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Cerebral palsy research news

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Interventions and Management

1. Feasibility of Using Joystick-Operated Ride-on-Toys to Promote Upper Extremity Function in Children With Cerebral Palsy: A Pilot Study
Nidhi Amonkar, Patrick Kumavor, Kristin Morgan, Deborah Bubela, Sudha Srinivasan

Pediatr Phys Ther. 2022 Aug 30. doi: 10.1097/PEP.0000000000000944. Online ahead of print.

Purpose: To evaluate the feasibility of implementation, acceptance, and perceived efficacy of a joystick-operated ride-on-toy intervention to promote upper extremity (UE) function in 3- to 14-year-old children with hemiplegic cerebral palsy. Methods: Exit questionnaires were collected from children, caregivers, and clinicians/camp staff following a 3-week ride-on-toy training program incorporated within a summer camp for children with hemiplegic cerebral palsy. Training encouraged children to use their affected UE to maneuver the ride-on-toy. Questionnaires included Likert scale and open-ended questions to assess enjoyment, acceptance, feasibility, and perceived efficacy of the training. Results: All stakeholder groups indicated that the training was enjoyable. Clinicians/staff and caregivers indicated that the training increased children's motivation to use their affected UE and reported perceived improvements in UE movement control and function following training. Conclusions: Our promising preliminary findings call for future research to systematically assess the efficacy of ride-on-toys to promote UE control and function in children with hemiplegic cerebral palsy. Supplemental Digital Content 1 video abstract, available at: http://links.lww.com/PPT/A404.

PMID: 36044637

2. Transition of Caregiver Perceptions after Pediatric Neuromuscular Scoliosis Surgery
Naoyuki Nakamura, Yuichiro Kawabe, Masatoshi Oba, Takako Momose, Jiro Machida, Yutaka Inaba

Spine Surg Relat Res. 2022 Feb 10;6(4):373-378. doi: 10.22603/ssrr.2021-0204. eCollection 2022.

Introduction: Spinal fusion for children with neuromuscular scoliosis has been known to improve sitting balance and quality of life as well as for high caregiver satisfaction. However, most studies performed were single surveys, and it remains unclear whether high satisfaction levels are maintained. Thus, in this article, we report the short- and medium-term improvements in caregiver standing assessment after neuromuscular scoliosis surgery in children with Gross Motor Function Classification System (GMFCS) level IV or V. Methods: In total, 18 patients with GMFCS levels IV and V were included in this study. The underlying diseases were typical cerebral palsy in 12 cases, chromosomal abnormalities in 5 cases, and congenital myopathy in 1 case. The median age at the time of surgery was 14.5 years. The medians for the first and second follow-up surveys were after 1.4 and 5.9 years, respectively. All the patients had undergone posterior spinal fusion, whereas 12 had undergone pelvic fixation. These patients were assessed using a caregiver questionnaire, in addition to patient demographic data and radiographic assessments. Results: The median BMI was 15.4 kg/m2 preoperatively, 16.6 kg/m2 at the first survey, and 17.1

kg/m2 at the second survey. The main Cobb angles were 97.5°, 36.5°, and 37.0° and the spino-pelvic obliquity angles were 22.5°, 6.0°, and 6.5° preoperatively, at the first survey and at the second survey, respectively. In the questionnaire, most domains were rated similarly in the first and second surveys, but the ratings for the "children's QOL" and "digestion and defecation" domains were noted to increase, while that for the "transfer" and "satisfaction with treatment" domains have decreased. Conclusions: Neuromuscular scoliosis surgery in children has been associated with extremely high treatment satisfaction in the early postoperative period. However, some caregivers showed a decline in the "transfer" and "treatment satisfaction" domains over time.

PMID: 36051682

3. Postoperative Immobilization After Hip Reconstruction in Cerebral Palsy: No Difference Between Hip Spica and Abduction Pillow
Alexander L Vasconcellos, Alex S Tagawa, Jason T Rhodes, Lori J Silveira, Austin A Skinner, David B Frumberg

Front Surg. 2022 Jun 6;9:863287. doi: 10.3389/fsurg.2022.863287. eCollection 2022.

Purpose: This study aims to compare radiographic outcomes and complication rates of immobilization with an abduction pillow to spica casting for postoperative care after a hip reconstruction with varus derotational proximal femur osteotomy (VDRO) with or without pelvic osteotomy for children with cerebral palsy (CP). Methods: 233 children (1-18 years old) diagnosed with CP that underwent VDRO with or without pelvic osteotomy were identified, of which 188 patients were immobilized with a spica cast and 45 were immobilized with an abduction pillow, based on surgeon preference. 123 (65%) in the Spica group and 21 (47%) in the pillow group had pelvic osteotomies. Demographic data and complication rates were collected. Radiographic parameters, including anatomic medial proximal femoral angle (aMPFA), acetabular index (AI) and migration percentage (MP), were measured for each patient at the completion of surgery, six weeks post-operatively, and one year post-operatively. Results: There was not a statistically significant difference in BMI ($p = 0.285$), gender distribution ($p = 0.984$), or median follow-up time ($p = 0.314$) between groups. Rates of complications were consistent among groups with no differences in instances of delayed unions ($p = 0.10$), subluxations ($p = 0.55$), infection ($p = 0.71$), or non-unions ($p = 0.10$). There was no statistically significant difference in number of patients with an ideal aMPFA, AI, or MP ($p = 0.44$, $p = 0.19$, $p = 1.00$) at one year post-operatively. Conclusions: Immobilization with an abduction pillow is a safe and effective alternative to hip spica casting following hip reconstruction.

PMID: 36034398

4. Effect of extracorporeal shock wave therapy on spastic equinus foot in children with unilateral cerebral palsy
Hatem A Emara, Ahmed H Al-Johani, Osama A Khaled, Walaa M Ragab, Abdullah M Al-Shenqiti

J Taibah Univ Med Sci. 2022 Feb 26;17(5):794-804. doi: 10.1016/j.jtumed.2021.12.010. eCollection 2022 Oct.

Objectives: This study aims to investigate the effects of radial extracorporeal shock wave therapy on selective motor control, spasticity, gross motor function, and balance in children with unilateral cerebral palsy. Methods: This randomised controlled study recruited 34 children aged 7-9 with spastic unilateral cerebral palsy. They were randomly allocated to either the control or study group. Both groups undertook traditional exercises for 12 weeks. The study group received shock waves (one session/ week) on the calf muscle (1500 shocks, frequency of 4 Hz, energy of 0.030 mJ/mm2). All children were evaluated at baseline and after 12 weeks using the Modified Ashworth Scale, a Biodex System 4 isokinetic dynamometer, dimensions D (standing) and E (walking) of the Gross Motor Function Measure - 88, the Trost Selective Motor Control test, and the single leg standing test. Results: Mixed analysis of variance and Mann-Whitney results showed significant improvement in eccentric peak torque, torque threshold angles, gross motor function, selective motor control, and balance in the study group compared with the control group ($p < 0.05$). Conclusions: Shock wave therapy may be a valuable instrument for reducing spasticity, improving the ability to isolate and control movement, and consequently, improving balance and gross motor function in children with unilateral cerebral palsy.

