Report of a workshop on research gaps in the treatment of cerebral palsy

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ABSTRACT

Cerebral palsy (CP) is heterogeneous in etiology and manifestations, making research into relevant therapies difficult and limiting the generalizability of the results. We report here on the NIH CP symposium, where stakeholders from academic, clinical, regulatory, and advocacy backgrounds discussed the major challenges and needs for moving forward with clinical research in CP, and outlined priorities and action items. New information is constantly generated through research into pathogenesis and etiology. Clinical research and new therapeutic approaches need to keep pace, through large data registry integration and new research designs. Development of standardized data collection, increasing academic focus on CP research, and iterative approaches to treatment throughout the patients' lives, have all been identified as areas of focus. The workshop identified critical gaps and areas of focus to increase the evidence base for therapeutic approaches to determine which treatments work best for which patients in the near future. These include consolidation and optimization of databases and registries, updates to the research methodology, and better integration of resources and stakeholders. ***Neurology*®** **2016;87:1293–1298**

GLOSSARY

CDE = common data element; **CP** = cerebral palsy; **CPRN** = Cerebral Palsy Research Network; **NINDS** = National Institute of Neurological Disorders and Stroke.

DEFINING THE PROBLEM Cerebral palsy (CP) is a group of neurologic disorders of motor control with onset early in development and persistence throughout the lifespan. CP is the most common cause of motor disability in childhood, with an incidence of 2 to 3 per 1,000 live births, occurring 20 to 30 times more frequently in premature or low-birth-weight infants.[1] These disturbances of movement and posture cause activity limitations.[2] Those activity limitations resulting from spinal or neuromuscular disorders are excluded from the diagnosis. Various etiologies can cause the CP clinical spectrum but all have a disruption of motor control in common. In addition to prematurity, other known etiologies include developmental defects of the brain, perinatal stroke, hypoxia, shock, and fetal or neonatal inflammation/infection. However, CP may also occur in low-risk children for whom there is no obvious etiology or risk factor. CP is often accompanied by comorbidities such as seizures, communication deficits, hearing and vision deficits, and intellectual disability. There is a wide spectrum of functional outcomes from normal educational, career, and social activities to complete disability and dependence.

An upper age limit for acquired pathology in the brain leading to CP is not absolute, but the onset of symptoms and the diagnosis are generally expected to occur by the age of 2. Given the heterogeneity in terms of etiology, pathology, clinical manifestations, and progression, it is best to consider CP as a collection of conditions rather than one uniform entity for developing treatment guidelines or conducting research on potential therapies.

To address pressing research challenges, the National Institute of Neurological Disorders and Stroke (NINDS) organized a workshop with the main goal of discussing research needed to determine best treatments for individuals with varying forms of CP and what resources are needed to fill critical gaps in knowledge and clinical practice. The 2-day meeting was cosponsored by the American Academy for Cerebral Palsy and Developmental Medicine, the Cerebral Palsy Foundation, Reaching for the Stars, and the Eunice Kennedy Shriver

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National Institute of Child Health and Human Development, and took place at the NIH in Bethesda, MD, in November 2014. The meeting convened more than 100 stakeholders in CP, including leading researchers on CP prevention and treatment, clinicians, project and data managers, individuals with CP, caregivers, advocacy organizations, and researchers and staff from NIH and the Centers for Disease Control and Prevention. We summarize here the major discussion themes and outcomes from this meeting.

VARIATIONS IN CLINICAL PRACTICE AND THE NEED FOR STANDARDIZATION The workshop highlighted the substantial variation in interventions prescribed for CP, and the lack of evidence for many of those interventions. The state of the science for efficacy of interventions in CP based on available data from randomized clinical trials[3] demonstrates few treatments with strong and consistent evidence in this population to improve functioning in childhood, or across the lifespan. There is no shortage of potential treatment options in the literature, but evidence concerning subgroup treatment responses, optimal timing, and sequencing of interventions, as well as the dosing and frequency, is often lacking.

