Cerebral palsy research news

Monday 15 March 2021

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Professor Nadia Badawi AM
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Interventions and Management

1. An intraoperative laterally placed distractor for gradual load sharing correction of severe spastic neuromuscular spinal deformity
Daniel R Bachman, Luv K Singh, John T Anderson, Richard M Schwend

Spine Deform. 2021 Mar 10. doi: 10.1007/s43390-021-00316-4. Online ahead of print.

Purpose: To analyze the overall deformity correction for severe neuromuscular scoliosis using laterally placed intra-operative distraction and compare to those receiving standard surgical technique. Methods: This was a retrospective, IRB-approved, cohort study of patients with GMFCS 4 or 5 spastic cerebral palsy with neuromuscular scoliosis, age greater than 10 years, who underwent posterior spinal fusion from 2007 to 2019. All patients had vectored cervical traction with Gardner-Wells tongs, with hips flexed in a relative sitting position. The study cohort underwent intraoperative, laterally placed correction using a distractor placed between two upper ribs and the ipsilateral greater trochanter while the control cohort did not. The 24 study patients were compared to 22 control patients. Results: Preoperative comparisons identified significant differences in Cobb angle, preoperative flexibility, and pelvic obliquity with the study group having larger, stiffer deformities with greater obliquity. There were no differences in pre-operative sagittal plane deformity. Mean post-operative upright Cobb angle correction was 67.3° ± 14.8° in the study and 55.3° ± 9.9° in the control group, representing a 66% and 60% correction, respectively. No neurological or other complications were noted from the use of this technique. Conclusion: The use of a laterally placed distraction device from upper ribs to ipsilateral greater trochanter allowed gradual lateral un-bending of large stiff neuromuscular spine deformities with greater correction than that of standard technique. In this small series, the technique allowed load-sharing during correction, with hips remaining in a functional sitting position, and without neurological complications. Level of evidence: Level III-retrospective cohort study.

PMID: 33689155

2. Targeted Physical Therapy Combined with Spasticity Management Changes Motor Development Trajectory for a 2-Year-Old with Cerebral Palsy
Corri L Stuyvenberg, Shaaron E Brown, Ketaki Inamdar, Megan Evans, Lin-Ya Hsu, Olivier Rolin, Regina T Harbourne, Sarah Westcott McCoy, Michele A Lobo, Natalie A Koziol, Stacey C Dusing

Case Reports J Pers Med. 2021 Feb 27;11(3):163. doi: 10.3390/jpm11030163.

Therapies for children with cerebral palsy (CP) often fail to address essential components of early rehabilitation: intensity, child initiation, and an embodied approach. Sitting Together And Reaching To Play (START-Play) addresses these issues while incorporating intensive family involvement to maximize therapeutic dosage. While START-Play was developed and tested on children aged 7-16 months with motor delays, the theoretical construct can be applied to intervention in children of broader ages and skills levels. This study quantifies the impact of a broader START-Play intervention combined with

Botulinum toxin-A (BoNT-A) and phenol on the developmental trajectory of a 24 month-old child with bilateral spastic CP. In this AB +1 study, A consisted of multiple baseline assessments with the Gross Motor Function Measure-66 and the Assessment of Problem Solving in Play. The research participant demonstrated a stable baseline during A and changes in response to the combination of BoNT-A/phenol and 12 START-Play sessions during B, surpassing the minimal clinically important difference on the Gross Motor Function Measure-66. The follow-up data point (+1) was completed after a second round of BoNT-A/phenol injections. While the findings suggest the participant improved his gross motor skills with BoNT-A/phenol and START-Play, further research is needed to generalize these findings.

PMID: 33673573

3. Skeletal Muscle in Cerebral Palsy: From Belly to Myofibril
Jason J Howard, Walter Herzog

Review Front Neurol. 2021 Feb 18;12:620852. doi: 10.3389/fneur.2021.620852. eCollection 2021.

This review will provide a comprehensive, up-to-date review of the current knowledge regarding the pathophysiology of muscle contractures in cerebral palsy. Although much has been known about the clinical manifestations of both dynamic and static muscle contractures, until recently, little was known about the underlying mechanisms for the development of such contractures. In particular, recent basic science and imaging studies have reported an upregulation of collagen content associated with muscle stiffness. Paradoxically, contractile elements such as myofibrils have been found to be highly elastic, possibly an adaptation to a muscle that is under significant in vivo tension. Sarcomeres have also been reported to be excessively long, likely responsible for the poor force generating capacity and underlying weakness seen in children with cerebral palsy (CP). Overall muscle volume and length have been found to be decreased in CP, likely secondary to abnormalities in sarcomerogenesis. Recent animal and clinical work has suggested that the use of botulinum toxin for spasticity management has been shown to increase muscle atrophy and fibrofatty content in the CP muscle. Given that the CP muscle is short and small already, this calls into question the use of such agents for spasticity management given the functional and histological cost of such interventions. Recent theories involving muscle homeostasis, epigenetic mechanisms, and inflammatory mediators of regulation have added to our emerging understanding of this complicated area.

PMID: 33679586

4. Greater Reliance on Cerebral Palsy-Specific Muscle Synergies During Gait Relates to Poorer Temporal-Spatial Performance Measures
Yushin Kim, Thomas C Bulea, Diane L Damiano

Front Physiol. 2021 Feb 23;12:630627. doi: 10.3389/fphys.2021.630627. eCollection 2021.

Children with cerebral palsy typically exhibit reduced complexity of muscle coordination patterns during walking; however, the specific patterns that characterize their gait abnormalities are still not well documented. This study aimed to identify the specific repertoire of muscle coordination patterns in children with CP during walking compared to same-aged peers without CP and their relationships to gait performance. To identify muscle coordination patterns, we extracted muscle synergies from 10 children with CP and 10 age-matched typically developing children (TD). K-mean clustering and discriminant analyses of all extracted synergies were used to group similar synergies. Then, weight-averaged z-scores were quantified for each cluster to determine their group-specific level. In this cohort, 10 of the 17 distinct clusters were largely CP-specific while six clusters were seen mainly in TD, and one was non-specific. CP-specific clusters generally showed merging of two TD synergies, excessive antagonist co-activation, decreased muscle activation compared to TD, and complex or atypical pattern. Significant correlations were found between weight-averaged z-scores and step length asymmetry, cadence asymmetry, self-selected treadmill speed and AP-COM displacement of the pelvis such that greater CP-specificity of muscle synergies was related to poorer performance, thus indicating that CP-specific synergies can influence motor dysfunction.

