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NEWS
Cerebral Palsy Research

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Interventions and Management

1. Psychometric and Clinimetric Properties of the Melbourne Assessment 2 in Children with Cerebral Palsy.

Wang TN, Liang KJ, Liu YC, Shieh JY, Chen HL.

Arch Phys Med Rehabil. 2017 Feb 27. pii: S0003-9993(17)30097-7. doi: 10.1016/j.apmr.2017.01.024. [Epub ahead of print]

OBJECTIVE: The Melbourne Assessment 2 (MA2) is increasingly used as an outcome measurement in clinical studies. The purposes of this study were to examine its psychometric and clinimetric properties. DESIGN: Psychometric and clinimetric study. SETTING: Community. PARTICIPANTS: Seventeen children with CP from 5 to 12 years were recruited for the estimation of the test-retest reliability and minimal detectable change (MDC). Thirty-five children with CP were recruited to receive an eight-week intensive neurorehabilitation intervention to estimate the validity, responsiveness, and minimal clinically important difference (MCID). INTERVENTIONS: Thirty-five children with CP received upper limb neurorehabilitation programs for eight weeks. MAIN OUTCOME MEASURES: The Melbourne Assessment 2 (MA2) and the criterion measures, including the Bruininks-Oseretsky Test of Motor Proficiency 2nd (BOT-2), the Box and Blocks Test (BBT), and the Pediatric Motor Activity Log-Revised (PMAL-R) were evaluated at pretreatment and posttreatment. RESULTS: The MA2 has four subscales: range of motion, fluency, accuracy, and dexterity. The test-retest reliability of the MA2 is high (ICC=0.92-0.98). The significant relationships between the MA2 and BBT, BOT-2, and PMAL-R support its validity. The significance of paired t test results ($p<0.001$) and large magnitudes of the SRM (1.70-2.00) confirm the responsiveness of the MA2. The MDC values of the four subscales of the MA2 are 2.85, 1.63, 1.97, and 1.84, respectively, and the suggested MCID values of these four subscales are 2.35, 3.20, 2.09, and 2.22, respectively, indicating the minimum scores of improvement to be interpreted as both statistically significant and clinically important. CONCLUSIONS: The findings of this study indicate that the MA2 has sound psychometric and clinimetric properties and is thus an adequate measurement for research and clinical applications.

PMID: 28254639

2. The cost-effectiveness of a web-based multimodal therapy for unilateral cerebral palsy: the Mitii randomized controlled trial.

Comans T, Mihala G, Sakzewski L, Boyd RN, Scuffham P.

Dev Med Child Neurol. 2017 Mar 1. doi: 10.1111/dmcn.13414. [Epub ahead of print]

AIM: To estimate the cost-effectiveness of the Mitii training system for improvements in upper limb function for children with unilateral cerebral palsy (CP). Mitii is a web-based programme delivered at home with set-up and monitoring by therapists. METHOD: A randomized controlled trial was conducted comparing the Mitii training programme to usual care. The Assessment of Motor and Process Skills (AMPS) and Canadian Occupational Performance Measure (COPM) were collected for each child at baseline and 20 weeks. Responders to training were characterized as those who met a minimally

important difference on either the AMPS (0.3 logits) or COPM (2 points). Costs of the intervention were calculated by quantifying the equipment and staff cost. A cost per responder was calculated for each of the outcome measures. RESULTS: A total of 102 participants (52 males, 50 females) were included in the analysis. There were significantly more responders in the training group on both the AMPS motor and process scales and the COPM performance and satisfaction scales. The cost per responder for the Mitii programme ranged from AU$3078 to AU$4191 depending on the scale used. INTERPRETATION: The cost of delivering the Mitii training system is modest relative to the improvements in function.

PMID: 28247406

3. Feasibility and effect of home-based therapy programmes for children with cerebral palsy: a protocol for a systematic review.

Beckers LW, Schnackers ML, Janssen-Potten YJ, Kleijnen J, Steenbergen B.

BMJ Open. 2017 Feb 24;7(2):e013687. doi: 10.1136/bmjopen-2016-013687.