One potential source of variability insufficiently accounted for in existing research is the heterogeneity of CP, which likely obscures the interpretation of data on treatment responses from mixed patient groups. For example, the differential response to therapeutic cooling in the neonate may well be related to differences in the etiology of an initial encephalopathic event.[4] It is therefore difficult for the family and the treating physician to determine which treatment fits best to an individual child, given each child's unique developmental goals and trajectories. There is a critical need for greater precision in diagnosis and treatment at the level of the individual with CP in order to develop best-practice approaches for providing comprehensive, optimal care from infancy through adulthood.

Another recognized clinical and research challenge in CP is the frequent lag in the diagnosis of CP, which affects the efficacy of any interventions best implemented early in infancy.[5] The ability to establish the diagnosis earlier, starting in infancy, was an agreed priority. Therefore, there is an urgent need for research in biomarkers and more reliable and feasible early clinimetric measures.

MECHANISMS Prematurity is a major cause of CP[6]; at least a third of individuals with CP are born prematurely. The insult common to all CP syndromes is a physical injury to the motor control pathways.

While the classic understanding of CP is as a nonprogressive injury, developmental dynamics has a major role in the clinical presentation and impact on potential therapeutic targets. As such, neuroplasticity is an underresearched opportunity for treating CP. While the potential for neuroplasticity involving repair of injury and recovery of function is highest early in life, evidence suggests that it has important roles in the adolescent and adult brain as well. Furthermore, even if starting with a static injury, the manifestations will change as the child grows, prompting the need for iterative changes to the therapeutic approaches.

NATURAL HISTORY AND AGE-SPECIFIC THERAPY Treatment goals and targets for those with CP vary across different life stages.

Prenatal and perinatal periods. Some progress has been made in CP prevention by more effective monitoring and treatment of maternal infection and the resultant inflammatory processes during the prenatal and perinatal periods.[7] Greater success in lowering the rates of prematurity may well be the single most effective strategy for reducing incidence of CP. Significant advances have been made in preventing specific causes of CP through public health efforts such as maternal rubella vaccinations, handwashing campaigns, in vitro fertilization transfer limits, and Rh factor screening in pregnancy and kernicterus prevention. Other treatments directed at reducing the risk or severity of CP in the infant born prematurely include antenatal steroids, magnesium sulfate before preterm delivery, caffeine, and therapeutic cooling in neonatal encephalopathy. Studies show that an enriched environment and tactile stimulation can also improve developmental outcomes.[8] Strategies in infancy center on avoidance of traumatic injury and include child restraints (seatbelts) and shaken baby prevention among others.

Childhood. In early childhood, the focus is usually on optimizing gross motor skills, treatment of hypertonia, and preventing contractures. The management of spasticity with botulinum toxin injectable therapies is one of the treatments with an established role in the management of spasticity.[9] In school age children and teens, more intense focus on tone management is necessary, as well as the prevention and treatment of secondary impairment. Rehabilitation therapy and counseling, and pain therapy, are all important components of treatment. New neurocognitive rehabilitation options are now being developed and validated.[10]

Adulthood. In adults, interventions shift more toward compensation for deficits and targeted interventions for specific impairments. For example, botulinum

toxin injectable therapies have an established role in the management of spasticity,[9] and maintaining a high level of fitness through regular physical activity has been shown to be an important factor for maintaining mobility.[11] A large challenge is access to specialized care, as CP therapy has to date been centered in pediatric care settings. Therapies in adults include providing adaptive equipment as capabilities change, targeted treatment for a specific deficit, or focusing on generalized strength and fitness. Adaptation, targeted physical therapy, and exercise are some specific examples. Prevention and management of secondary damage are important additional goals.[12] Specific counseling and guidance must be directed at social factors such as employment in adults.[13]

All ages. Active interventions and skill training can harness neuroplasticity capabilities.[14,15] In addition, the concept of muscle plasticity is a potential opportunity, as activity (or lack thereof) continues to transform muscle anatomy throughout life.[16] This can be an important therapeutic target at all ages.

