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Report on the Sixth Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) Symposium, “Anesthesia and Neurodevelopment in Children”

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Abstract

On April 14–15, 2018, the Sixth Biennial Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) Symposium convened at Columbia University Medical Center and New York Presbyterian/Morgan Stanley Children’s Hospital of New York. Since its inception over 10 years ago, the PANDA Symposium has served as a key forum for clinicians, researchers, and other major stakeholders to gather and review the current state of pre-clinical and clinical research related to anesthetic neurotoxicity in the developing brain. It has also served as an important venue for participants to gain insight and leverage support from various public and private regulatory bodies. Goals of this year’s meeting included assessments of how current knowledge has evolved, endeavors to develop common outcome measures, and formulations of future directions for research and policy. The Symposium program highlighted a diverse body of cutting-edge work, from results of pre-clinical and clinical studies to updates in clinical practice and policymaking.

Keywords

symposium; neurodevelopment; anesthetic neurotoxicity; pediatric anesthesia

PROCEEDINGS OF THE SIXTH BIENNIAL SYMPOSIUM ON ANESTHESIA AND NEURODEVELOPMENT IN CHILDREN

On April 14–15, 2018, the Sixth Biennial Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) Symposium convened at Columbia University Medical Center and New York Presbyterian/Morgan Stanley Children’s Hospital of New York. The symposium began with opening remarks from Dr. Guohua Li, the Symposium host and program organizer, Dr. Ansgar Brambrink, Chairman of the Department of Anesthesiology at Columbia University Medical Center, and Dr. Lena S. Sun, the Medical Director of SmartTots, Principal Investigator of the PANDA study, and Chief of the Division of Pediatric Anesthesia at Columbia University Medical Center. There were a total of 113 registrants, representing various academic institutions across the United States, Europe, and Canada and key federal agencies, such as the National Institutes of Health (NIH) and the Food and Drug

Administration (FDA) (Table 1). As in past years, the Symposium was co-sponsored by SmartTots (the public-private partnership between the FDA and the International Anesthesia Research Society), New York Presbyterian/Morgan Stanley Children's Hospital, and the Department of Anesthesiology at Columbia University Medical Center.

REPORT OF THE OUTCOMES WORKSHOP SEPTEMBER 2017

The morning session began with a summary of the Outcomes Workshop sponsored by SmartTots in September 2017 and was moderated by Cynthia Salorio, Ph.D., Director of Rehabilitation Outcomes and Related Research and Clinical Neuropsychologist at the Kennedy Krieger Institute. Details on this session can be found in the article entitled, "September Outcomes Workshop 2017: Notes from a round table discussion about outcome measures" in the current issue.¹ Tracy King, M.D., M.P.H., Medical Officer at the National Institute of Child Health and Human Development, led off the session and reviewed different types of clinical outcome measurements and discussed the importance of agreeing on common outcome measures that can be used across an area of research. She presented examples of research groups that have pursued common outcome measure efforts. These included investigators that study Fragile X syndrome and traumatic brain injury as well as some consortia in the Rare Disease Clinical Research Network.² She also presented information about the NIH Toolbox, a set of tablet-based neurobehavioral measurements that assess cognitive, emotional, sensory, and motor functions designed for use across a wide domain of studies.³ Her key recommendation to the pediatric anesthesia community was to consider convening a process to develop common outcome measures for use across future studies of the neurodevelopmental impacts of anesthesia exposure.

The second speaker, Jack M. Fletcher, Ph.D., Chairman of the Department of Psychology at the University of Houston, spoke about the many challenges of neurodevelopmental outcomes research. He highlighted the inherent complexity of human development and the difficulty in attempting to detect faint signals within a complicated gene-environment synergy. He recommended defining clear outcomes of interest and a neurotoxicity phenotype, as well as thinking critically about how and when to assess these outcomes. Specifically, he emphasized the importance of performing comprehensive assessments by looking at multiple neurodevelopmental endpoints. The next speaker, Dr. Salorio, continued the discussion about when and how to best measure outcomes during neurodevelopment. Participants agreed that it will be critical to apply results from pre-clinical studies, particularly those exploring neuronal biomarkers and neuroimaging correlates, to inform and effectively design future clinical studies.