INTRODUCTION: Given the promising advantages of upper extremity home-based programmes in children with cerebral palsy (CP), a systematic review of the available literature on this topic is warranted. The purpose of the systematic review described in this protocol is to investigate currently available home-based occupational therapy and physiotherapy programmes regarding both their feasibility and effect. METHODS AND ANALYSIS: This protocol describes a systematic review, developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015. Studies will be included in which primary data are collected, participants are children aged <18 years with any type of CP and the intervention of interest is a home-based occupational therapy or physiotherapy intervention. Comparators of interest are: no therapy, care as usual, centre-based occupational therapy or physiotherapy, an alternative home-based programme and a medical intervention. Studies will be included that report either on feasibility (ie, acceptability, demand, implementation, practicality, adaptation, expansion or integration) or on efficacy/effectiveness (ie, child-related upper extremity outcomes within all International Classification of Functioning, Disability and Health levels or parent-related/caregiver-related outcomes on the psychological and social domain). Relevant studies will be identified by searching the databases MEDLINE, EMBASE, CINAHL, PsycINFO, PEDro, OTSeeker and CPCI-S as well as the trial registers ICTRP and CENTRAL, the reference lists of included records and by circulating a bibliography of the included records to authors of included studies. There will be no restrictions on language or year of publication. The search strategy consists of terms related to the population and intervention. Data will be extracted in duplicate using a digital data extraction form.

PMID: 28237960

4. Effectiveness of robot-assisted gait training in children with cerebral palsy: a bicenter, pragmatic, randomized, cross-over trial (PeLoGAIT).

Ammann-Reiffer C, Bastiaenen CH, Meyer-Heim AD, van Hedel HJ.

BMC Pediatr. 2017 Mar 2;17(1):64. doi: 10.1186/s12887-017-0815-y.

BACKGROUND: Walking ability is a priority for many children with cerebral palsy (CP) and their parents when considering domains of importance regarding treatment interventions. Partial body-weight supported treadmill training has become an established therapeutic treatment approach to address this demand. Further, new robotic rehabilitation technologies have increasingly been implemented in the clinical setting to allow for longer training sessions with increased step repetitions while maintaining a consistent movement pattern. But the current evidence about its clinical effectiveness in pediatric rehabilitation is weak. The aim of this research project is therefore to investigate the effectiveness of robot-assisted gait training on improvements of functional gait parameters in children with cerebral palsy. METHODS/DESIGN: Children aged 6 to 18 years with bilateral spastic cerebral palsy who are able to walk at least 14 m with or without walking aids will be recruited in two pediatric therapy centers in Switzerland. Within a pragmatic cross-over design with randomized treatment sequences, they perform 5 weeks of robot-assisted gait training (three times per week with a maximum of 45 min walking time each) or a 5-week period of standard treatment, which is individually customized to the needs of the child and usually consists of 1-2 sessions of physiotherapy per week and additional hippotherapy, circuit training as well as occupational therapy as necessary. Both interventions take place in an outpatient setting. The percentage score of the dimension E of the Gross Motor Function Measure-88 (GMFM-88) as primary outcome as well as the dimension D of the GMFM-88, 6-minute and 10-meter walking tests as secondary outcomes are assessed before and at the end of each intervention period. Additionally, a 5-week follow-up assessment is scheduled for the children who are assigned to the standard treatment first. Treatment effects, period effects as well as follow-up effects are analyzed with paired analyses and independent test statistics are used to assess carry-over effects.

DISCUSSION: Although robot-assisted gait training has become an established treatment option to address gait impairments, evidence for its effectiveness is vague. This pragmatic trial will provide important information on its effects under clinical outpatient conditions.

PMID: 28253887

5. Predictors for anterior pelvic tilt following surgical correction of flexed knee gait including patellar tendon shortening in children with cerebral palsy.

Böhm H, Hösl M, Döderlein L.