PMID: 36050947

5. Analysis of Joint Power and Work During Gait in Children With and Without Cerebral Palsy
Priyam Hazra, Sheila Gibbs, Graham Arnold, Sadiq Nasir, Weijie Wang

Indian J Orthop. 2022 Jul 14;56(9):1647-1656. doi: 10.1007/s43465-022-00691-8. eCollection 2022 Sep.

Purpose: To compare joint work in the lower limb joints during different sub-phases of the gait cycle between Cerebral Palsy (CP) and healthy children. Methods: Eighteen CP and 20 healthy children's gait data were collected. The CP group included orthoses, intra-muscular injection of botulinum toxin and surgery groups. A motion capture system was used to collect gait data. Joint work was calculated as positive and negative components in six subphases during gait and normalised by speed when comparing the groups. Results: The CP group had a slower walking speed, smaller stride length and longer stance phase than the healthy group. Hip max positive work was 0.12 ± 0.02 Jkg-1/ms-1 for the CP group in pre-mid-stance but 0.07 ± 0.01 Jkg-1/ms-1 for the healthy group during the terminal phase. In terminal stance, ankle positive work was significantly lower in the CP group (0.12 ± 0.01) than in the healthy group (0.18 ± 0.01). The knee showed a similar distribution of positive work in the stance phase for the two groups. In the ankle and hip, the CP group had energy generation mainly in midstance while the healthy group was mainly in terminal stance. In the ankle, the CP group had larger energy absorption in mid-stance than the healthy children group, while the CP group showed lower energy generation in the terminal stance phase than seen in the healthy group. Conclusion: The qualitative and quantitative analysis of joint work provides useful information for clinicians in the treatment and rehabilitation of CP patients.

PMID: 36046224

6. Reliability and discriminant validity of the quantitative timed up and go in typically developing children and children with cerebral palsy GMFCS levels I-II
Julianna Smith, Michelle DiVito, Andrea Fergus

J Pediatr Rehabil Med. 2022 Aug 26. doi: 10.3233/PRM-210034. Online ahead of print.

Purpose: The purpose of this study was to examine the reliability, and discriminant validity of the Quantitative Timed up and Go (QTUG) in typically developing (TD) children and children with cerebral palsy (CP). Methods: Twenty-eight TD children and 8 with CP (GMFCS I-II) completed 3 TUG trials while wearing QTUG sensors. Test-retest reliability and discriminative ability were examined for the 57 constituent parameters of the TUG. Relationships between age and these parameters were also examined. Results: Forty-four of the parameters demonstrated moderate to excellent test-retest reliability, with measures of angular velocity being the most reliable. Twenty-six parameters were different between TD children and those with CP, and twenty-eight gait parameters demonstrated correlations with age, further supporting its discriminative ability. Conclusion: The QTUG is a clinically feasible tool that is capable of both reliably measuring and discriminating many of the movement parameters with the TUG mobility task in TD children and those with CP GMFCS I-II. The results of the present study provide preliminary evidence that the QTUG can discriminate between children on several of the gait parameters within the TUG.

PMID: 36031915

7. Physical therapy with hippotherapy compared to physical therapy alone in children with cerebral palsy: Systematic review and meta-analysis
No authors listed

Dev Med Child Neurol. 2022 Aug 27. doi: 10.1111/dmcn.15399. Online ahead of print.

No abstract available

PMID: 36030376

8. Detection of periodontal disease activity based on histatin degradation in individuals with cerebral palsy
Gabriela M de Gutierrez, Lina M Marin, Yizhi Xiao, Andrea Escalante-Herrera, Maria T B R Santos, Walter L Siqueira

Heliyon. 2022 Aug 13;8(8):e10134. doi: 10.1016/j.heliyon.2022.e10134. eCollection 2022 Aug.

Objectives: This proof-of-concept study aimed at evaluating the proteolytic profile of histatin 1 and 5 in saliva of adolescents with spastic cerebral palsy (CP) with gingivitis. Methods: This cross-sectional study included 24 individuals allocated into three groups: G1 (CP with gingivitis; n = 8), G2 (without CP and without gingivitis; n = 8), and G3 (without CP and with gingivitis; n = 8). The gingival index (GI) and simplified oral hygiene index (OHI-S) were evaluated. Whole saliva was collected and used to assess the rate and mode of histatin 1 and 5 at different times. The degradation products were visualized after cationic PAGE and the protein band densities (BDs) were compared with a protein standard. Fragmentation products were collected from the gel, pooled by group and characterized by mass spectrometry. BDs and gingival health parameters were analyzed by One-Way ANOVA or Kruskal Wallis tests, whereas poisson multilevel regression was used to the factors that influenced histatin degradation ($\alpha = 5\%$). Results: Groups G1 and G3 differed significantly on OHI-S, visible biofilm, oral calculus and GI ($p < 0.001$). Poisson Regression showed that: 1) CP and gingivitis influenced the degradation of histatin 1 and 5 ($p < 0.05$); 2) The degradation of histatin 5 was influenced by age and male sex ($p < 0.05$); and 3) GI influenced significantly the degradation of histatin 1 ($p < 0.001$). Unique histatin degradation peptides were identified in individuals with gingivitis. Conslusions: These data demonstrated that both the kinetics and pattern of histatins degradation differ according to the gingival health or disease conditions.

PMID: 36046535

9. Vitamin D levels in children with cerebral palsy
Nurdan Paker, Tugce Yavuz Mollavelioglu, Derya Bugdaycı, Kadriye Ones, Ayse Nur Bardak, Ilhan Karacan, Ilgın Yıkıcı, Fatma Nur Kesiktas

J Pediatr Rehabil Med. 2022 Aug 23. doi: 10.3233/PRM-190622. Online ahead of print.