PMID: 33708139

5. The relationship of trunk kinematics and kinetics with lower limb pathology during gait in children with spastic cerebral palsy

Damien Kiernan

Gait Posture. 2021 Mar 1;86:33-37. doi: 10.1016/j.gaitpost.2021.02.032. Online ahead of print.

Background: Trunk control during gait in children with cerebral palsy (CP) is known to be impaired. While differentiation of trunk movement between CP subtypes (unilateral/bilateral) has been examined, differentiation of lower lumbar spinal loading has not been considered. Furthermore, the relationship between lower lumbar loading and lower limb pathology has not been reported. Research question: How do lower lumbar spinal kinetics differ during unilateral and bilateral CP gait and what is the relationship between trunk kinematics and L5/S1 kinetics with lower limb pathology? Methods: Three-dimensional thorax kinematics and L5/S1 kinetics were measured during gait with children divided into 3 groups (unilateral CP (n = 21), bilateral CP (n = 31) and typical development (TD) (n = 26)). Differences in thorax kinematics and reactive forces and moments at L5/S1 between groups were analysed using Statistical Parametric Mapping. Correlation coefficients were calculated between Gait Profile Score (GPS) and kinematic measures of the thorax and kinetics at L5/S1. Results: An increased ipsilateral bending moment was present for unilateral CP in the coronal plane (55-70% Gait Cycle (GC), $p < 0.001$), while children with bilateral CP demonstrated two distinct increased peaks during mid-stance (10-30 % GC, $p < 0.001$) and mid-swing (60-80% GC, $p = 0.004$) compared to TD. RMS and RoM thorax flexion, side flexion and L5/S1 lateral bend moment demonstrated significant moderate correlations with GPS. Significance: This study confirmed an increased involvement at the trunk and of lower lumbar spinal loading for children with bilateral CP compared to unilateral CP. It has been suggested that altered trunk movement in CP gait may be a combination of both a compensation for lower limb pathology and an underlying deficit. Our result of positive yet moderate correlations between GPS and trunk movement and lower spinal loading support this theory.

PMID: 33677176

6. Towards validation and standardization of automatic gait event identification algorithms for use in paediatric pathological populations
Rosa M S Visscher, Sailee Sansgiri, Marie Freslier, Jaap Harlaar, Reinald Brunner, William R Taylor, Navrag B Singh

Gait Posture. 2021 Mar 1;86:64-69. doi: 10.1016/j.gaitpost.2021.02.031. Online ahead of print.

Background: To analyse and interpret gait patterns in pathological paediatric populations, accurate determination of the timing of specific gait events (e.g. initial contract - IC, or toe-off - TO) is essential. As currently used clinical identification methods are generally subjective, time-consuming, or limited to steps with force platform data, several techniques have been proposed based on processing of marker kinematics. However, until now, validation and standardization of these methods for use in diverse gait patterns remains lacking. Research questions: 1) What is the accuracy of available kinematics-based identification algorithms in determining the timing of IC and TO for diverse gait signatures? 2) Does automatic identification affect interpretation of spatio-temporal parameters? Methods: 3D kinematic and kinetic data of 90 children were retrospectively analysed from a clinical gait database. Participants were classified into 3 gait categories: group A (toe-walkers), B (flat IC) and C (heel IC). Five kinematic algorithms (one modified) were implemented for two different foot marker configurations for both IC and TO and compared with clinical (visual and force-plate) identification using Bland-Altman analysis. The best-performing algorithm-marker configuration was used to compute spatio-temporal parameters (STP) of all gait trials. To establish whether the error associated with this configuration would affect clinical interpretation, the bias and limits of agreement were determined and compared against inter-trial variability established using visual identification. Results: Sagittal velocity of the heel (Group C) or toe marker configurations (Group A and B) was the most reliable indicator of IC, while the sagittal velocity of the hallux marker configuration performed best for TO. Biases for walking speed, stride time and stride length were within the respective inter-trial variability values. Significance: Automatic identification of gait events was dependent on algorithm-marker configuration, and best results were obtained when optimized towards specific gait patterns. Our data suggest that correct selection of automatic gait event detection approach will ensure that misinterpretation of STPs is avoided.

PMID: 33684617

7. Plantar flexor voluntary activation capacity, strength and function in cerebral palsy
Shari M O'Brien, Timothy J Carroll, Lee A Barber, Glen A Lichtwark

Eur J Appl Physiol. 2021 Mar 9. doi: 10.1007/s00421-021-04638-z. Online ahead of print.

Purpose: Distal lower limb motor impairment impacts gait mechanics in individuals with cerebral palsy (CP), however, the contribution of impairments of muscle activation to reduced gross motor function (GMF) is not clear. This study aimed to investigate deficits in plantar flexion voluntary activation capacity in CP compared to typically developed (TD) peers, and evaluate relationships between voluntary activation capacity, strength and GMF. Methods: Fifteen ambulant individuals with spastic CP (23 ± 6 years, GMFCS I-III) and 14 TD (22 ± 2 years) people participated. Plantar- and dorsiflexion strength were assessed with a dynamometer. Voluntary activation capacity was assessed using the interpolated twitch technique via single twitch supramaximal tibial nerve stimulation. GMF was assessed using the timed upstairs test, 10 m walk test, muscle power sprint test and six-minute walk test. Results: Plantar- and dorsiflexion strength were 55.6% and 60.7% lower in CP than TD ($p < 0.001$). Although voluntary activation capacity was 17.9% lower on average for CP than TD ($p = 0.039$), 46.7% of individuals with CP achieved a sufficiently high activation to fall within one standard deviation of the TD mean. Plantar flexion voluntary activation capacity did not correlate with strength ($R2 = 0.092$, $p = 0.314$) or GMF measures in the high functioning CP group (GMFCS I-II). Conclusion: In contrast to previous research, plantar flexion activation capacity did not strongly predict weakness or reduced GMF. We propose that muscle size contributes more to weakness than voluntary activation capacity in high functioning individuals with CP and that relationships between muscle activation and functional capacity are complicated by effects at multiple joints.