Gait Posture. 2017 Feb 21;54:8-14. doi: 10.1016/j.gaitpost.2017.02.015. [Epub ahead of print]

INTRODUCTION: Patellar tendon shortening procedure within single event multilevel surgeries was shown to improve crouch gait in Cerebral Palsy (CP) patients. However, one of the drawbacks associated to the correction of flexed knee gait may be increased pelvic anterior tilt with compensatory lumbar lordosis. RESEARCH QUESTION: Which CP patients are at risk for excessive anterior pelvic tilt following correction of flexed knee gait including patellar tendon shortening? METHODS: 32 patients with CP between 8 and 18 years GMFCS I&II were included. They received patellar tendon shortenings within multilevel surgery. Patients with concomitant knee flexor lengthening were excluded. Gait analysis and clinical testing was performed pre- and 24.1 (SD=1.9) months postoperatively. Patients were subdivided into more/less than 5° increase in anterior pelvic tilt. Preoperative measures indicating m. rectus and m. psoas shortness, knee flexor over-length, hip extensor and abdominal muscle weakness and equinus gait were compared between groups. Stepwise multilinear regression of the response value increase in pelvic tilt during stance phase was performed from parameters that were significantly different between groups. RESULTS: 34% of patients showed more than 5° increased pelvic anterior tilt postoperatively. Best predictors for anterior pelvic tilt from preoperative measures were increased m. rectus tone and reduced hip extension during walking that explained together 39% of the variance in increase of anterior pelvic tilt. DISCUSSION: Every third patient showed considerable increased pelvic tilt following surgery of flexed knee gait. In particular patients with preoperative higher muscle tone in m. rectus and lower hip extension during walking were at risk and both features need to be addressed in the therapy.

PMID: 28242571

6. Part 2: Adaptation of Gait Kinematics in Unilateral Cerebral Palsy Demonstrates Preserved Independent Neural Control of Each Limb.

Bulea TC, Stanley CJ, Damiano DL.

Front Hum Neurosci. 2017 Feb 13;11:50. doi: 10.3389/fnhum.2017.00050. eCollection 2017.

Motor adaptation, or alteration of neural control in response to a perturbation, is a potential mechanism to facilitate motor learning for rehabilitation. Central nervous system deficits are known to affect locomotor adaptation; yet we demonstrated that similar to adults following stroke, children with unilateral brain injuries can adapt step length in response to unilateral leg weighting. Here, we extend our analysis to explore kinematic strategies underlying step length adaptation and utilize dynamical systems approaches to elucidate how neural control may differ in those with hemiplegic CP across legs and compared to typically developing controls. Ten participants with hemiplegic CP and ten age-matched controls participated in this study. Knee and hip joint kinematics were analyzed during unilateral weighting of each leg in treadmill walking to assess adaptation and presence and persistence of after-effects. Peak joint angle displacement was used to represent changes in joint angles during walking. We examined baseline and task-specific variability and local dynamic stability to evaluate neuromuscular control across groups and legs. In contrast to controls, children with unilateral CP had asymmetries in joint angle variability and local dynamic stability at baseline, showing increased variability and reduced stability in the dominant limb. Kinematic variability increased and local stability decreased during weighting of ipsilateral and contralateral limbs in both groups compared to baseline. After weight removal both measures returned to baseline. Analogous to the temporal-spatial results, children with unilateral CP demonstrated similar capability as controls to adapt kinematics to unilateral leg weighting, however, the group with CP differed across sides after weight removal with dominant limb after-effects fading more quickly than in controls. The change in kinematics did not completely return to baseline in the non-dominant limb of the CP group, producing a transient improvement in joint angle symmetry. Recent studies demonstrate that neural control of gait is multi-layered with distinct circuits for different types of walking and for each leg. Remarkably, our results demonstrate that children with unilateral brain injury retain these separate circuits for each leg during walking and, importantly, that those networks can be adapted independently from one another to improve symmetry in the short term.

PMID: 28243195

7. Long-term therapy with intrathecal baclofen improves quality of life in children with severe spastic cerebral palsy.

Kraus T, Gegenleitner K, Svehlik M, Novak M, Steinwender G, Singer G.

