Institutes of Health
  - Celebrate Hope Foundation
Goals of the BVMC

- To carry out multi-centered research better understand, diagnose and treat
  - Cavernous Capillary Malformation
  - Sturge-Weber syndrome
  - Hereditary Hemorrhagic Telangiectasia
Aims of Sturge-Weber syndrome Project

- Aim 1: Develop a SWS National De-identified Database
- Aim 2: To develop new vascular urine biomarkers
- Aim 3: To discover the somatic mutation causing SWS

- Pilot project: SWS Biomarker development
- Training Project: Aspirin and Stimulant Experience at KKI center
Aim 1: National Database

- De-identified Database housed at University of South Florida
- SWF assisting in screening-subjects must have SWS brain involvement shown on MRI
- Consent and questionnaire can be done over phone OR at center visit
- Goal to gather data for study and for future research
Participating Centers

- Hunter Nelson Sturge-Webber Center at the Kennedy Krieger Institute/ Johns Hopkins (Comi)
- Wayne State University (Chugani)
- Nationwide Children’s Hospital (Lo)
- Thomas Jefferson University – Wills Eye Institute (Levin)
- Baylor College of Medicine, Texas Children’s Hospital (Wilfong)
National Database: Future Directions

- Working with the participating centers and PIs to summarize and publish data so far
- Current data will serve as pilot data for the renewal of the Consortium Grant application
- This database can be used in the future to recruit for studies.
Aim 2: Urine SWS biomarkers study

- Variability in severity and responses in SWS a challenge in treatment
  - A good biomarker should be safe to do, not very expensive, and should be predictive of disease severity, progression or response
  - A good biomarker is helpful for clinical trials and in clinical care of patients
  - We collected urines and SWS neurologic scores from the same visits and compared to controls (KKI center only).
Urine Blood Vessel biomarkers in SWS: Recently published data

- MMP2 and MMP9 more likely to be urine of children and adults with SWS
- MMP9 levels were higher in females with SWS than in males
- Higher MMPs were associated with worse neurologic scores at the time of the clinical visit
- Higher bFGF levels were associated with improved clinical outcome a year after sample collection.

Urine SWS Biomarkers: Future directions

- We are continuing to study these biomarkers over time and relate them to the medication the subjects take and their neurologic scores.
- We will propose in renewal to continue studying these biomarkers as we take next steps towards clinical trials.
Pilot Study: Other SWS biomarkers

- Quantitative EEG
- Transcranial doppler
- Medical rehabilitation scales
- Optical coherence tomography
Future of SWS Biomarkers

- Biomarkers will have an important role in future clinical trials.
- Enable us to have primary and secondary endpoints to measure and determine effectiveness of treatment.
- May become ways of safely monitoring patient clinical status and treatment responses.
Aim 3: Evidence for a somatic mutation in SWS

- Localized asymmetric abnormalities in vascular development of brain, eye and skin (*Happle, J Am Acad Derm, 1987*)
- Report of one of two monozygotic twins with SWS (*Pedailles, Eur Neurol, 1993*)
- Increased fibronectin expression in SWS PWS fibroblasts (*Comi et al, Ped Res 2003*)
- Chromosomal abnormalities reported in 2 fibroblast cultures from SWS affected regions (*Huq et al, Neurology 2002*)

(Sabin FR. Carnegie Contrib Embryol, 1917)
Drs. Marchuk, Comi, and Pevsner contributed equally to this article.
Thoughts

- The somatic mosaic mutation in GNAQ results in hyper-activation of pathways important in many cell functions.
- A great deal is known about these pathways.
- The same mutation, occurring in a different cell type, at a different time in development, results in a vascular malformation instead of a tumor.
How can you help?

- National De-identified database: We urgently need participants to contribute to the national de-identified database. Please see SWF staff or myself if you are interested.

- Participate in research where possible.

- Tissue donation is critical. We know the gene, but still need tissue to answer really important next questions.

- Donate. Have a fundraiser. Every donation counts and the need is great!
The Brain Vascular Malformation Consortium has made significant advances in our understanding of SWS and laying the foundation for clinical trials and new future treatments.

Our multi-centered consortium will lay the foundation for future clinical trials.

New promising neurologic biomarkers are currently being developed.

With the discovery of the somatic mutation causing SWS we are standing at the dawn of a new day for SWS—the promise is great...

….. and our work continues.