Purpose: The aim of this study was to assess serum vitamin D levels and related factors in children with cerebral palsy (CP). Methods: One hundred and nineteen children with CP between the ages of 1 year to 10 years 9 months who were admitted to the children's inpatient rehabilitation unit of a tertiary rehabilitation hospital between January 1, 2017, and December 31, 2018, were included in this study. Demographic and clinical characteristics were obtained from the patient files. CP types and serum 25 hydroxyvitamin D (25OHD) levels were recorded. Gross Motor Function Classification System (GMFCS) was used to assess the functional level. Results: Mean age was 5.1±2.9 years. Forty-two (35.3%) were girls, 105 (88.3%) were spastic, and 14 (11.7%) were ataxic and mixed type CP. Mean GMFCS level was 4 (IQR:2). Thirty-one (26.1%) were getting extra liquid feed while the rest were eating a normal diet. Mean serum 25OHD level was 27.4±15.7 (3-79) ng/mL. Vitamin D levels were normal in 68 children (57.1%), whereas 36 (30.3%) had vitamin D insufficiency and 15 (12.6%) showed vitamin D deficiency. Those whose serum vitamin D levels were within a normal range had a median age of 3.8 (IQR:4.2) years. On the other hand, mean age was 6.4 (4.3) years for those with low vitamin D level ($p < 0.0001$). Vitamin D level was 19.8 (21.4) ng/mL in those ($n = 88$) who had regular diets, whereas it was 31.0 [16] ng/mL in those ($n = 31$) who were getting extra liquid feed ($p = 0.015$). There was no statistically significant correlation between vitamin D level and gender, GMFCS, CP type, season or antiepileptic drug treatment. A binary logistic regression model showed that older age and having only regular meals were significant risk factors for low vitamin D. Conclusion: In this study, 42.9% of the children with CP had low vitamin D. Older children with CP or those who had regular diets were higher risk groups in terms of low vitamin D.

PMID: 36031913

10. Longitudinal neurological analysis of moderate and severe pediatric cerebral visual impairment
Andres Jimenez-Gomez, Kristen S Fisher, Kevin X Zhang, Chunyan Liu, Qin Sun, Veeral S Shah

Front Hum Neurosci. 2022 Aug 16;16:772353. doi: 10.3389/fnhum.2022.772353. eCollection 2022.

Introduction: Cerebral visual impairment (CVI) results from damage to cerebral visual processing structures. It is the most common cause of pediatric visual impairment in developed countries and rising in prevalence in developing nations. There is

currently limited understanding on how neurologic, developmental, and ophthalmic factors predict outcome for pediatric CVI. Method: A retrospective manual chart review of pediatric CVI patients seen at the tertiary pediatric hospital neurology and neuro-ophthalmology service between 2010 and 2019 was conducted. Patients were stratified into severity groups (based on a custom CVI grading score), and followed over time to identify outcome predictors. Collected baseline characteristics included perinatal, genetic, developmental, and neurologic history, along with neuroimaging and fundoscopic findings on examination. Longitudinal data collected included age, seizure control, and type of therapy received. Linear mixed-effect models were used for longitudinal CVI grade outcome analysis. Results: A total of 249 individuals spanning 779 patient visits were identified. Mean age at diagnosis was 18.8 ± 16.8 months (2-108 months). About 64.3% were born at term age. Perinatal history revealed hypoxic ischemic encephalopathy (HIE) in 16.5%, intraventricular hemorrhage (IVH) in 11.6%, and seizures in 21.7%. At presentation, 60.3% had a diagnosis of cerebral palsy and 84.7% had developmental delay. Among all subjects, 78.6% had epilepsy; 33.8% had an epileptic encephalopathy, with spasms/hypsarrhythmia being most common. Abnormal neuroimaging was present in 93.8%. Genetic anomalies were present in 26.9%. Baseline visual examination revealed no blink-to-light (BTL) in 24.5%; only BTL in 34.5%, fixation/tracking in 26.5%, and optokinetic drum follow in 14.4%. Longitudinal data analysis showed that perinatal history of HIE, a positive epilepsy history, using multiple (≥3) epilepsy medications, cerebral palsy, and abnormal fundoscopic findings were all negatively associated with CVI grade change over time. After controlling for significant confounders, receiving any type of therapy [early childhood intervention (ECI), physical and occupational therapy (PT/OT), refractive error correction or glasses] was significantly associated with longitudinal improvement in CVI grade compared to patients who did not receive any therapy, with glasses yielding the largest benefit. Conclusion: This study offers extensive insights into neurologic, developmental and ophthalmologic features in patients with moderate to severe CVI. In concordance with previous findings, aspects of perinatal history and epilepsy/seizure control may help inform severity and prognosis in the general neurology or ophthalmology clinic. Conversely, these aspects, as well as genetic and specific epilepsy traits may alert vision health care providers in the clinic to pursue visual evaluation in at-risk individuals. Longitudinal follow-up of CVI patients showed that interventional therapies demonstrated vision function improvement greater than no therapy and maturational development.

PMID: 36051970

11. Health-related quality of life in adolescents with cerebral palsy; a cross-sectional and longitudinal population-based study
Selma Mujezinović Larsen, Terje Terjesen, Reidun B Jahnsen, Trond H Diseth, Kjersti Ramstad

Child Care Health Dev. 2022 Aug 30. doi: 10.1111/cch.13055. Online ahead of print.

Aims: The aims of this population-based cross-sectional and longitudinal study were to investigate different aspects of health-related quality of life (HRQoL) in adolescents with cerebral palsy (CP), to define possible changes in HRQoL from childhood to adolescence, and to identify factors associated with low HRQoL in adolescence. Methods: Proxy-reports of 64 adolescents, aged 12-17 years, with bilateral CP in GMFCS levels III-V participating in a surveillance program, included five of the six domains from the HRQoL instrument Caregivers Priorities & Child Health Index of Life with Disabilities (CPCHILD): (1) Activities of Daily Living and Personal Care, (2) Positioning, Transfer and Mobility, (3) Comfort and Emotions, (5) General Health and (6) Overall Quality of Life, and the two questions on pain from the Child Health Questionnaire (CHQ). Fifty-eight participants comprised the longitudinal sample. Results: From childhood to adolescence, the mean CPCHILD domain scores decreased slightly in General Health and remained unchanged in the other four domains. In the domain General Health, the number of medications increased, which was the reason for the score decrease. Pain severity increased significantly. Severe motor impairment was associated with low scores in domains 1, 2, 3 and 5, and more severe pain with low scores in domains 2, 3, 5 and 6. A low domain score in childhood was associated with a low score in each corresponding domain in adolescence. Interpretation An assessment of HRQoL should be included in CP surveillance programs because this could identify needs for interventions in individuals with severe CP. This study indicates the importance of improved pain management in both children and adolescents with severe CP.

PMID: 36041889

12. Teleintervention for users of augmentative and alternative communication devices: A systematic review
Saranda Bekteshi, Marco Konings, Petra Karlsson, Tamaya Van Criekinge, Bernard Dan, Elegast Monbaliu

Review Dev Med Child Neurol. 2022 Aug 31. doi: 10.1111/dmcn.15387. Online ahead of print.