Eur J Paediatr Neurol. 2017 Feb 11. pii: S1090-3798(17)30098-3. doi: 10.1016/j.ejpn.2017.01.016. [Epub ahead of print]

INTRODUCTION: Children with severe spastic cerebral palsy (CP) are highly limited in daily life activities causing a reduced quality of life (QoL). This is partly due to an increased muscle tone causing pain and contractures. Continuous intrathecal infusion of baclofen (ITB) reduces the spasticity of affected patients. The hypothesis of the present study was that ITB leads to a significant improvement of QoL in non-ambulant children with CP. PATIENTS AND METHODS: 13 patients (10 male, 3 female, mean age 14 years) were included. Mean time between pump implantation and follow-up was 60 months (range, 12-100). QoL was assessed before and after baclofen pump implantation using standardized questionnaires (CP CHILD, KINDL). Spasticity was evaluated using the modified Ashworth Scale (MAS) at the two time points. RESULTS: QoL evaluated with the CPCHILD questionnaire and the KINDL improved from pre - implantation to follow-up. MAS markedly decreased from 3.8 to 1.7. All interviewed participants indicated that their expectations had been met and that they would choose ITB treatment again. CONCLUSION: Intrathecal treatment of baclofen is an excellent method for spasticity management in children with severe cerebral palsy. Quality of life sustainably improves, parents' satisfaction is high and the level of spasticity decreases. Therefore, baclofen treatment can be highly recommended in non-ambulant children with CP suffering from spasticity.

PMID: 28237420

8. Comments on: "Total hip replacement in young non-ambulatory cerebral palsy patients" by C. Morin et al., published in Orthop Traumatol Surg Res 2016 30;102:845-849.

Fontaine CJ.

Orthop Traumatol Surg Res. 2017 Feb 27. pii: S1877-0568(17)30053-1. doi: 10.1016/j.otsr.2017.02.002. [Epub ahead of print]

[Commentary on the original article by Morin et al]

PMID: 28254469

9. Bone mineral density and insulin-like growth factor-1 in children with spastic cerebral palsy.

Nazif H, Shatla R, Elsayed R, Tawfik E, Osman N, Korra S, Ibrahim A.

Childs Nerv Syst. 2017 Feb 24. doi: 10.1007/s00381-017-3346-9. [Epub ahead of print]

BACKGROUND: Children with cerebral palsy (CP) have significant decrease linear growth rate and low bone mineral density (BMD). AIMS: This study is to evaluate BMD in children with CP and its relation to the levels of insulin-like growth factor-1 (IGF-1). SUBJECTS AND METHODS: This cross-sectional study was carried out on 58 children suffering from spastic CP with the age range 4-12 years compared to 19 controls. All assessed by dual energy x-ray absorptiometry (DXA) to measure BMD, serum level of IGF-1, and serum vitamin D. The patients were classified according to their GMFCS. RESULTS: Fractures were reported in seven (12.1%) of cases. Our study demonstrated that, IGF-1 level and BMD decrease in correlation with the severity of CP. IGF-1correlates positively with serum vitamin D, BMI, and BMD. CP children with severe GMFCS level or who use anticonvulsive drugs are at a high risk for low BMD and low levels of IGF-1. CONCLUSION: Both BMD and IGF-1 were significantly in low children with spastic CP; IGF-1 negatively correlates with the severity of osteopenia in children with spastic. Children with CP who are not independently ambulant or with severe GMFCS level or who use anticonvulsive drugs are at a high risk for developing low BMD.

PMID: 28236062

10. Theory of mind, emotional and social functioning, and motor severity in children and adolescents with dystonic cerebral palsy.

Adegboye D, Sterr A, Lin JP, Owen TJ.

Eur J Paediatr Neurol. 2017 Jan 31. pii: S1090-3798(17)30073-9. doi: 10.1016/j.ejpn.2017.01.013. [Epub ahead of print]

AIMS: This cross-sectional study aimed to investigate whether children and adolescents with dystonic cerebral palsy (CP) present with emotional and social difficulties along side motor limitations. PARTICIPANTS/MEASURES: Twenty-two verbal and nonverbal children and adolescents with dystonic CP were compared with a normative sample of twenty children and adolescents on measures of theory of mind (ToM), emotion regulation (ER), and social difficulties (SD). RESULTS: Higher social and emotional difficulties were found in the dystonic CP group compared to the control group. Nonverbal participants with dystonic CP were found to present with greater social impairment and lower ToM ability than their verbal counterparts. Emotional regulation and hyperactivity and attentional difficulties (HAD) significantly predicted ToM ability and social difficulties. Lower Gross Motor Function Classification System (GMFCS) level and IQ also contributed to differences in ToM ability. INTERPRETATION: Findings support the need for greater attention to the emotional health and social development of children/adolescents with dystonic CP, along with assessments of motor difficulties in the planning and implementation of interventions and individual care plans. Further research is needed to explore links between motor disorder and mental state understanding in this clinical group.