LESSONS LEARNED: NEUROIMAGING STUDIES AND NEURODEVELOPMENTAL OUTCOMES RESEARCH

The next session highlighted pioneering research efforts attempting to link neuroimaging findings to neurodevelopmental outcomes. This session was moderated by Virginia Rauh, Sc.D., Professor of Population and Family Health at Columbia University Medical Center and Director of the Child, Adolescent and Family Health Certificate. Details on this session

can be found in the article entitled, “Using neuroimaging to study the effects of pain, analgesia, and anesthesia on brain development” in the current issue.⁴

Ashok Panigrahy, M.D., Radiologist-In-Chief of the Department of Pediatric Radiology at the Children’s Hospital of Pittsburgh (of the University of Pittsburgh School of Medicine), presented his research investigating the impact of congenital heart disease on large-scale brain networks in relation to neurobehavioral outcomes.⁵ He described the approach of measuring global and regional cerebral blood flow and water diffusion on brain magnetic resonance imaging (MRI) as a surrogate for clinical neurologic outcomes.⁶ Currently, a randomized clinical trial studying the neuroprotective effects of dexmedetomidine in infant cardiac surgery is underway and investigators are utilizing advanced MRI computational techniques to look at neural network connectivity and link those findings to neurodevelopmental outcomes.

The next speaker, Dr. Emily Tam, M.D., F.R.C.P., M.A.S., Pediatric Neurologist and Associate Scientist at The Hospital for Sick Children in Toronto, described her research which focuses on the use of neuroimaging techniques to determine the neurodevelopmental consequences of pain and analgesia in preterm newborns. She explained that pain appears to affect thalamic development negatively in this population,⁷ analgesia with morphine may impair cerebellar growth,⁸ and anxiolysis or sedation with midazolam may impair hippocampal growth.⁹ She further explained that it is challenging to tease out the effects of pain versus analgesia on neurodevelopmental outcomes.

ENGAGING STAKEHOLDERS FOR RESEARCH

Details of this session can be found in the articles entitled, “Engaging stakeholders to promote safe anesthesia and sedation care in young children”¹⁰ and “Reaching parents through an online community”¹¹ in the current issue. Anne Boat, M.D., Associate Professor of Anesthesiology in the Department of Anesthesia at Cincinnati Children’s Hospital Medical Center, began the session by presenting the novel implementation of an online platform called, “The Family Talkboard”, to engage patients and families at Cincinnati’s Children’s Hospital. She explained that the platform serves as an interactive forum for families to engage in moderator-mediated dialogue with other members and with the medical community. It is uniquely accessible and flexible, which enables a wide outreach. The Talkboard has a growing membership (over 200 members) and has been used successfully in quality improvement/outcomes research intended to improve waiting room experiences, patient and family needs in the hospital, and provider communication.

Next, Robert H. Dworkin, Ph.D., Professor in the Department of Anesthesiology and Perioperative Medicine and Research, School of Medicine and Dentistry, University of Rochester Medical Center and Director of Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), discussed the development of ACTTION as a public-private partnership with the FDA. He described the mission of ACTTION in promoting innovative activities to expedite the discovery and development of novel therapeutics and coordinating collaborations amongst stakeholders.¹² Key learning points from his experiences with ACTTION included prioritizing initiatives

that lead to meaningful impact for a relatively modest cost, obtaining early and frequent input from stakeholders, and engaging and mentoring junior investigators to advance future research.

Next, Dr. Tracy King provided an update on research changes to NIH clinical trials policies. These changes were driven largely by data showing low rates of publication of results from NIH-funded clinical trials. NIH clinical trial reforms include changes to the NIH definition of a clinical trial, changes to NIH funding opportunity announcements, and new requirements for dissemination of clinical trial information through timely registration on clinicaltrials.gov.¹³ They also include the expectation that all new proposals for multi-site studies involving human subjects will use a single IRB for all domestic sites.¹⁴

The session finished with a presentation by Sharon Hertz, M.D., Director of the Division of Anesthesia, Analgesia, and Addiction Products within the U.S. FDA, on perspectives from the FDA. Dr. Hertz explained that patient engagement at the FDA remains a high priority. The 21st Century Cures Act builds upon the FDA's ongoing work, which incorporates patient perspectives into the development of drugs. Multiple initiatives and groups such as the Patient Focused Drug Development and the Patient Representative Program seek to further this cause.