Aim: To synthesize existing evidence on the effectiveness of speech-language teleinterventions delivered via videoconferencing to users of augmentative and alternative communication (AAC) devices. Method: A systematic literature search was conducted in 10 electronic databases, from inception until August 2021. Included were speech-language teleinterventions delivered by researchers and/or clinicians via videoconferencing to users of AAC devices, without restrictions on chronological age and clinical diagnosis. The quality of the studies included in the review was appraised using the Downs and Black checklist and the Single-Case Experimental Design Scale; risk of bias was assessed using the Risk Of Bias In Non-Randomized Studies - of Interventions and the single-case design risk of bias tools. Results: Six teleinterventions including 25 participants with a variety of conditions, such as Down syndrome, autism, Rett syndrome, and amyotrophic lateral sclerosis met the inclusion criteria. Five studies used a single-case experimental design and one was a cohort study. Teleinterventions included active consultation (n = 2), functional communication training (n = 2), brain-computer interface (n = 1), and both teleintervention and in-person intervention (n = 1). All teleinterventions reported an increase in participants' independent use of AAC devices during the training sessions compared to baseline, as well as an overall high satisfaction and treatment acceptability. Interpretation: Speech-language teleinterventions for users of AAC devices show great potential for a successful method of service delivery. Future telehealth studies with larger sample sizes and more robust methodology are strongly encouraged to allow the generalization of results across different populations.

PMID: 36047007

13. Telehealth and remote interventions for children with cerebral palsy: A scoping review
Marina Pagaki-Skaliora, Eileen Morrow, Tim Theologis

JMIR Rehabil Assist Technol. 2022 Aug 29. doi: 10.2196/36842. Online ahead of print.

Background: Remote treatment, or telehealth, has shown promise for children with cerebral palsy (CP) prior to 2020; however, the beginning of the global COVID-19 pandemic limiting access to hospitals for face-to-face treatments has driven the requirements for telehealth and led to a surge in development. Due to the recent developments, there has been limited synthesis of the available evidence of telehealth for children with CP. Objective: To analyse and summarise the existing evidence for telehealth interventions for the treatment of children with CP and identify any areas requiring further research. Methods: A scoping review was performed. A systematic search of available literature in Medline and Pubmed was performed during July 2021. Inclusion criteria for articles were: primary research and systematic reviews, investigating telehealth, including children with CP, published between 2010-2021, and written in English. Exclusion criteria were: secondary research other than systematic reviews, intervention which did not meet the World Health Organisation definition of telehealth, all participants were over 18, children's results were not reported separately, or there were no results reported for children with CP. A scoping review was chosen due to the expected heterogeneity of the participants, as well as expected small sample sizes and inconsistency of measured outcomes; therefore narrative reporting of results was considered appropriate. Results: Six papers were identified which included the results of nine studies. Two of the included articles were systematic reviews, which included results of three studies each. These studies, together with five primary research articles were included in this scoping review. The existing evidence is of low methodological quality, primarily consisting of case series. There is some evidence that requirements of telehealth differ depending on the children's developmental stage and functional level. Telehealth is reported to reduce caregiver burden. There is mixed evidence on children's compliance with telehealth. Overall, the results of telehealth interventions for the treatment of children with CP were positive, indicating either comparable or improved results compared with children receiving usual face-to-face care. Conclusions: The evidence base is lacking in breadth and methodological quality to provide robust clinical recommendations. Most studies investigated hand function only, indicating the limited scope of existing research. However, this review shows that telehealth has demonstrated potential to improve function for children with CP while making healthcare services more accessible and reducing carer burden. Areas requiring further research include telehealth interventions for the lower limb, postural management, pain control and the barriers to implementing telehealth.

PMID: 36041012

14. Risk Factors for Term-Born Periventricular White Matter Injury in Children With Cerebral Palsy: A Case-Control Study
Amaar Marefi, Nafisa Husein, Mary Dunbar, Deborah Dewey, Nicole Letourneau, Maryam Oskoui, Adam Kirton, Michael I Shevell, Canadian Cerebral Palsy Registry (CCPR)

Neurology. 2022 Aug 30;10.1212/WNL.0000000000201274. doi: 10.1212/WNL.0000000000201274. Online ahead of print.

Objective: The aim of this study was to identify possible risk factors associated with term born children with cerebral palsy (CP) and periventricular white matter injury (PVWMI) on imaging. Methods: This is a case-controlled study restricted to term born children with CP with the cases extracted from the Canadian Cerebral Palsy Registry (CCPR) and controls from Alberta Pregnancy Outcomes and Nutrition (APrON) Study. A diagnosis of PVWMI was made based on expert categorization of MRI reports. Risk factor variables were selected a priori; these included pregnancy complications, antenatal toxin exposure, perinatal infection, sex, small for gestational age, and perinatal adversity (i.e. neonatal encephalopathy presumably on the basis of intrapartum hypoxia-ischemia). We used multivariable analyses to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). Results: A total of 160 cases (7.06% of the registry sample) were compared to 1950 controls. Of the term born PVWMI participants, 59.4% were males and 13.5 % were born to mothers of extreme maternal age. Multivariable analysis of each risk factor controlled for weight showed PVWMI is associated with pregnancy complications (OR=3.35; 95% CI=2.23-4.94), antenatal toxin exposure (OR=2.45; 95% CI=1.67-3.55), perinatal infection (OR=3.61; 95% CI=1.96-6.29) and perinatal adversity (OR=2.03; 95% CI=1.42-2.94). Term born males were not more likely to have PVWMI compared to females (OR=1.37; 95% CI=0.98-1.93). Multiple regression analyses suggested independent associations between PVWMI and pregnancy complications (OR=3.75; 95% CI 2.46-5.62), antenatal toxin exposure (OR=2.80; 95% CI 1.88-4.12), perinatal infection (OR=4.62; 95% CI 2.46-8.42) and perinatal adversity (OR=2.49; 95% CI= 1.71-3.69). Conclusions: Risk factors such as pregnancy complications, antenatal toxin exposure, perinatal infection as well as perinatal adversity are associated with PVWMI in term born children, suggesting perhaps variable interactions between antenatal and perinatal factors to yield this under-recognized CP phenotype.

PMID: 36041870

15. Use of parenteral nutrition in the first postnatal week in England and Wales: an observational study using real-world data
James Webbe, Cheryl Battersby, Nicholas Longford, Kayleigh Oughham, Sabita Uthaya, Neena Modi, Chris Gale

BMJ Paediatr Open. 2022 Aug;6(1):e001543. doi: 10.1136/bmjpo-2022-001543.

Background: Parenteral nutrition (PN) is used to provide supplemental support to neonates while enteral feeding is being established. PN is a high-cost intervention with beneficial and harmful effects. Internationally, there is substantial variation in how PN is used, and there are limited contemporary data describing use across Great Britain. Objective: To describe PN use in the first postnatal week in infants born and admitted to neonatal care in England, Scotland and Wales. Method: Data describing neonates admitted to National Health Service neonatal units between 1 January 2012 and 31 December 2017, extracted from routinely recorded data held the National Neonatal Research Database (NNRD); the denominator was live births, from Office for National Statistics. Results: Over the study period 62 145 neonates were given PN in the first postnatal week (1.4% of all live births); use was higher in more preterm neonates (76% of livebirths at <28 weeks, 0.2% of term livebirths) and in neonates with lower birth weight. 15% (9181/62145) of neonates given PN in the first postnatal week were born at term. There was geographic variation in PN administration: the proportion of live births given PN within neonatal regional networks ranged from 1.0% (95% CIs 1.0 to 1.0) to 2.8% (95% CI 2.7 to 2.9). Conclusions and relevance: Significant variation exists in neonatal PN use; it is unlikely this reflects optimal use of an expensive intervention. Research is needed to identify which babies will benefit most and which are at risk of harm from early PN. Trial registration number: ClinicalTrials.gov: NCT03767634; registration date: 6 December 2018.