PMID: 33687530

8. The Development and Evaluation of the Powered Mobility Function Scale (PMFS) for Children and Adolescents with Cerebral Palsy
Tal Krasovsky, Chana Shammah, Anat Addes, Amichai Brezner, Sharon Barak

Dev Neurorehabil. 2021 Mar 11;1-10. doi: 10.1080/17518423.2021.1898057. Online ahead of print.

Aims: To describe the development and evaluation of a novel task-based measure of powered mobility function: the Powered Mobility Function Scale (PMFS).Methods: PMFS was developed in Hebrew in four phases, with feedback from clinicians and clients. Psychometric properties (inter-rater, test-retest reliability, concurrent, convergent and known-groups validity) were evaluated for N = 49 children and adolescents with Cerebral Palsy (11.1 ± 4.8y) using Powered Mobility Program (PMP), Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS) and Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)Results: PMFS development involved 3 versions over three years. Inter-rater reliability was κ=0.75-0.95 (video/observation). Test-retest reliability was κ=0.93-0.96. Concurrent validity (PMP) was ρ =-0.84-to-0.96. Convergent validity (PEDI-CAT) was ρ =-0.47-to-0.70. Known-groups validity (GMFCS/MACS) demonstrated medium effect sizes (r = 0.33-0.46)Conclusions: PMFS is valid and reliable for measuring powered mobility function in children and adolescents with CP. Future validation of the English version of PMFS is warranted.

PMID: 33703993

9. Neuroradiologic Features Associated With Severe Restriction of Functional Mobility in Children With Cerebral Palsy in North India
Jayanti Prabha, Areesha Alam, Chandrakanta Kumar, Rashmi Kumar, Neera Kohli

J Child Neurol. 2021 Mar 12;883073821993613. doi: 10.1177/0883073821993613. Online ahead of print.

Background: Few studies have focused on magnetic resonance imaging (MRI) brain findings associated with functional mobility in cerebral palsy. Objective: To determine association between MRI findings and Gross Motor Functional Classification System (GMFCS) levels in cerebral palsy. Methods: Prospective-observational study conducted in Pediatric Neurology Clinic at a public teaching hospital, Northern India. First 3 new cases of cerebral palsy were enrolled on particular neuro-clinic day per week for 1 year. Functional mobility was classified according to GMFCS. Association between MRI findings, cerebral palsy type, and GMFCS levels were evaluated using $\chi 2$ test. Results: A total of 138 cases (mean age 2.71 [SD = 1.91] years; male [64.5%]) were enrolled. Reported types of cerebral palsy were as follows: spastic quadriplegia (47.8%), spastic diplegia (28.35%), spastic hemiplegia (11.6%), extrapyramidal (6.5%), and ataxic/hypotonic (5.8%). GMFCS were classified into level 1 (13%), level 2 (7.2%), level 3 (4.3%), level 4 (10.9%), and level 5 (64.5%). Spastic quadriplegia and extrapyramidal cerebral palsy were significantly associated with higher (severe) levels (IV and V), whereas spastic diplegia and hemiplegia were significantly associated with lower (mild) levels (I-III) of GMFCS. MRI features of periventricular white matter injury, deep gray matter injury, basal ganglia and thalamic changes, and superficial gray matter injury were significantly associated with severe levels of GMFCS (V and IV). MRI was normal in 8 children (5 = mild category, 3 = severe category).

Conclusion: Severe cerebral palsy is most often associated with spastic quadriplegia, extrapyramidal cerebral palsy, superficial gray matter lesions, deep gray matter lesions, and periventricular white matter injury. This information is useful for anticipating and addressing the needs of children with cerebral palsy and for prognostication.

PMID: 33709827

10. Does sports-specific training improve measures of impairment developed for para sport classification? A multiple-baseline, single-case experiment
Paula J Wilson, Mark J Connick, Iain M Dutia, Emma M Beckman, Angelo Macaro, Sean M Tweedy

J Sports Sci. 2021 Mar 11;1-10. doi: 10.1080/02640414.2021.1883309. Online ahead of print.

Conceptually, sports-specific training should not influence measures of impairment used to classify Para athletes. This study evaluated the extent to which measures of strength, range of movement and coordination developed for Para swimming classification changed in response to a performance-focused swimming programme. A five-phase multiple-baseline, single-case experimental research design was utilized. Three participants with cerebral palsy and high support needs completed the 64 -week study, which included two 16-week performance-focused swimming training blocks. Swimming speed, isometric shoulder extension strength, shoulder flexion range of movement and upper limb coordination were monitored throughout.Interrupted Time-Series Simulation Method analysis demonstrated large, significant changes in swimming speed (m/s) during the first (d = 2.17; 95% CI 0.45-3.88; p = 0.01) and second (d = 2.59; 95% CI 1.66-3.52; p = 0.00) training blocks. In contrast, changes in strength, range of movement and coordination were predominantly trivial and non-significant. This was the first study to investigate training responsiveness of measures developed for Para sport classification. Results indicate that despite significantly improved swimming performance, impairment measures remained relatively stable, and therefore these measures of impairment may be valid for the purposes of Para swimming classification. Further research is required in elite athletes, different sports and different impairment types.

PMID: 33704022

11. Characterization of physical literacy in children with chronic medical conditions compared to healthy controls: a cross-sectional study
Jeffrey Do, Angelica Blais, Brian Feldman, Leonardo R Brandão, Jane Lougheed, Daniela Pohl, Robert J Klaassen, Donna L Johnston, Denise De Laat, Johannes Roth, Sherri Lynne Katz, Anna McCormick, F Virginia Wright, Gail Macartney, Hugh J McMillan, Sunita Venkateswaran, Erick Sell, Asif Doja, Katherine M Matheson, Addo Boafo, Patricia E Longmuir

Appl Physiol Nutr Metab. 2021 Mar 9. doi: 10.1139/apnm-2020-0957. Online ahead of print.