ANESTHESIA EXPOSURE IN CHILDREN DURING SURGICAL AND NON-SURGICAL PROCEDURES

Details on this session can be found in the article entitled, "Anesthesia exposure in children: Practitioners respond to the 2016 FDA drug safety communication" in the current issue.¹⁵ Constance Houck, M.D., F.A.A.P., Associate Professor in Anesthesia at Harvard Medical School and Clinical Director of the Surgical Hospitalist Program at Boston Children's Hospital, moderated this session and commenced by reviewing the FDA warning labels that have recently been added to anesthetics and sedatives. In December 2016, the FDA issued a warning that highlighted the possible neurodevelopmental effects of repeated exposures or lengthy anesthesia for children younger than 3 years of age with a specific advisory for pregnant women during the third trimester of gestation to seek medical counseling. In April 2017, the FDA specifically added label information, stating that animal studies demonstrated neurotoxicity following exposure to general anesthetic agents and that healthcare professionals should follow their usual practice of parent/patient counseling. As part of this session, invited panel discussants were specifically asked to comment on how these FDA warning labels have changed their practice, how they currently counsel their patients and families, and whether any official guidelines have been proposed or discussed by their representative surgical societies. Panel discussants, representing a wide range of fields, included: Dr. Thomas A. Imahiyerobo, Craniofacial Surgeon and Plastic Surgeon at New York Presbyterian Hospital/Columbia University Medical Center, Dr. William Middlesworth, Pediatric Surgeon at New York Presbyterian Hospital/Columbia University Medical Center, Dr. Lynne R. Ferrari, Pediatric Anesthesiologist at Boston Children's Hospital, Dr. Dena Goffman, Obstetrician at New York Presbyterian Hospital/Columbia University Medical Center, Dr. Joshua Hyman, Pediatric Orthopedic Surgeon at New York

Presbyterian Hospital/Columbia University Medical Center, and Dr. Grace S. Hyun, Pediatric Urologist at NYU Langone Hospital-Brooklyn. Pediatric surgeons stated that their peer group is generally aware of the concept of anesthetic-mediated neurotoxicity, and they have noticed heightened awareness and concern expressed by parents. With regard to preoperative counseling, surgeons stated that they usually discuss the definitive evidence of toxicity found in various animal models, but highlight that the implications for clinical practice remain unclear. There was consensus that the timing of non-elective or semi-elective procedures has not significantly changed, although most practitioners were amenable to postponing completely elective surgery.

Although the majority of surgical societies have avoided making official statements or recommendations following the issuance of the FDA warning, the American College of Obstetrics and Gynecologists (ACOG) released a notable statement in conjunction with the American Society of Anesthesiology (ASA) in 2017.¹⁶ In this statement, both the ACOG and ASA underscored the fact that none of the currently used anesthetic agents has ever been shown to have teratogenic effects in humans when used at standard concentrations at any gestational age. Furthermore, they stressed that pregnant women should never be denied necessary surgery, and advised that, if possible, non-urgent surgery should be performed during the second trimester. A lively discussion ensued where panelists and attendees had the opportunity to debate the optimal timing of surgical procedures.

OUTCOMES RESEARCH IN VULNERABLE PEDIATRIC POPULATIONS

Day 2 of the Symposium began with a discussion of outcomes in vulnerable populations. Sulpicio Soriano, M.D., BCH Endowed Chair in Pediatric Neuroanesthesia, Professor in Anesthesia at Harvard Medical School, served as the moderator for this session. Details on this session can be found in the article entitled, “Outcomes research in vulnerable pediatric populations” in the current issue.¹⁷

Thomas G. Diacovo, M.D., Chief of the Division of Newborn Medicine at Children’s Hospital of Pittsburgh of UPMC and Director of Neonatal Cardiovascular Research at the Heart Institute, discussed the paucity of overall research and clinical trials within the neonatal population. He reviewed the various challenges of conducting neonatal research from the viewpoint of the FDA. He provided details about The International Neonatal Consortium, which was launched in May 2015, to form a predictable regulatory path for evaluating the safety and efficacy of therapies for neonates.¹⁸

The following speaker, Johanna Calderon, Ph.D., Staff Scientist and Instructor at Harvard Medical School, spoke about her research investigating long-term neurodevelopmental outcomes in children with congenital heart disease.^{19, 20} She explained that neurodevelopmental and psychiatric issues have emerged as the most common long-term comorbidities in this vulnerable population, and there appears to be a characteristic, “neurodevelopmental signature” associated with congenital heart disease. Caleb Ing, M.D., Herbert Irving Assistant Professor of Anesthesiology (in Epidemiology) at Columbia University Medical Center, was the next discussant. He presented his research findings exploring neurodevelopmental outcomes in anesthesia-exposed twins using a Medicaid

dataset. Using propensity scores matching exposed with unexposed children across four different types of surgical procedures, Dr. Ing found that there was an increased risk of developmental delay and behavioral disorders in exposed children regardless of age of exposure. However, the magnitude of this risk was not statistically different.²¹ He commented on the need to expand study subjects to include families who are socioeconomically disadvantaged, as they may represent a more vulnerable population with a less favorable neurodevelopmental trajectory.