PMID: 28237421

11. Immigrant Generational Status and Developmental Problems among Prematurely Born Children.

Bediako PT, BeLue R, Hillemeier MM.

J Immigr Minor Health. 2017 Mar 1. doi: 10.1007/s10903-017-0560-1. [Epub ahead of print]

Immigrants in the U.S. often have comparatively favorable health outcomes despite relative socioeconomic disadvantage- a phenomenon termed the Immigrant Paradox. This study examined the relationship between family immigrant status and developmental problems among children born preterm. The 2011-2012 National Survey of Children's Health data collected through a telephone based survey based on parental report of prematurity and other comorbidities were analyzed using multivariate logistic regression analysis to examine seven developmental outcomes. Preterm 1st/2nd generation children had fewer developmental problems than preterm 3rd generation children. Controlling for socioeconomic status and other covariates, 1st/2nd generation children had significantly lower odds of developmental delay, cerebral palsy, epilepsy, and hearing problems. Consistent with the Immigrant Paradox, prematurely born children of immigrants had comparable or better developmental outcomes than preterm children of US born parents despite socioeconomic disadvantage. Further research to explicate mechanisms responsible for the protective health effects observed is warranted.

PMID: 28251422

12. Leisure participation-preference congruence of children with cerebral palsy: a Children's Assessment of Participation and Enjoyment International Network descriptive study.

Imms C, King G, Majnemer A, Avery L, Chiarello L, Palisano R, Orlin M, Law M.

Dev Med Child Neurol. 2017 Apr;59(4):380-387. doi: 10.1111/dmcn.13302. Epub 2016 Nov 5.

AIM: To examine participation-preference congruence, regional differences in participation-preference congruence, and predictors of whether children with cerebral palsy participate in preferred activities. METHOD: The sample (n=236) included 148 males and 88 females aged 10 to 13 years, living in Victoria, Australia (n=110), Ontario (n=80), or Quebec (n=46), Canada. Ninety-nine (41.9%) were classed at Gross Motor Function Classification System (GMFCS) level I; 89 (37.7%) at GMFCS level II/III; and 48 (20.3%) at GMFCS level IV/V. Participants completed the Children's Assessment of Participation and Enjoyment and Preferences for Activity of Children questionnaires. Regional comparisons were performed using one-way analyses of variance and factors influencing participation-preference congruence were explored using multiple linear regression. RESULTS: The proportion of children doing non-preferred activities in each activity type was generally low (2-

17%), with only one regional difference. Higher proportions were not doing preferred active physical (range 23.2-29.1% across regions), skill-based (range 21.7-27.9% across regions), and social activities (range 12.8-14.5% across regions). GMFCS level was the most important predictor associated with not doing preferred activities. INTERPRETATION: Children with cerebral palsy did not always participate in preferred active physical and skill-based activities. Understanding discrepancies between preferences and actual involvement may allow families and rehabilitation professionals to address participation barriers.

PMID: 28252187

13. Deliberately Light Interpersonal Contact Affects the Control of Head Stability During Walking in Children and Adolescents with Cerebral Palsy.

Schulleri KH, Burfeind F, Höß-Zenker B, Feketené Szabó É, Herzig N, Ledebt A, Johannsen L.