To determine the physical literacy, defined as the capability for a physically active lifestyle, of children with medical conditions compared with healthy peers, this multicenter cross-sectional study recruited children with medical conditions from cardiology, neurology (including concussion), rheumatology, mental health, respirology, oncology, hematology, and rehabilitation (including cerebral palsy) clinics. Participants aged 8-12 years (N=130; mean age: 10.0±1.44 years; 44% female) were randomly matched to three healthy peers from a normative database, based on age, sex, and month of testing. Total physical literacy was assessed by the Canadian Assessment of Physical Literacy, a validated assessment of physical literacy measuring physical competence, daily behavior, knowledge/understanding, and motivation/confidence. Total physical literacy mean scores(/100) did not differ (t(498)=-0.67; p=0.44) between participants (61.0±14.2) and matched healthy peers (62.0±10.7). Children with medical conditions had lower mean physical competence scores (/30; -6.5 [-7.44, -5.51]; p<0.001) but higher mean motivation/confidence scores (/30; 2.6 [1.67, 3.63]; p<0.001). Mean daily behavior and knowledge/ understanding scores did not differ from matches (/30; 1.8 [0.26, 3.33]; p=0.02; /10; -0.04 [-0.38, 0.30]; p=0.81; respectively). Children with medical conditions are motivated to be physically active but demonstrate impaired movement skills and fitness, suggesting the need for targeted interventions to improve their physical competence. Novelty bullets: • Physical literacy in children with diverse chronic medical conditions is similar to healthy peers • Children with medical conditions have lower physical competence than healthy peers, but higher motivation and confidence • Physical competence (motor skill, fitness) interventions, rather than motivation or education, are needed for these youth.

PMID: 33689492

12. Measure of Early Vision Use: development of a new assessment tool for children with cerebral palsy
Belinda Deramore Denver, Elspeth Froude, Peter Rosenbaum, Christine Imms

Disabil Rehabil. 2021 Mar 10;1-11. doi: 10.1080/09638288.2021.1890241. Online ahead of print.

Purpose: To report the development of an assessment tool to describe "how vision is used" for children with cerebral palsy. Method: Measurement development consisted of three steps: (i) an online survey to explore the relevance and comprehensiveness of visual behaviours identified in a previous conceptualisation study; (ii) construction of items and a rating scale for the new measure; and (iii) cognitive interviews to explore comprehensibility and refine the measure in preparation for field testing. Survey respondents were 130 parents of children with cerebral palsy, eight adults with cerebral palsy, and 108 clinicians (n = 246). Nine parents participated in the interviews. Results: The new tool, the Measure of Early Vision Use, is a 14-item descriptive measure of typical performance of visual behaviours observable in everyday activities, as rated by parent/caregiver observation. Each item is rated on a 4-point ordinal scale. Conclusions: This new measure is conceptually grounded within the Activity level domain of the International Classification of Functioning, Disability and Health as a measure of a single visual ability construct. The target population is children with cerebral palsy, and using parent report the Measure of Early Vision Use describes both strengths and limitations in using vision. This study addressed the selection of items and response options for the new scale, and provides evidence to support content relevance, comprehensiveness and comprehensibility from key stakeholders. Further research will explore psychometric properties and clinical utility.Implications for rehabilitationThe ability to use vision in daily activities is relevant to the development and learning of all children, so the availability of a method for describing visual abilities has potential for diverse research and clinical purposes.The Measure of Early Vision Use is a parent-report tool that provides a criterion-referenced method for quantifying and describing how children use vision in typical daily activities to support intervention planning.Clinicians and parents wishing to measure vision use in children with cerebral palsy can be confident about the rigorous methods used to develop this tool, including consultation with key stakeholders.

PMID: 33689557

13. Stability of the Communication Function Classification System among Children with Cerebral Palsy in South Korea
Eun-Young Park

Int J Environ Res Public Health. 2021 Feb 15;18(4):1881. doi: 10.3390/ijerph18041881.

Interest in the prognosis of skill levels has been an important issue among children with cerebral palsy (CP). This study aimed to verify the stability of the Communication Function Classification System (CFCS) in 2- to 18-year-old children with CP. Data collected from 171 children with CP who received rehabilitation therapy in hospitals or attended special elementary schools in South Korea were reviewed. They were divided into two groups, children <4 years and children ≥4 years. Participants were evaluated over 1-year and 2-year intervals from the first rating. Agreement between the three measurements and the weighted kappa were analyzed. At the 1-year interval, results demonstrated a high agreement rate of the CFCS in children ≥4 years old, and during the 2-year interval the study revealed a low agreement rate in children aged 2-4 years. The results indicated the stability of the CFCS in children ≥4 years old but some change of the CFCS in 2- to 4-year-old children. Moreover, the findings suggested that the change of the CFCS varied with time and age. Based on these results, it is recommended that the CFCS assessments be performed periodically, especially among 2- to 4-year-old children with CP.

PMID: 33671982

14. Dishes Adapted to Dysphagia: Sensory Characteristics and Their Relationship to Hedonic Acceptance
Gorka Merino, Maria Remedios Marín-Arroyo, María José Beriain, Francisco C Ibañez

Foods. 2021 Feb 23;10(2):480. doi: 10.3390/foods10020480.

Dishes whose texture has been modified for dysphagia undergo changes in other sensory characteristics as well. Therefore, it is necessary to identify these characteristics in adapted dishes and their relationship to hedonic acceptance. In the present work, the sensory characteristics of five dishes adapted to dysphagia associated with cerebral palsy were investigated using the check-

all-that-apply method. A hedonic evaluation with a panel of non-dysphagic judges was performed to relate the degree of acceptance with the sensory characteristics of the adapted dishes. The identification of the original non-adapted dish as well as the relationship between the hedonic evaluation by non-dysphagic judges and dysphagic judges were explored. The main attributes of the dishes adapted to dysphagia were "homogeneity" and "easy-to-swallow". Attributes that increased the hedonic evaluation were "flavorful", "flavor of the original dish", "soft texture", "easy-to-swallow", and "odor of the original dish". The attributes that decreased the hedonic evaluation were "thick mash" and "bland". The fish dish was the only one correctly identified more than 62.5% of the time. The adapted dishes received scores above 4.7 out of 9.0 in the hedonic evaluation. The most accepted dishes were the chicken stew and the chickpea stew. Except for the pasta dish, the test yielded similar results to those obtained with dysphagic judges. The texture-modified dishes were correctly characterized and accepted. This study shows that all the sensory characteristics of the adapted dishes are crucial for acceptance and identification.

PMID: 33672336

15. Effects of Melatonin on Neurobehavior and Cognition in a Cerebral Palsy Model of plppr5-/- Mice
Yuxiao Sun, Liya Ma, Meifang Jin, Yuqin Zheng, Dandan Wang, Hong Ni

Front Endocrinol (Lausanne). 2021 Feb 22;12:598788. doi: 10.3389/fendo.2021.598788. eCollection 2021.