PMID: 36053624

16. Small-for-gestational-age affects outcomes on singletons and inborn births in extremely preterm infants: a Japanese cohort study
Hideyo Suenaga

Am J Perinatol. 2022 Aug 30. doi: 10.1055/a-1933-4627. Online ahead of print.

Objective: This study aimed to compare the short- and long-term outcomes of extremely preterm small-for-gestational-age (SGA) infants and appropriate-for-gestational-age (AGA) infants in Japan. Study design: We retrospectively assessed 434 SGA and 1716 AGA infants born at 22-27 weeks of gestational age (GA), between 2003 and 2012. Infants were followed up for 3 years, and the clinical characteristics and outcomes were compared. Fisher's exact and Student's t-tests were used for independent sample comparison. Logistic regression was used to identify associated factors. Results: The prevalence of intraventricular hemorrhage ¯ Grade 3 was significantly lower (adjusted odds ratio (aOR), 0.28; 95% confidence interval (CI),

0.11-0.72), and the prevalence of bronchopulmonary dysplasia at 36 weeks GA and the need for home oxygen therapy, significantly higher (aOR, 2.20; 95% CI, 1.66-2.91 and aOR, 2.46; 95% CI, 1.75-3.47, respectively) in SGA infants than in AGA infants. SGA infants born at > 23 weeks GA had a significantly higher prevalence of developmental quotient (DQ) < 70 (aOR, 1.69; 95% CI, 1.08-2.65). Those born at > 25 weeks GA showed a significantly higher prevalence of cerebral palsy (CP) and visual impairment (aOR, 1.92; 95% CI, 1.09-3.39 and aOR, 2.42; 95% CI, 1.21-4.86, respectively). Conclusions: In SGA infants, birth at GA > 23 weeks is an independent risk factor for DQ < 70, and birth at GA > 25 weeks is an independent risk factor for CP and visual impairment. However, we did not consider nutritional and developmental factors, and a longer follow-up would help assess neurodevelopmental outcomes.

PMID: 36041470

17. Serial Long-Term Growth and Neurodevelopment of Very-Low-Birth-Weight Infants: 2022 Update on the Korean Neonatal Network
Ga Won Jeon, Jang Hoon Lee, Minkyung Oh, Yun Sil Chang

J Korean Med Sci. 2022 Aug 29;37(34):e263. doi: 10.3346/jkms.2022.37.e263.

Background: We aimed to evaluate the long-term growth and neurodevelopmental outcomes of very-low-birth-weight infants (VLBWIs, birth weight < 1,500 g) born between 2013, the establishment of the Korean Neonatal Network (KNN), and 2018, both at 18-24 months of corrected age and three years of age, using a nationwide large cohort, and to evaluate whether these outcomes have improved over time since 2013. Methods: This study used data from the annual reports of the KNN for 18-24 months of corrected age (follow-up 1) and three years of age (follow-up 2). Follow-up 1 data were collected from 10,065 eligible VLBWIs born between January 1, 2013, and December 31, 2018. Follow-up 2 data were collected from 8,156 eligible VLBWIs born between January 1, 2013, and December 31, 2017. Results: The overall follow-up rates of VLBWIs at follow-ups 1 and 2 were 74.6% (7,512/10,065) and 57.7% (4,702/8,156), respectively. The overall mortality rate between discharge from the neonatal intensive care unit and follow-up 1 was 1% (104/10,065). The overall mortality rate between follow-ups 1 and 2 was 0.049% (4/8,156). Growth restrictions decreased over time, especially weight growth restrictions, which significantly decreased according to era (17% in infants born in 2013-2014 and 13% in infants born in 2017-2018). Fewer infants were re-hospitalized and required rehabilitative support according to era at follow-up 1. More infants had language developmental delays and required language support according to era, both at follow-ups 1 and 2. The incidence of cerebral palsy has significantly decreased over time, from 6% in infants born in 2013-2014 to 4% in infants born in 2017-2018 at follow-up 1, and from 8% in infants born in 2013-2014 to 5% in infants born in 2017 at follow-up 2. Conclusion: Long-term outcomes of VLBWIs regarding weight growth and cerebral palsy, the most common motor disability in childhood, have improved serially according to era since 2013. However, the rate of infants with language delays requiring language support has increased according to era. Further studies are required on the increased trends of language delay and language support while improving motor outcomes.

PMID: 36038959

18. Postnatal Growth Trajectories and Neurodevelopmental Outcomes Following Bevacizumab Treatment for Retinopathy of Prematurity
David L Zhang, Hawke H Yoon, Raye-Ann O deRegnier, Jennifer Arzu, Safa Rahmani

Clin Ophthalmol. 2022 Aug 20;16:2713-2722. doi: 10.2147/OPTH.S378520. eCollection 2022.

Purpose: To investigate the postnatal growth and neurodevelopment of infants with retinopathy of prematurity (ROP) treated with intravitreal bevacizumab (IVB). Patients and methods: This was a retrospective comparative study. A total of 262 infants were divided among three study groups: 22 treated with intravitreal bevacizumab, 55 treated with laser, and 185 with ROP that resolved without treatment. Infants with nonviable course or hydrocephalus, a source of non-physiologic weight gain, were excluded. Neurodevelopment was assessed with Bayley III scores at 17-28 months if available and presence of hearing loss or cerebral palsy. Weekly weight, height, and head circumference from birth through 50 weeks postmenstrual age (PMA) were modeled to determine differences in growth trajectories following treatment. Results: Comparison of postnatal growth curves from the time of treatment to 50 weeks PMA showed no significant differences in growth trajectories between groups after adjusting for the corresponding growth parameters at birth. Comparison of Bayley scores in patients with available data (n = 120) showed no significant differences. There was an increased risk of cerebral palsy in the IVB group after logistic regression adjusting for baseline confounders, but this did not retain statistical significance after applying the false discovery rate

correction for multiple testing. Conclusion: To our knowledge, this is the first large retrospective study to examine longitudinal growth in infants treated with IVB compared to controls. There were no significant differences in postnatal growth or neurodevelopmental outcomes between groups, which overall continue to support the safety of bevacizumab treatment for ROP.