Arch Phys Med Rehabil. 2017 Feb 27. pii: S0003-9993(17)30099-0. doi: 10.1016/j.apmr.2017.01.026. [Epub ahead of print]

OBJECTIVE: To evaluate the potential of deliberately light interpersonal touch (IPT) for reducing excessive head and trunk sway during self-paced walking in children and adolescents with cerebral palsy (CP). DESIGN: Quasi-experimental, proof-of-concept study with between-groups comparison. SETTING: Ambulant care facility, community center. PARTICIPANTS: 26 individuals with CP (spastic and ataxic; GMFCS I-III; mean=9.8y; f=11, m=15) and in 39 typically developed (TD) children and adolescents (mean=10.0y; f=23, m=16). INTERVENTIONS: ipt applied by a therapist to locations at the back and the head. MAIN OUTCOME MEASURES: As primary outcomes head and trunk sway during self-paced walking were assessed by inertial measurement units. Secondary outcomes were average step length and gait speed. RESULTS: CP group: apex and occiput IPT reduced head velocity sway compared to thoracic IPT (both p=0.04) irrespective of individuals' specific clinical symptoms. TD group: all testing conditions reduced head velocity sway compared to walking alone (all $p \leq 0.03$) as well as in apex and occiput IPT compared to paired walking (both $p \leq 0.02$). CONCLUSIONS: Deliberately light IPT at the apex of the head alters control of head sway in children and adolescents with CP. The effect of IPT varies as a function of contact location and acts differently in TD individuals.

PMID: 28254638

14. Self-concept research in cerebral palsy: development of a population-specific measure.

Causgrove Dunn J.

Dev Med Child Neurol. 2017 Feb 28. doi: 10.1111/dmcn.13407. [Epub ahead of print]

[This commentary is on the original article by Cheong et al.]

PMID: 28244591

Prevention and Cure

15. Cerebral Palsy-Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention.

Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O.

Front Pediatr. 2017 Feb 13;5:21. doi: 10.3389/fped.2017.00021. eCollection 2017.

Cerebral palsy (CP) is the most common motor disability in childhood. This syndrome is the manifestation of intrauterine pathologies, intrapartum complications, and the postnatal sequel, especially among preterm neonates. A double hit model theory is proposed suggesting that an intrauterine condition along with intrapartum or postnatal insult lead to the development of CP. Recent reports demonstrated that treatment during the process of preterm birth such as magnesium sulfate and postnatal

modalities such as cooling may prevent or reduce the prevalence of this syndrome. Moreover, animal models demonstrated that postnatal treatment with anti-inflammatory drugs coupled with nanoparticles may affect the course of the disease in pups with neuroinflammation. This review will describe the changes in the epidemiology of this disease, the underlying prenatal mechanisms, and possible treatments that may reduce the prevalence of CP and alter the course of the disease.

PMID: 28243583

16. Primary Human Cytomegalovirus (HCMV) Infection in Pregnancy.

Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K.

Dtsch Arztebl Int. 2017 Jan 27;114(4):45-52. doi: 10.3238/arztebl.2017.0045.

BACKGROUND: In 0.5-4% of pregnancies, the prospective mother sustains a primary infection with human cytomegalovirus (HCMV). An HCMV infection of the fetus in the first or second trimester can cause complex post-encephalitic impairment of the infant brain, leading to motor and mental retardation, cerebral palsy, epilepsy, retinal defects, and progressive hearing loss. METHODS: This review is based on pertinent publications from January 2000 to October 2016 that were retrieved by a selective search in PubMed employing the terms "cytomegalovirus and pregnancy" and "congenital cytomegalovirus." RESULTS: 85-90% of all neonates with HCMV infection are asymptomatic at birth. The main long-term sequela is hearing impairment, which develops in 8-15% of these affected children. Hygienic measures can lower the risk of primary HCMV infection in pregnancy by 50-85%. The first randomized and controlled trial (RCT) of passive immunization with an HCMV-specific hyper - immune globulin (HIG) preparation revealed a trend toward a lower risk of congenital transmission of the virus (30% versus 44% with placebo, $p = 0.13$). The effect of HIG was more marked in the initial non-randomized trial (15% versus 40%, $p = 0.02$). The RCT also showed HIG to be associated with a higher frequency of fetal growth retardation and premature birth (13% versus 2%, $p = 0.06$). Valaciclovir is a further, non-approved treatment option. CONCLUSION: In the absence of an active vaccine against HCMV, counseling about hygienic measures may currently be the single most effective way to prevent congenital HCMV infection. Moreover, HCMV serologic testing is recommended in the guideline of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF). Further randomized trials of treatment with HIG and with valaciclovir are urgently needed so that the options for the prevention and treatment of congenital HCMV infection can be assessed.