The final speaker in this session was Mary Woods Byrne, Ph.D., C.P.N.P., F.A.A.N, Stone Foundation and Elise D. Fish Professor of Health Care for the Underserved (in Nursing) and Professor of Anesthesiological Sciences (in Anesthesiology) at Columbia University Medical Center. She spoke about her extensive experiences working with a unique, vulnerable population of incarcerated mothers and their children. She described that she has successfully developed ethnographic, cross-sectional, and longitudinal studies looking at child developmental and parental outcomes.²² Dr. Byrne summarized the challenges of conducting a clinical research program within a non-healthcare/prison setting.²³ Furthermore, she spoke about the concept of a “therapeutic nursery” within the prison environment and the importance of developing alternative community sentencing and services.

DEVELOPMENTAL NEUROTOXICITY RESEARCH 2018

Dr. Guohua Li moderated the session on developmental neurotoxicity research. More details can be found in the article entitled, “Developmental neurotoxicity research: An update” in the current issue.²⁴ Dr. Jenny Waspe proposed the use of the Adverse Outcome Pathways (AOPs) methodology when studying anesthetic developmental neurotoxicity. She explained that this approach has been used with success when evaluating other types of toxicologic exposures.²⁵ Dr. Ansgar Brambrink subsequently shared his work with neonatal macaques and highlighted the nonhuman primate model as a valuable one in which to study anesthetic neurotoxicity. His recent work has shown that a 3-hour isoflurane exposure triggered apoptotic cell death in neonatal macaque brain.²⁶

MODERATED POSTER SESSIONS

Details about the moderated poster session can be found in the two summary articles in the current issue.^{27, 28} The moderated poster sessions occurred at the conclusion of the Symposium. The first session featured results from recent clinical research. Dr. Jamie Sinton shared her data from a retrospective review evaluating the indications and diagnostic yield for brain MRI with anesthesia in children under 3 years of age. Dr. Tom Hansen provided an overview of his systematic review of the neurocognitive outcomes used in studies of pediatric anesthesia neurotoxicity. Dr. Ruth Graham discussed the application of a stress-diathesis model to children undergoing anesthesia and surgery.

In the second poster session, researchers presented findings from pre-clinical studies related to anesthetic neurotoxicity. Dr. Philip Morgan shared his work on high-throughput screening for inhibitors of anesthetic-induced neurotoxicity in the *Caenorhabditis elegans* model. He

also discussed the clinical significance of studying anesthesia-induced neurotoxicity in mice as an experimental paradigm. Dr. Philip Adams presented his research evaluating the effect of intraoperative isoflurane exposure and dexmedetomidine on frontal lobe connectivity in neonates with congenital heart disease. Dr. Jing Xu presented her findings noting that early postnatal exposure to general anesthesia disrupts oligodendrocyte development and myelin formation in the hippocampus. The following presenter, Dr. Jimcy Platholi, shared his research on isoflurane-mediated inhibition of brain-derived neurotrophic factor release, leading to reduced synaptic vesicle exocytosis and dendritic spine loss. Dr. Sulpicio Soriano summarized his investigation, showing that ketamine modulates disc1-gsk-3 β interaction in a rat model of anesthetic-induced developmental neuronal apoptosis. Finally, Dr. Pratheeban Nambyiah presented a new approach to investigating anesthesia-induced neurotoxicity by way of quantitative behavioral analysis of *C. elegans* during development.

Summary

The Sixth PANDA Symposium was another successful gathering of clinicians, researchers, and stakeholders. The two-day meeting provided a platform for discussion, debate, and reflection on anesthesia-induced neurotoxicity in the developing brain. Attendees were able to share up-to-date research findings and engage in valuable dialogue with each other. All participants agreed that future endeavors should focus on advances in pre-clinical science and meaningful translation into the clinical realm, so that practitioners can ensure the safe and effective anesthesia-related care of infants and children.

Acknowledgments

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Table 1.

List of institutions & agencies represented at the 2018 Sixth PANDA Symposium

Boston Children's Hospital
Children Hospital of Philadelphia
Cincinnati Children's Hospital Medical Center
Columbia University Medical Center/New York Presbyterian Hospital
Cornell University/New York Presbyterian Hospital
Emory University Hospital
Health Sciences Centre – Winnipeg
Icahn School of Medicine at Mount Sinai-New York City
International Anesthesia Research Society
Istituto Giannina Gaslini
John Hopkins Medical Institution
Kennedy Krieger Institution
Montefiore Medical Center
National Institutes of Health
New York University Medical Center
Seattle Children's Hospital
The Hospital for Sick Children (SickKids)
Texas Children's Hospital
University of California San Francisco
University of Houston
University of Iowa University of Kentucky
University of Pittsburgh Medical Center
University of Rochester Medical Center
University of Texas Southwestern Medical Center
University of Wisconsin
U.S. Federal Drug Administration