PMID: 36035240

19. Current concepts of corticosteroids use for prevention of bronchopulmonary dysplasia
Serafina Perrone, Serena Orlando, Chiara Petrolini, Francesca Marinelli, Sabrina Moretti, Mara Corradi, Maurizio Giordano, Giuseppe De Bernardo

Curr Pediatr Rev. 2022 Aug 4. doi: 10.2174/1573396318666220804100251. Online ahead of print.

Despite the use of antenatal steroids, surfactants and protective ventilation, bronchopulmonary dysplasia (BPD) affects 10-89% of preterm infants. Since lung inflammation is central to the BPD pathogenesis, postnatal systemic corticosteroids could reduce the risk of BPD onset in preterm infants, but short and long-term adverse consequences have been underlined in literature after their use (i.e. hyperglycaemia, hypertension, hypertrophic cardiomyopathy, growth failure, gastrointestinal bleeding, cerebral palsy). To avoid their adverse effects, alternative therapeutic strategies such as postponing corticosteroid administration, lowering the cumulative dose, giving pulse rather than continuous doses, or individualizing the dose according to the respiratory condition of the infant have been proposed. Dexamethasone nonetheless remains the first line drug for newborns with severe pulmonary disease beyond the second to third week of life. Hydrocortisone administration in very preterm infants does not appear to be associated with any neurotoxic effects, even if its efficacy in the prevention and treatment of BPD has yet to be clearly demonstrated. Alternative methods of corticosteroids administration seem promising. A positive effect on BPD prevention occurs when budesonide is nebulized and intratracheally instilled with surfactant, but more data are required to establish safety and efficacy in preterm newborns. Additional studies are still needed before the chronic lung disease issue and its related challenges can be solved.

PMID: 36043724

20. Continuous local anaesthetic wound infusion of bupivacaine for postoperative analgesia in neonates: a randomised control trial (CANWIN Study)
Himanshu Popat, Rajeshwar Angiti, Jeewan Jyoti, Annabel Webb, Elizabeth Barnes, Robert Halliday, Nadia Badawi, Jonathan de Lima, Kaye Spence, Gordon Thomas, Albert Shun

BMJ Paediatr Open. 2022 Aug;6(1):e001586. doi: 10.1136/bmjpo-2022-001586.

Objective: To determine the effect of continuous wound infusion of local anaesthetic drug (bupivacaine) on total amount of systemic opioid use in the first 72 hours in newborn infants undergoing laparotomy. Design: A two-arm parallel, open-label randomised controlled trial. Setting: A quaternary newborn intensive care unit. Patients: Infants>37 weeks of gestation undergoing laparotomy for congenital or acquired abdominal conditions. Interventions: Continuous wound infusion of local anaesthetic (bupivacaine) for the first 72 hours along with systemic opioid analgesia (catheter group) or only systemic opioid analgesia (opioid group). Main outcome: Total amount of systemic opioid used within the first 72 hours post laparotomy. Results: The study was underpowered as only 30 of the expected sample size of 70 infants were enrolled. 16 were randomised to catheter group and 14 to opioid group. The two groups were similar at baseline. There was no significant difference between the groups for the primary outcome of median total systemic opioid use in the first 72 hours post laparotomy (catheter 431.5 µg/kg vs opioid 771 µg/kg, difference -339.5 µg/kg, 90% CIhigh 109, p value 0.28). There was no significant difference between the groups for any of the secondary outcomes including pain scores, duration of mechanical ventilation, time to reach full feeds and duration of hospital stay. There were no adverse events noted. Conclusion: Continuous wound infusion of local anaesthetic along with systemic opioid analgesia is feasible. The lack of a difference in total systemic opioid use in the first 72 hours cannot be reliably interpreted as the study was underpowered. Trial registration number: ACTRN12610000633088.

PMID: 36053616

21. The Genetic Landscape of Complex Childhood-Onset Hyperkinetic Movement Disorders
Belén Pérez-Dueñas, Kathleen Gorman, Anna Marcé-Grau, Juan D Ortigoza-Escobar, Alfons Macaya, Federica R Danti, Katy Barwick, Apostolos Papandreou, Joanne Ng, Esther Meyer, Shekeeb S Mohammad, Martin Smith, Francesco Muntoni, Pinki Munot, Johanna Uusimaa, Päivi Vieira, Eammon Sheridan, Renzo Guerrini, Jan Cobben, Sanem Yilmaz, Elisa De Grandis, Russell C Dale, Roser Pons, Kathryn J Peall, Vincenzo Leuzzi, Manju A Kurian

Mov Disord. 2022 Aug 25. doi: 10.1002/mds.29182. Online ahead of print.

Background and objective: The objective of this study was to better delineate the genetic landscape and key clinical characteristics of complex, early-onset, monogenic hyperkinetic movement disorders. Methods: Patients were recruited from 14 international centers. Participating clinicians completed standardized proformas capturing demographic, clinical, and genetic data. Two pediatric movement disorder experts reviewed available video footage, classifying hyperkinetic movements according to published criteria. Results: One hundred forty patients with pathogenic variants in 17 different genes (ADCY5, ATP1A3, DDC, DHPR, FOXG1, GCH1, GNAO1, KMT2B, MICU1, NKX2.1, PDE10A, PTPS, SGCE, SLC2A1, SLC6A3, SPR, and TH) were identified. In the majority, hyperkinetic movements were generalized (77%), with most patients (69%) manifesting combined motor semiologies. Parkinsonism-dystonia was characteristic of primary neurotransmitter disorders (DDC, DHPR, PTPS, SLC6A3, SPR, TH); chorea predominated in ADCY5-, ATP1A3-, FOXG1-, NKX2.1-, SLC2A1-, GNAO1-, and PDE10A-related disorders; and stereotypies were a prominent feature in FOXG1- and GNAO1-related disease. Those with generalized hyperkinetic movements had an earlier disease onset than those with focal/segmental distribution (2.5 ± 0.3 vs. 4.7 ± 0.7 years; P = 0.007). Patients with developmental delay also presented with hyperkinetic movements earlier than those with normal neurodevelopment (1.5 ± 2.9 vs. 4.7 ± 3.8 years; P < 0.001). Effective disease-specific therapies included dopaminergic agents for neurotransmitters disorders, ketogenic diet for glucose transporter deficiency, and deep brain stimulation for SGCE-, KMT2B-, and GNAO1-related hyperkinesia. Conclusions: This study highlights the complex phenotypes observed in children with genetic hyperkinetic movement disorders that can lead to diagnostic difficulty. We provide a comprehensive analysis of motor semiology to guide physicians in the genetic investigation of these patients, to facilitate early diagnosis, precision medicine treatments, and genetic counseling. © 2022 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

PMID: 36054588

22. Hereditary spastic paraparesis (HSP) presenting as cerebral palsy due to ADD3 variant with mechanistic insight provided by a Drosophila γ-adducin model
Silvia Beatriz Sanchez Marco, Edgar Buhl, Rosie Firth, Bangfu Zhu, Mary Gainsborough, Ana Beleza-Meireles, Sandra Moore, Richard Caswell, Karen Stals, Sian Ellard, Cameron Kennedy, James J L Hodge, Anirban Majumdar

Clin Genet. 2022 Aug 31. doi: 10.1111/cge.14220. Online ahead of print.