Other symptomatic therapeutic resources exist, and differ with the disability type and level. Recent developments include deep brain stimulation, targeting primarily the dystonic component,[17] neuromodulation and motor training paradigms for functional recovery,[18] and chemodenervation (botulinum toxins) for spasticity, with expanding options and indications.[19–21]

RESEARCH METHODOLOGY **Data, registries, patient, and family involvement.** Population-based CP registries exist worldwide, and mainly tabulate rates and types of CP. More recently, these have been utilized to also track health outcomes across large populations.[22] There is growing interest in registries as a basis for tracking clinical outcomes and for quality improvement or research on treatment effectiveness.[23] Some of the large recent efforts include the PCORnet network,[24] which has funded 11 Clinical Data Research Networks and 18 Patient Powered Research Networks. However, integrating the available information in a standardized format across multiple sites is very difficult, and financial support for these efforts is another formidable challenge. Large multinational consortia would have the potential to create large registries, which could in turn provide data that could be used for research and guidelines. One example is from PCORI (Patient-Centered Outcomes Research Institute), which is helping to build large data networks and support large-scale pragmatic clinical trials that address major health issues as identified and prioritized by the patients themselves. Additional resources that might be harnessed include currently funded government initiatives (NIH, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality) and existing databases generated through clinical data collection, such as the Kaiser Permanente, Veterans Administration, or other large health care systems networks. A group of workshop participants were tasked with determining a strategy for a national registry and substantial progress has been made since the workshop to establish a center-based registry called the Cerebral Palsy Research Network (CPRN).

In an effort to increase the ability to assimilate research data across studies and to accelerate the conduct of clinical trials, common data elements (CDEs) have been developed by the NINDS for a large number of disorders to standardize data collection.[25,26] Development of CDEs is in progress by the American Academy for Cerebral Palsy and Developmental Medicine with NINDS guidance. This is essential if larger registries or research databases are to be established; otherwise, the outcomes data will continue to amass as an amalgam of diverse and unusable data points. This group is collaborating with the CPRN (cpresearch.net) on standardizing the collection of data for the CPRN registry.

Patients and families are most often the first to identify symptoms and areas of intervention. This high sensitivity can be utilized on a large scale. Many families of patients with CP are already connected through social media, and this has the potential to serve as a basis for a reporting and research infrastructure.

The need for updated approaches. Randomized controlled trials continue to have a role but have been limited in CP for many reasons, such as difficulties with equipoise on the part of clinicians and/or families, insufficient patient enrollment, the need to suspend or constrain confounding treatments during a trial, funding issues that relate to tight budgets, and lack of sufficiently well-designed research proposals.

Practice-based evidence studies, designed to systematically collect data from large numbers of patients within the context of clinical care across a network of centers, can be an important alternative to demonstrate the comparative effectiveness of treatments. These studies can allow for prospective comparisons among different treatment strategies, controlling for patient differences. The experience with this approach in other conditions, such as stroke, has been promising.[27]

Large patient registries using CDEs and quality-controlled samples may provide one method of tracking large numbers of patients longitudinally, and

generating relevant data. Another advantage is the ability to blend clinical care with research data collection, which allows faster completion of studies.

Outcome measures and therapeutic targets must be relevant both from an individual patient perspective and from a population health perspective. There is often a divergence between the outcomes reported in clinical and research contexts and the perceived relevance for patients and observers/caretakers. The International Classification of Functioning, Disability and Health developed by the World Health Organization provides a well-accepted framework for conceptualizing the bidirectional and multifaceted relationships between health and functioning and how they are influenced by personal and environmental factors. This has spurred the development of many new outcome measures in rehabilitation that are clearly more relevant to the everyday lives of those with health conditions.

Quality-of-life issues are often the major priority for patients and families. Continued development and refinement of health-related quality-of-life measures should proceed with input from and relevance to patients and families, with greater reliability. Challenges are the variability of individual patient goals, feasibility of these goals, and a way to calculate the amount of desired improvement at the level of an individual and apply these metrics in a meaningful way to evaluate outcomes in large cohorts.

Additional objective outcome measures should be developed, reducing the variability and subjectivity of assessments. These should be feasible and affordable for large-scale implementation. These include imaging, electrophysiologic and instrumented motor assessments, daily activity sensing and monitoring, and computer modeling.