Cerebral palsy (CP), a group of clinical syndromes caused by non-progressive brain damage in the developing fetus or infant, is one of the most common causes of lifelong physical disability in children in most countries. At present, many researchers believe that perinatal cerebral hypoxic ischemic injury or inflammatory injury are the main causes of cerebral palsy. Previous studies including our works confirmed that melatonin has a protective effect against convulsive brain damage during development and that it affects the expression of various molecules involved in processes such as metabolism, plasticity and signaling in the brain. Integral membrane protein plppr5 is a new member of the plasticity-related protein family, which is specifically expressed in brain and spinal cord, and induces filopodia formation as well as neurite growth. It is highly expressed in the brain, especially in areas of high plasticity, such as the hippocampus. The signals are slightly lower in the cortex, the cerebellum, and in striatum. Noteworthy, during development plppr5 mRNA is expressed in the spinal cord, i.e., in neuron rich regions such as in medial motor nuclei, suggesting that plppr5 plays an important role in the regulation of neurons. However, the existing literature only states that plppr5 is involved in the occurrence and stability of dendritic spines, and research on its possible involvement in neonatal ischemic hypoxic encephalopathy has not been previously reported. We used plppr5 knockout (plppr5-/-) mice and their wild-type littermates to establish a model of hypoxicischemic brain injury (HI) to further explore the effects of melatonin on brain injury and the role of plppr5 in this treatment in an HI model, which mainly focuses on cognition, exercise, learning, and memory. All the tests were performed at 3-4 weeks after HI. As for melatonin treatment, which was performed 5 min after HI injury and followed by every 24h. In these experiments, we found that there was a significant interaction between genotype and treatment in novel object recognition tests, surface righting reflex tests and forelimb suspension reflex tests, which represent learning and memory, motor function and coordination, and the forelimb grip of the mice, respectively. However, a significant main effect of genotype and treatment on performance in all behavioral tests were observed. Specifically, wild-type mice with HI injury performed better than plppr5-/- mice, regardless of treatment with melatonin or vehicle. Moreover, treatment with melatonin could improve behavior in the tests for wild-type mice with HI injury, but not for plppr5-/- mice. This study showed that plppr5 knockout aggravated HI damage and partially weakened the neuroprotection of melatonin in some aspects (such as novel object recognition test and partial nerve reflexes), which deserves further study.

PMID: 33692754

16. Autonomous nervous system regulation of pain in children with cerebral palsy
Inmaculada Riquelme, Raphael Silva do Rosário, Kari Vehmaskoski, Pekka Natunen, Pedro Montoya

Brain Inj. 2021 Mar 7;1-7. doi: 10.1080/02699052.2020.1863469. Online ahead of print.

Aim: Children with cerebral palsy (CP) have increased pain sensitivity and recurrent pain episodes; however, pain is underreported in children with intellectual impairment. Cardiac autonomic regulation is imbalanced in chronic pain conditions and neurological disorders. This study aims at exploring the autonomous nervous system regulation of pain in children with CP compared with typically developing peers (TDP).Method: Heart rate variability (HRV) was recorded during 24 hours in 26 children with CP and 26 TDP, and examined offline at baseline (sleeping, seated rest) and during spontaneous pain events. Pain and fatigue, HRV indices (linear indices on time - IBI, SDNN, RMSSD - and frequency domains - high, low, and very low

frequency - and non-linear indices - Hurst coefficient and multiscale entropy) were computed.Results: Children with CP showed comparable HRV during daily conditions and similar reductions after pain events than their TDP, regardless of their level of intellectual impairment. Interpretation: Children with CP have an intact autonomic regulation in acute pain events. HRV could be an accurate pain biomarker in children with CP and intellectual disability.What this paper adds: Autonomic regulation in acute pain is efficient in children with cerebral palsy.Heart rate variability indices can be reliable pain biomarkers in intellectual impairment.

PMID: 33682539

17. Development of equations and software for estimating weight in children with cerebral palsy
Maria de Las Mercedes Ruiz Brunner, Maria Elisabeth Cieri, Charlene Butler, Eduardo Cuestas

Dev Med Child Neurol. 2021 Mar 10. doi: 10.1111/dmcn.14857. Online ahead of print.

Aim: To develop equations and software to estimate weight using segmental measures for children with cerebral palsy (CP). Method: This was a cross-sectional study. Children and adolescents with CP of both sexes from 2 to 19 years old from five cities in Argentina were included. Weight, mid-upper arm circumference (MUAC), and clinical covariables were collected. Linear regression models with weight as the dependent variable and body segment lengths as predictors were developed and compared for R2 , adjusted R2 , and the root mean square of the error. Results: In total, 381 children and adolescents (mean age 10y 5mo [SD 4y 9mo], range 2-19y; 231 males, 150 females) with a confirmed diagnosis of CP were included. Gross motor function based on the Gross Motor Function Classification System (GMFCS) was as follows: level I, 59; II, 55; III, 59; IV, 69; V, 139. The interaction between weight and other variables such as MUAC, sex, GMFCS, and age was analysed. The concordance correlation coefficient between estimated and observed weight was 0.94 (95% CI 0.93-0.95). From the results of the equations, a free software tool, named Weight Calculator CP, was developed. Interpretation: Weight in children with CP can be predicted using MUAC, GMFCS, and age. Weight Calculator CP can be used in clinical practice when direct weight cannot be obtained.

PMID: 33694223

18. Layer-specific parameters of intracortical microstimulation of the somatosensory cortex
Morgan E Urdaneta, Nicolas G Kunigk, Francisco Delgado, Shelley Fried, Kevin J Otto

J Neural Eng. 2021 Mar 11. doi: 10.1088/1741-2552/abedde. Online ahead of print.

Intracortical microstimulation (ICMS) of the primary somatosensory cortex (S1) has shown great progress in restoring touch sensations to patients with paralysis. Stimulation parameters such as amplitude, phase duration, and frequency can influence the quality of the evoked percept as well as the amount of charge necessary to elicit a response. Previous studies in V1 and auditory cortices have shown that the behavioral responses to stimulation amplitude and phase duration change across cortical depth. However, this depth-dependent response has yet to be investigated in S1. Similarly, to our knowledge, the response to microstimulation frequency across cortical depth remains unexplored. To assess these questions, we implanted rats in S1 with a microelectrode with electrode-sites spanning all layers of the cortex. A conditioned avoidance behavioral paradigm was used to measure detection thresholds and responses to phase duration and frequency across cortical depth. Analogous to other cortical areas, the sensitivity to charge and strength-duration chronaxies in S1 varied across cortical layers. Likewise, the sensitivity to microstimulation frequency was layer dependent. These findings suggest that cortical depth can play an important role in the fine-tuning of stimulation parameters and in the design of intracortical neuroprostheses for clinical applications.