Introduction: Cerebral palsy (CP) causes neurological disability in early childhood. Hypoxic-ischaemic injury plays a major role in its aetiology, nevertheless, genetic and epigenetic factors may contribute to the clinical presentation. Mutations in ADD3 (encoding γ-adducin) gene have been described in a monogenic form of spastic quadriplegic cerebral palsy (OMIM 601568). Methods: We studied a sixteen-year-old male with spastic diplegia. Several investigations including neurometabolic testing, brain and spine magnetic resonance imaging (MRI) and CGH-Array were normal. Further, clinical genetics assessment and Whole Exome Sequencing (WES) gave the diagnosis. We generated an animal model using Drosophila to study the effects of γ-adducin loss and gain of function. Results: WES revealed a biallelic variant in the ADD3 gene, NM_016824.5(ADD3): c.1100G>A, p.(Gly367Asp). Mutations in this gene have been described as an ultra-rare autosomal recessive which is a known form of inherited cerebral palsy. Molecular modelling suggests that this mutation leads to a loss of structural integrity of γ-adducin and is therefore expected to result in a decreased level of functional protein. Pan-neuronal over-expression or knock-down of the Drosophila ortholog of ADD3 called hts caused a reduction of life span and impaired locomotion thereby phenocopying aspects of the human disease. Conclusion: Our animal experiments present a starting point to understand the biological processes underpinning the clinical phenotype and pathogenic mechanisms, to gain insights into potential future methods for treating or preventing ADD3 related spastic quadriplegic cerebral palsy.

PMID: 36046955

23. Discrimination between hereditary spastic paraplegia and cerebral palsy based on gait analysis data: A machine learning approach
Bruce A MacWilliams, Kristen L Carroll, Alan K Stotts, Lynne M Kerr, Michael H Schwartz

Gait Posture. 2022 Aug 17;98:34-38. doi: 10.1016/j.gaitpost.2022.08.011. Online ahead of print.

Background: There is no current consensus on how to differentiate between hereditary spastic paraplegia and spastic cerebral palsy on the basis of clinical presentation. Several previous studies have investigated differences in kinematic parameters obtained from clinical gait analysis. None have attempted to combine multiple gait and physical exam measures to discriminate between these two diagnoses. This study aims to investigate the ability of a machine learning approach using data from clinical gait analysis to differentiate these cohorts. Methods: A retrospective analysis of a gait database compiled a dataset of 179 gait and physical exam variables from 28 individuals (62 analyses) diagnosed with hereditary spastic paraplegia and 678 (1504 analyses) with bilateral spastic cerebral palsy. This data was used in a Bayesian additive regression tree (BART) analysis classified by medical record diagnosis. A 10-fold cross validation generated probabilistic distribution that each analysis was from an individual carrying the hereditary spastic paraplegia diagnosis. A diagnostic probability cutoff threshold balanced type I and type II errors. Predicted versus actual diagnoses were classified into a contingency table. Results: The algorithm was able to correctly classify the two diagnoses with 91% specificity and 90% sensitivity. Conclusions: A machine learning approach using data from clinical gait analysis was able to distinguish participants with hereditary spastic paraplegia from those with bilateral spastic cerebral palsy with high specificity and sensitivity. This algorithm can be used to assess if individuals seen for gait disorders who do not yet have a definitive diagnosis have characteristics associated with hereditary spastic paraplegia. The results of the model inform the decision to suggest genetic testing to either confirm or refute the diagnosis of hereditary spastic paraplegia.

PMID: 36041285

24. Five-year risk of fracture and subsequent fractures among adults with cerebral palsy
Daniel G Whitney, Gregory A Clines, Aleda M Leis, Michelle S Caird, Edward A Hurvitz

Bone Rep. 2022 Aug 20;17:101613. doi: 10.1016/j.bonr.2022.101613. eCollection 2022 Dec.

Background: Epidemiologic evidence documenting the incidence of fracture and subsequent fractures among adults with cerebral palsy (CP) is lacking, which could inform fracture prevention efforts. The objective was to characterize the 5-year rate of initial and subsequent fragility fractures among adults with CP. Methods: This retrospective cohort study used Medicare claims from 01/01/2008-12/31/2019 from adults ≥18 years old with CP (n = 44,239) and elderly ≥65 years old without CP (n = 2,176,463) as a comparison. The incidence rate (IR), IR ratio (IRR), and site distribution were estimated for the initial and subsequent fragility fractures over 5-years by sex and age. Results: The IR of fragility fracture at any site over the 5-year follow-up was similar for 18-30-year-old men with CP (IR = 5.2; 95%CI = 4.4-5.9) and 30-34-year-old women with CP (IR = 6.3; 95%CI = 5.3-7.2) compared to the same sex youngest-old (65-74 years old) without CP (IRR = 1.09 and 0.94, respectively, both P > 0.05), and increased with older age for those with CP. The number of fragility fractures and IR of subsequent fragility fractures was similar for young men and middle-aged women with CP compared to elderly without CP, and increased with older age for those with CP. The proportion of fragility fracture at the tibia/fibula decreased while the vertebral column and multiple simultaneous sites (most involved hip/lower extremities) increased with older age. Conclusion: Young and middle-aged adults with CP had similar-to-worse initial and subsequent fragility fracture profiles compared to the general elderly population- a well characterized group for bone fragility. Findings emphasize the need for fracture prevention efforts at younger ages for CP, possibly by ~5 decades younger.

PMID: 36052289

25. Post-fracture rehabilitation pathways and association with mortality among adults with cerebral palsy
Daniel G Whitney, Tao Xu, Dayna Ryan, Daniel Whibley, Michelle S Caird, Edward A Hurvitz, Heidi Haapala

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Objective: Rehabilitation may mitigate the high mortality rates and health declines post-fracture for adults with cerebral palsy,

but this is understudied. The objectives were to characterize the post-fracture rehabilitation pathways and identify their association with 1-year survival among adults with cerebral palsy. Methods: A retrospective cohort study of adults with cerebral palsy with a fragility fracture with continuous health plan enrollment ≥1-year prior to and ≥1 day after their fracture date was performed using a random 20% Medicare fee-for-service dataset. Participants were categorized as a home discharge or inpatient rehabilitation admission post-fracture. For the home discharge cohort, weekly exposure to outpatient physical/occupational therapy (PT/OT) was examined up to 6-month post-fracture. Cox regression examined the association between time-varying PT/OTuse within 6-month post-fracture and mortality from 30 days to 1-year post-fracture before and after adjusting for confounders (e.g. medical complexity). Results: Of 3598 adults with cerebral palsy with an incident fragility fracture, 74% were discharged home without inpatient rehabilitation; they were younger, but more medically complex compared to the 26% admitted to inpatient rehabilitation. Among the home discharge cohort (n = 2662), 43.1% initiated PT/OTwithin 6-month post-fracture, and cumulative PT/OTexposure post-fracture was associated with improved survival; for example, per 3 weeks of PT/OTexposure, the adjusted mortality rate was 40% lower (95% confidence interval (CI) = 0.41-0.89). Conclusions: Most adults with cerebral palsy with a fragility fracture were discharged home rather than to inpatient rehabilitation, and only 43.1% of that group initiated outpatient PT/OTwithin 6 months post-fracture. Receiving outpatient PT/OTwas associated with improved 1-year survival.