NEW THERAPEUTIC RESOURCES AND RESEARCH DIRECTIONS While the primary focus of the meeting was on advancing research that leads to improved medical care for individuals with CP, many attendees addressed the need to continue research that leads to greater insights into possible causes of or risk factors for CP, potential cures or prevention of different forms of CP, and for neuroprotective or neuroregenerative strategies post injury. Basic and translational research is informing diagnosis and therapy directions. Some recent developments include advances in genetic and epigenetic factors associated with CP risk and response to treatment,[28] computational modeling, and exploring the role of cell-based therapies.[29]

1. *Genomic diagnoses* can provide specific etiologies or comorbid diagnoses for CP or a CP syndrome,[30,31] and can serve as the basis for further phenotypic refinement and classification, enabled by rapid advances in the usability and efficacy of genetic diagnostic tools.[32]
2. *Cell-based therapy studies* have been conducted in small trials utilizing neural progenitor cells, umbilical cord mononuclear cells, and mesenchymal stem cells. These have been generally safe[33] and showed potential for limited improvement, although much more data are needed. Limited data exist for autologous cord blood therapy and autologous bone marrow mesenchymal cell therapy.[34,35] Some follow-up safety data are becoming available.[36] Despite this recent progress, designing cell therapy studies remains challenging, and ethical concerns need to be addressed. Most of the data available to date originate from various parts of the world, and integrating the various regulatory and research methodology approaches remains a future challenge. However, collaboration promises to provide a path forward for this promising avenue for prevention and treatment.
3. *Combining current therapeutic modalities*. For example, in a study in children and young adults with CP-related spasticity, adding rehabilitation to botulinum denervation resulted in further benefit.[37] Neuromodulation therapies are relatively limited in their benefit but can be used in combination for specific symptomatic targets.[17]

GAPS AND RECOMMENDATIONS Major gaps were identified. The major ones, which can affect progress and therapeutic developments, include:

- A knowledge and translational research gap, between basic and clinical research and between outcomes data and clinical practice
- A communication and collaboration gap among patients, researchers, and clinicians
- A talent gap, in a lack of scientific investigators interested in pursuing CP research

Recommendations include:

- Better communication and integration of information between basic and clinical research and between clinical research and clinical practice outcomes
- Better communication and more collaboration among patients, families, treating physicians, and clinical researchers
- Support and training opportunities for investigators from outside the field to pursue CP research

PRIORITIES AND PROPOSED ACTION ITEMS

- Create a national registry for CP
- Establish career awards to expand the researcher base

- Organize a workshop on basic and translational science
- Stimulate the creation of comparative effectiveness research efforts that leverage newer methodologies (practice-based evidence) and build off of a standardized data model for CP
- Develop research projects focused on the needs of adults with CP

To address improving coordination of research efforts to be able to compare or combine data, the workshop concluded that consolidating patient registries and databases should be a priority. The goal should be consolidation nationally and potentially internationally.

Also, to be effective, funding for CP research needs to be informed by the needs of the community, feasibility, and up-to-date research information. Research in CP needs to be advanced at a more rapid pace. One way to improve the research environment is through concerted efforts to attract researchers to the field through attractive career and funding opportunities. It was also recommended that an additional research meeting be convened with a more specific focus on gaps and achievements in basic and translational research in CP.

Study designs in the field of CP need to be revisited and updated. Studies that compare effectiveness of different therapies for specific populations, with large prospective observational designs, should both complement, and, in some cases, replace classic randomized controlled trial designs. The development of CDEs for CP will facilitate CP research by giving researchers and clinicians a standardized framework, so that people describing CP symptoms, signs, severities, and outcomes are using the same language. CDEs will enable data from different CP clinical studies, registries, and CE studies to be shared and in a meaningful way.

Finally, many attendees proposed that there be greater consideration of research focused on the needs of adults with CP in various aspects of health-related quality of life. Better ways to transition care from childhood to adulthood need to be addressed. Issues faced by adults may also inform treatment priorities earlier in life that may have the greatest effect throughout the lifespan.

AUTHOR CONTRIBUTIONS

Codrin Lungu: study concept and design, writing the first draft, critical revision of the manuscript for important intellectual content. Deborah Hirtz: study concept and design, critical revision of the manuscript for important intellectual content. Diane Damiano: study concept and design, critical revision of the manuscript for important intellectual content. Paul Gross: study concept and design, critical revision of the manuscript for important intellectual content. Jonathan Mink: study concept and design, critical revision of the manuscript for important intellectual content.

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