PMID: 33706301

19. "Prenatal tobacco smoke exposure and neurological impairment at 10 years of age among extremely preterm children: a prospective cohort"
Kartik K Venkatesh, Alan Leviton, Raina N Fichorova, Robert M Joseph, Laurie M Douglass, Jean A Frazier, Karl Ck Kuban, Hudson P Santos Jr, Rebecca C Fry, T Michael O'Shea

BJOG. 2021 Mar 7. doi: 10.1111/1471-0528.16690. Online ahead of print.

Objective: To determine the association between prenatal tobacco smoke exposure and neurological impairment at 10 years of age among children born extremely preterm (<28 weeks gestation). Design: The Extremely Low Gestational Age Newborn (ELGAN) Study, a prospective cohort SETTING: 10-year follow-up of extremely preterm infants born between 2002-2004 at 14 U.S. hospitals METHODS: Prenatal tobacco smoke exposure was defined as a mother's report at enrollment of active (i.e., maternal) and passive smoking during pregnancy. Poisson regression with generalized estimating equations was used. Models adjusted for mother's age, race/ethnicity, education, insurance, pre-pregnancy body mass index, U.S region, multiple gestation, and infant's sex; and in sensitivity analysis, gestational age at delivery and clinical subtype of preterm birth, given their classification as intermediate and non-confounding variables. Main outcomes: Neurological impairment at 10 years, epilepsy, cerebral palsy, and cognitive impairment. Results: Of 1,200 ELGAN study survivors, 856 were assessed at 10 years of age with neurological outcomes, of whom 14% (118/856) to active tobacco exposure during pregnancy and 24% (207/852) to passive tobacco exposure. Compared to children who were not exposed prenatally to tobacco, children exposed to active tobacco use during pregnancy had a higher risk of epilepsy (14% vs. 5%; aRR: 1.68, 95% CI: 1.45 to 1.92). This risk remained after adjustment for gestational age at delivery and clinical subtype of preterm birth. Prenatal tobacco smoke exposure was not associated with other assessed neurological outcomes, including cerebral palsy and multiple measures of cognitive impairment. Conclusions: Among children born extremely preterm, prenatal active tobacco smoke exposure was associated with an increased risk of epilepsy at 10 years of life.

PMID: 33682301

20. Health-Related Quality of Life and Family Functioning of Primary Caregivers of Children with Cerebral Palsy in Malaysia

Kelvin Ying, Hans Van Rostenberghe, Garry Kuan, Mohammad Haris Amirul Mohd Yusoff, Siti Hawa Ali, Nik Soriani Yaacob

Int J Environ Res Public Health. 2021 Feb 28;18(5):2351. doi: 10.3390/ijerph18052351.

Caregiving for children with cerebral palsy (CP) has proved to negatively impact on the physical and psychological well-being of their primary caregivers. The aim of the current study was to examine the overall impact of caregiving for children with CP on the primary caregivers' health-related quality of life (HRQOL) and family functioning, and to identify potential factors associated with primary caregivers' HRQOL and family functioning. The cross-sectional study involved a total of 159 primary caregivers of children with CP with a mean age of 42.8 ± 8.4 years. Demographic data and information on the physical and leisure activities of the primary caregivers were collected, and their quality of life (QOL) was measured based on the self-reported Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM). Primary caregivers in the current study have shown good HRQOL and family functioning, with scores of 82.4 and 85.3 out of 100, respectively. Through multiple linear regression analyses, the mother's level of education, family monthly income, sleeping problems in children with CP, and the existence of children with other types of disability have been identified as factors contributing to HRQOL and family functioning. The findings help set out the course for stakeholders to establish action to enhance the QOL of primary caregivers.

PMID: 33670850

21. Development and sensibility assessment of a health-related quality of life instrument for adults with severe disabilities who are non-ambulatory

Trees A L Zalmstra, Agnes Elema, Willemijn van Gils, Heleen A Reinders-Messelink, Corry K van der Sluis, Annette A J van der Putten

J Appl Res Intellect Disabil. 2021 Mar 5. doi: 10.1111/jar.12873. Online ahead of print.

Background: Insight in health-related quality of life (HRQoL) of adults with severe disabilities who are non-ambulatory is important, but a measure is lacking. The aim was to develop a HRQoL measure for this group. Method: The developmental process consisted of the adaptation process of a proxy HRQoL measure for children with severe disabilities who are non-ambulatory and the assessment of the sensibility of the developed instrument. A three-step process was used: focus groups, e-survey and interviews. Results: In total, 72% of the items remained unchanged. Three new items and one element to an existing item were added. In ten items, the formulation of the items was adapted to the target group. Concerning the sensibility,

respondents suggested minor changes to the instruction and the output scales. Conclusions: This study has yielded a proxy HRQoL measure for adults with severe disabilities who are non-ambulatory, the CPADULT, with good sensibility.

PMID: 33675148

22. Parent mediated intervention programmes for children and adolescents with neurodevelopmental disorders in South Asia: A systematic review
Kamrun Nahar Koly, Susanne P Martin-Herz, Md Saimul Islam, Nusrat Sharmin, Hannah Blencowe, Aliya Naheed

PLoS One. 2021 Mar 11;16(3):e0247432. doi: 10.1371/journal.pone.0247432. eCollection 2021.