PMID: 28241924

17. Olig1 is required for Noggin-induced neonatal myelin repair.

Sabo JK, Heine V, Silbereis JC, Schirmer L, Levison SW, Rowitch DH.

Ann Neurol. 2017 Mar 2. doi: 10.1002/ana.24907. [Epub ahead of print]

Objective - Neonatal white matter injury (NWMI) is a lesion found in preterm infants that can lead to cerebral palsy. Although antagonists of bone morphogenetic protein (BMP) signaling, such as Noggin, promote oligodendrocyte precursor cell (OPC) production after hypoxic-ischemic injury, the downstream functional targets are poorly understood. The bHLH protein Olig1 promotes oligodendrocyte (OL) development and is essential during remyelination in adult mice. Here, we investigated whether Olig1 function is required downstream of BMP antagonism for the response to injury in the neonatal brain. Methods - We used wild type and Olig1 mutant mice subjected to neonatal stroke and postnatal neural progenitor cultures, and we analyzed Olig1 expression in human postmortem samples from neonates that suffered hypoxic-ischemic encephalopathy (HIE). Results - Olig1-null neonatal mice showed significant hypomyelination after moderate neonatal stroke. Surprisingly, damaged white matter tracts in Olig1-/- mice lacked Olig2+ OPCs and instead proliferating neuronal precursors and GABAergic interneurons were present. We demonstrate that Noggin-induced OPC production requires Olig1 function. In postnatal neural progenitors, Noggin governs production of OLs versus interneurons through Olig1-mediated repression of Dlx1/2 transcription factors. Additionally, we observed that Olig1 and the BMP signaling effector pSMAD1/5/8 are elevated in the subventricular zone (SVZ) of human infants with HIE compared to controls. Interpretation - These findings indicate that Olig1 has a critical function in the regulation of the postnatal neural progenitor cell production in response to Noggin.

PMID: 28253550

18. Comparative analysis of curative effect of bone marrow mesenchymal stem cell and bone marrow mononuclear cell transplantation for spastic cerebral palsy.

Liu X, Fu X, Dai G, Wang X, Zhang Z, Cheng H, Zheng P, An Y.

J Transl Med. 2017 Feb 24;15(1):48. doi: 10.1186/s12967-017-1149-0.

BACKGROUND: Bone marrow mesenchymal stem cells (BMMSCs) and bone marrow mononuclear cells (BMMNCs) are both used to treat spastic cerebral palsy. However, the differences in therapeutic effect remain unknown. METHODS: A total of 105 patients with spastic cerebral palsy were enrolled and randomly assigned to three groups: the BMMSC group, the BMMNC group and the control group. Patients in both transplantation groups received four intrathecal cell injections. Patients in the control group received Bobath therapy. The gross motor function measure (GMFM) and the fine motor function measure (FMFM) were used to evaluate the therapeutic efficacy before transplantation and 3, 6, and 12 months after transplantation. RESULTS: Three months after cell transplantation, scores in the A dimension of GMFM and the A and C dimensions of FMFM scores in the BMMSC group are all higher than those of the BMMNC and the control groups ($P < 0.05$). Six months after cell transplantation, scores in the A, B dimensions of GMFM and the A, B, C, D, and E dimensions of FMFM scores in the BMMSC group are higher than those of the BMMNC and the control groups ($P < 0.05$). Twelve months after cell transplantation, scores in the A, B, and C dimensions of GMFM and the A, B, C, D, and E dimensions of FMFM scores in the BMMSC group are all higher than those of the BMMNC and the control groups ($P < 0.05$). No obvious adverse effects were investigated during follow-up. CONCLUSIONS: BMMSC transplantation for the treatment of cerebral palsy is safe and feasible, and can improve gross motor and fine motor function significantly. In addition, compared with BMMNC, the motor function of children improved significantly in terms of gross motor and fine motor functions.

PMID: 28235424