PMID: 36039504

Prevention and Cure

26. Neonatal Hypoxic-Ischemic Encephalopathy: Perspectives of Neuroprotective and Neuroregenerative Treatments
Karina A Pedroza-García, Denisse Calderón-Vallejo, J Luis Quintanar

Neuropediatrics. 2022 Aug 28. doi: 10.1055/s-0042-1755235. Online ahead of print.

Hypoxic-ischemic encephalopathy (HIE) is a serious condition that could have deleterious neurological outcomes, such as cerebral palsy, neuromotor disability, developmental disability, epilepsy, and sensitive or cognitive problems, and increase the risk of death in severe cases. Once HIE occurs, molecular cascades are triggered favoring the oxidative stress, excitotoxicity, and inflammation damage that promote cell death via apoptosis or necrosis. Currently, the therapeutic hypothermia is the standard of care in HIE; however, it has a small window of action and only can be used in children of more than 36 gestational weeks; for this reason, it is very important to develop new therapies to prevent the progression of the hypoxic-ischemic injury or to develop neuroregenerative therapies in severe HIE cases. The objective of this revision is to describe the emerging treatments for HIE, either preventing cell death for oxidative stress, excitotoxicity, or exacerbated inflammation, as well as describing a new therapeutic approach for neuroregeneration, such as mesenchymal stem cells, brain-derived neurotrophic factor, and gonadotropin realizing hormone agonists.

PMID: 36030792

27. Safety and feasibility of autologous cord blood infusion for improving motor function in young children with cerebral palsy in Japan: A single-center study
Hiroaki Kikuchi, Shiho Saitoh, Terumasa Tsuno, Rina Hosoda, Nobuyasu Baba, Feifei Wang, Naomi Mitsuda, Masayuki Tsuda, Nagamasa Maeda, Yusuke Sagara, Mikiya Fujieda

Brain Dev. 2022 Aug 29;S0387-7604(22)00154-1. doi: 10.1016/j.braindev.2022.08.004. Online ahead of print.

Introduction: Cerebral palsy (CP) is the most prevalent motor disorder of childhood. It typically results from in utero or perinatal brain injury. Recently, it has been reported that autologous cord blood (ACB) infusion for children with CP improved gross motor function and brain connectivity, but unfortunately, it has never been tried in Japan. We conducted a pilot study of the infusing of ACB, which was delivered from private bank, in the children with CP to assess the safety and feasibility to the procedure as well as any effect in improving neurological function. Methods: After demonstrating the induction of tissue regeneration in animal model studies conducted a single-arm pilot study of intravenous ACB infusion in 6 young Japanese children with CP (ages 1-6 years). Primary outcomes were safety assessed by vital signs, clinical symptoms, and blood and

urinary examinations at baseline and 1 weeks, 1, 2 and 3 years after treatment. In addition, motor function evaluations, neurodevelopmental examinations, magnetic resonance imaging, and electroencephalography (EEG) were performed at the same time. Results: Infusion was generally well-tolerated, although one patient experienced microhematuria 1 year after treatment and another one patient experienced febrile convulsion once 9 months after treatment. These events were transient, no relapse was seen during observation study. All patients improved a median of 6.8 points on the 1-year Gross Motor Functional Measure-66 (GMFM-66) scores, greater than predicted by age and severity. Furthermore, the 2-year and 3-year GMFM-66 scores were also greater than expected (median 6.2 points and 5.5 points, respectively). Overall scales and language -social scales of the developmental quotient (DQ) improved in 3 of 6 patients, who had greater changes in their GMFM-66 scores than the other cases after treatment. There were no significant correlations among the GMFM-66 scores, DQ, and infusion cell counts. Conclusion: ACB infusion was safe and feasible for clinical use in patients with CP. However, much more clinical study with larger numbers of patients and in-depth studies of treatment mechanism of CP are needed.

PMID: 36050140

28. Caffeine Restores Neuronal Damage and Inflammatory Response in a Model of Intraventricular Hemorrhage of the Preterm Newborn

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Front Cell Dev Biol. 2022 Aug 12;10:908045. doi: 10.3389/fcell.2022.908045. eCollection 2022.

Germinal matrix-intraventricular hemorrhage (GM-IVH) is the most frequent intracranial hemorrhage in the preterm infant (PT). Long-term GM-IVH-associated sequelae include cerebral palsy, sensory and motor impairment, learning disabilities, or neuropsychiatric disorders. The societal and health burden associated with GM-IVH is worsened by the fact that there is no successful treatment to limit or reduce brain damage and neurodevelopment disabilities. Caffeine (Caf) is a methylxanthine that binds to adenosine receptors, regularly used to treat the apnea of prematurity. While previous studies support the beneficial effects at the brain level of Caf in PT, there are no studies that specifically focus on the role of Caf in GM-IVH. Therefore, to further understand the role of Caf in GM-IVH, we have analyzed two doses of Caf (10 and 20 mg/kg) in a murine model of the disease. We have analyzed the short (P14) and long (P70) effects of the treatment on brain atrophy and neuron wellbeing, including density, curvature, and phospho-tau/total tau ratio. We have analyzed proliferation and neurogenesis, as well as microglia and hemorrhage burdens. We have also assessed the long-term effects of Caf treatment at cognitive level. To induce GM-IVH, we have administered intraventricular collagenase to P7 CD1 mice and have analyzed these animals in the short (P14) and long (P70) term. Caf showed a general neuroprotective effect in our model of GM-IVH of the PT. In our study, Caf administration diminishes brain atrophy and ventricle enlargement. Likewise, Caf limits neuronal damage, including neurite curvature and tau phosphorylation. It also contributes to maintaining neurogenesis in the subventricular zone, a neurogenic niche that is severely affected after GM-IVH. Furthermore, Caf ameliorates small vessel bleeding and inflammation in both the cortex and the subventricular zone. Observed mitigation of brain pathological features commonly associated with GM-IVH also results in a significant improvement of learning and memory abilities in the long term. Altogether, our data support the promising effects of Caf to reduce central nervous system complications associated with GM-IVH.

PMID: 36035990