Objective: Parent-mediated programmes have been found to be cost effective for addressing the needs of the children and adolescents with Neurodevelopmental Disorders (NDD) in high-income countries. We explored the impact of parent-mediated intervention programmes in South Asia, where the burden of NDD is high. Methods: A systematic review was conducted using the following databases; PUBMED, MEDLINE, PsycINFO, Google Scholar and Web of Science. Predefined MeSH terms were used, and articles were included if published prior to January 2020. Two independent researchers screened the articles and reviewed data. Outcomes measures: The review included studies that targeted children and adolescents between 1 and 18 years of age diagnosed with any of four specific NDDs that are commonly reported in South Asia; Autism Spectrum Disorder (ASD), Intellectual Disability (ID), Attention Deficit Hyperactivity Disorder (ADHD) and Cerebral Palsy (CP). Studies that reported on parent or child outcomes, parent-child interaction, parent knowledge of NDDs, or child activities of daily living were included for full text review. Results: A total of 1585 research articles were retrieved and 23 studies met inclusion criteria, including 9 Randomized Controlled Trials and 14 pre-post intervention studies. Of these, seventeen studies reported effectiveness, and six studies reported feasibility and acceptability of the parent-mediated interventions. Three studies demonstrated improved parent-child interaction, three studies demonstrated improved child communication initiations, five studies reported improved social and communication skills in children, four studies demonstrated improved parental knowledge about how to teach their children, and four studies reported improved motor and cognitive skills, social skills, language development, learning ability, or academic performance in children. Conclusion: This systematic review of 23 studies demonstrated improvements in parent and child skills following parent-mediated intervention in South Asia. Additional evaluations of locally customized parent-mediated programmes are needed to support development of feasible interventions for South Asian countries.

PMID: 33705420

23. Care coordination for children with special healthcare needs anticipating transition: A program evaluation
Beth Morton, Elizabeth G Damato, Mary R Ciccarelli, Jackson Currie

J Pediatr Nurs. 2021 Mar 9;61:7-14. doi: 10.1016/j.pedn.2021.02.024. Online ahead of print.

Purpose: Nearly 20% of U.S. children have special healthcare needs (CSHCN). Difficulties experienced with navigating the array of services for these children has highlighted the value of care coordination to improve care, reduce costs and increase satisfaction. This study evaluated the services delivered within a care coordination program at a transition consultation center for CSHCN. It also compared the advancement of youth by age group toward graduation criteria. Design and methods: Using a program evaluation method, data were collected via a retrospective chart review. The convenience sample included clinical records from 100 patients aged 11-22 who had a chronic disease or disability. Results: The comparison of services for those with diagnoses of autism spectrum disorder, cerebral palsy and Down syndrome were uniformly high in supporting primary care and health care financing. Medicaid waiver assistance was provided more frequently to younger adolescents while older adolescents more commonly received support in all other graduation criteria, including primary and specialty care, healthcare financing and decision-making supports. Conclusions: Youth served in a transition care coordination program receive a high volume and broad array of services. There are some variations in the types of services by diagnosis and level of support need. Older youth show greater advancement toward graduation criteria. Practice implications: This in-depth chart review provides a valuable description of the activities of care coordinators serving CSHCN enduring transition. It enables development of targeted strategies for building care coordination programming and sets an example for the design of future research studies on this topic.

PMID: 33711643

24. Early identification and intervention in developmental coordination disorder: lessons for and from cerebral palsy
Diane L Damiano

Dev Med Child Neurol. 2021 Mar 8. doi: 10.1111/dmcn.14829. Online ahead of print.

PMID: 33686677

25. Cases of Infantile Paralysis-Paraplegia by Rheumatic Metastasis, Ending in Hemiplegia and Recovery, and Cerebral Paralysis
J J Caldwell

Dent Regist. 1878 Feb;32(2):60-65.

PMID: 33699451

26. Objective and Clinically Feasible Analysis of Diffusion MRI Data can Help Predict Dystonia After Neonatal Brain Injury
Keerthana Chintalapati, Hanyang Miao, Amit Mathur, Jeff Neil, Bhooma R Aravamuthan

Pediatr Neurol. 2020 Nov 22;118:6-11. doi: 10.1016/j.pediatrneurol.2020.11.011. Online ahead of print.

Background: Dystonia in cerebral palsy is debilitating but underdiagnosed precluding targeted treatment that is most effective if instituted early. Deep gray matter injury is associated with dystonic cerebral palsy but is difficult to quantify. Objective and clinically feasible identification of injury preceding dystonia could help determine the children at the highest risk for developing dystonia and thus facilitate early dystonia detection. Methods: We examined brain magnetic resonance images from four- to five-day-old neonates after therapeutic hypothermia for hypoxic-ischemic encephalopathy at a tertiary care center. Apparent diffusion coefficient values in the striatum and thalamus were determined using a web-based viewer integrated with the electronic medical record (IBM iConnect Access). The notes of specialists in neonatal neurology, pediatric movement disorders, and pediatric cerebral palsy (physicians most familiar with motor phenotyping after neonatal brain injury) were screened for all subjects through age of five years for motor phenotype documentation. Results: Striatal and thalamic apparent diffusion coefficient values significantly predicted dystonia with receiver operator characteristic areas under the curve of 0.862 (P = 0.0004) and 0.838 (P = 0.001), respectively (n = 50 subjects). Striatal apparent diffusion coefficient values less than 1.014 × 10-3 mm2/s provided 100% specificity and 70% sensitivity for dystonia. Thalamic apparent diffusion coefficient values less than 0.973 × 10-3 mm2/s provided 100% specificity and 80% sensitivity for dystonia. Conclusions: Lower striatal and thalamic apparent diffusion coefficient values predicted dystonia in four- to five-day-old neonates who underwent therapeutic hypothermia for hypoxic ischemic encephalopathy. Objective and clinically feasible neonatal brain imaging assessment could help increase vigilance for dystonia in cerebral palsy.

PMID: 33677143

27. Head circumference trajectory in children with perinatal stroke
Amanda Leong, Amalia Floer, Adam Kirton, Aleksandra Mineyko

J Child Neurol. 2021 Mar 8;883073821996103. doi: 10.1177/0883073821996103. Online ahead of print.

Background: Perinatal stroke is a leading cause of hemiparetic cerebral palsy and lifelong disability. Neurodevelopmental outcomes are difficult to predict and markers of long-term poor outcome continue to be investigated. Deceleration in growth of head circumference has been associated with worse developmental outcomes in neonatal brain injury. We hypothesized that perinatal stroke would result in decreased rates of head growth during childhood that would be associated with worse developmental outcomes. Methods: Patients with magnetic resonance imaging (MRI)-confirmed neonatal arterial ischemic

stroke and arterial presumed perinatal ischemic stroke were identified from a population-based research cohort (Alberta Perinatal Stroke Project). Demographics and occipital-frontal circumference data were collected from medical records. Head growth was compared to typically developing control charts using a 2-tailed t test. The Fisher exact test was used to examine associations between Pediatric Stroke Outcome Measures (PSOM) scores and occipital-frontal head circumference. Results: Three hundred fifteen occipital-frontal head circumference measurements were collected from 102 patients (48 female, 54 male), over a median of 3.2 years (standard deviation = 5.18, range = 0-18.3). After 3 months for female patients and 1 year for male patients, occipital-frontal head circumference deviated and remained below normal growth trajectories ($P < .05$) with a large effect size (Cohen $d > 0.8$). Poor outcome (PSOM ≥ 1) was associated with smaller occipital-frontal head circumference ($P < .05$). Conclusion: Head growth deceleration is observed in children with perinatal arterial ischemic stroke and is associated with poor outcome. Head circumference may be a tool to alert clinicians to the potential of abnormal neurologic outcome.

PMID: 33683972

28. Early Diagnostics and Early Intervention in Neurodevelopmental Disorders-Age-Dependent Challenges and Opportunities
Mijna Hadders-Algra

Review J Clin Med. 2021 Feb 19;10(4):861. doi: 10.3390/jcm10040861.

This review discusses early diagnostics and early intervention in developmental disorders in the light of brain development. The best instruments for early detection of cerebral palsy (CP) with or without intellectual disability are neonatal magnetic resonance imaging, general movements assessment at 2-4 months and from 2-4 months onwards, the Hammersmith Infant Neurological Examination and Standardized Infant NeuroDevelopmental Assessment. Early detection of autism spectrum disorders (ASD) is difficult; its first signs emerge at the end of the first year. Prediction with the Modified Checklist for Autism in Toddlers and Infant Toddler Checklist is possible to some extent and improves during the second year, especially in children at familial risk of ASD. Thus, prediction improves substantially when transient brain structures have been replaced by permanent circuitries. At around 3 months the cortical subplate has dissolved in primary motor and sensory cortices; around 12 months the cortical subplate in prefrontal and parieto-temporal cortices and cerebellar external granular layer have disappeared. This review stresses that families are pivotal in early intervention. It summarizes evidence on the effectiveness of early intervention in medically fragile neonates, infants at low to moderate risk, infants with or at high risk of CP and with or at high risk of ASD.

PMID: 33669727

29. The Medical Benefits of Vitamin K 2 on Calcium-Related Disorders
Zeyad Khalil, Benyamin Alam, Amir Reza Akbari, Harbans Sharma

Review Nutrients. 2021 Feb 21;13(2):691. doi: 10.3390/nu13020691.

Background: Due to the potentially crucial role of vitamin K2 in calcium metabolism, a deficit can disrupt many mechanisms, resulting in an array of different issues, such as broken bones, stiff arteries and poor fertility. Although there has been existing research, the potential of vitamin K2 as a treatment for conditions including cerebral palsy, parathyroid disease, heart disease and gastrointestinal disease is unknown. This review discusses the biochemistry of vitamin K and the metabolism of calcium, followed by an analysis of the current literature available on vitamin K2 and its prospects. Methods: Using public libraries including PubMed and Wiley, we searched for existing research on the metabolism and use of vitamin K2 that has been conducted in the preceding two decades. Results: Data indicated that vitamin K2 had a positive impact on osteoporosis, cardiovascular disease, parathyroid disorders, cerebral palsy and sperm motility. Conclusion: Due to the existence of confounding variables and limitations in the quality and volume of research conducted, further investigation must be done to see whether the beneficial effects seen are reproducible and must assess the viability of vitamin K2 as treatment in isolation for these conditions.

PMID: 33670005

30. Variant recurrence confirms the existence of a FBXO31-related spastic-dystonic cerebral palsy syndrome
Ivana Dzinovic, Matej Škorvánek, Petra Pavelekova, Chen Zhao, Boris Keren, Sandra Whalen, Somayeh Bakhtiari, Sheng Chih Jin, Michael C Kruer, Robert Jech, Juliane Winkelmann, Michael Zech

Ann Clin Transl Neurol. 2021 Mar 6. doi: 10.1002/acn3.51335. Online ahead of print.

The role of genetics in the causation of cerebral palsy has become the focus of many studies aiming to unravel the heterogeneous etiology behind this frequent neurodevelopmental disorder. A recent paper reported two unrelated children with a clinical diagnosis of cerebral palsy, who carried the same de novo c.1000G > A (p.Asp334Asn) variant in FBXO31, encoding a widely studied tumor suppressor not previously implicated in monogenic disease. We now identified a third individual with the recurrent FBXO31 de novo missense variant, featuring a spastic-dystonic phenotype. Our data confirm a link between variant FBXO31 and an autosomal dominant neurodevelopmental disorder characterized by prominent motor dysfunction.

PMID: 33675180

31. Whole genome methylation and transcriptome analyses to identify risk for cerebral palsy (CP) in extremely low gestational age neonates (ELGAN)
An N Massaro, Theo K Bammler, James W MacDonald, Krystle M Perez, Bryan Comstock, Sandra E Juul

Sci Rep. 2021 Mar 5;11(1):5305. doi: 10.1038/s41598-021-84214-9.

Preterm birth remains the leading identifiable risk factor for cerebral palsy (CP), a devastating form of motor impairment due to developmental brain injury occurring around the time of birth. We performed genome wide methylation and whole transcriptome analyses to elucidate the early pathogenesis of CP in extremely low gestational age neonates (ELGANs). We evaluated peripheral blood cell specimens collected during a randomized trial of erythropoietin for neuroprotection in the ELGAN (PENUT Trial, NCT# 01378273). DNA methylation data were generated from 94 PENUT subjects (n = 47 CP vs. n = 47 Control) on day 1 and 14 of life. Gene expression data were generated from a subset of 56 subjects. Only one differentially methylated region was identified for the day 1 to 14 change between CP versus no CP, without evidence for differential gene expression of the associated gene RNA Pseudouridine Synthase Domain Containing 2. iPathwayGuide meta-analyses identified a relevant upregulation of JAK1 expression in the setting of decreased methylation that was observed in control subjects but not CP subjects. Evaluation of whole transcriptome data identified several top pathways of potential clinical relevance including thermogenesis, ferroptossis, ribosomal activity and other neurodegenerative conditions that differentiated CP from controls.

PMID: 33674671