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Interventions and Management

1. *Dev Med Child Neurol.* 2015 Jan 27. doi: 10.1111/dmcn.12702. [Epub ahead of print]

Randomized comparison trial of density and context of upper limb intensive group versus individualized occupational therapy for children with unilateral cerebral palsy.

Sakzewski L1, Miller L, Ziviani J, Abbott DF, Rose S, Macdonell RA, Boyd RN.

AIM: To determine whether short-term intensive group-based therapy combining modified constraint-induced movement therapy and bimanual therapy (hybrid-CIMT) is more effective than an equal total dose of distributed individualized occupational therapy (standard care) on upper limb motor and individualized outcomes. **METHOD:** Fifty-three children with unilateral cerebral palsy (69% males; mean age 7y 10mo, SD 2y 4mo; Manual Ability Classification System level I, n=24; level II, n=23) were randomly allocated, and 44 received either hybrid-CIMT (n=25) or standard care (n=19). Standard care comprised six weekly occupational therapy sessions and a 12-week home programme. Outcomes were assessed at baseline, 13 weeks, and 26 weeks after treatment. **RESULTS:** Groups were equivalent at baseline. Standard care achieved greater gains on satisfaction with occupational performance after intervention (estimated mean difference -1.2, 95% CI -2.2 to -0.1; p=0.04) and Assisting Hand Assessment at 26 weeks (estimated mean difference 3.1, 95% CI 0.2-6.0; p=0.04). Both groups demonstrated significant improvements in dexterity of the impaired upper limb, and bimanual and occupational performance over time. The differences between groups were not clinically meaningful. **INTERPRETATION:** There were no differences between the two models of therapy delivery. Group-based intensive camps may not be readily available; however, individualized standard care augmented with a home programme may offer an effective alternative but needs to be provided at a sufficient dose.

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2. *Acta Orthop.* 2015 Jan 30:1-7. [Epub ahead of print]

Gait improvement surgery in ambulatory children with diplegic cerebral palsy.

Terjesen T1, Lofterød B, Skaaret I.

Background and purpose - Instrumented 3-D gait analyses (GA) in children with cerebral palsy (CP) have shown improved gait function 1 year postoperatively. Using GA, we assessed the outcome after 5 years and evaluated parental satisfaction with the surgery and the need for additional surgery. **Patients and methods** - 34 ambulatory children with spastic diplegia had preoperative GA. Based on this GA, the children underwent 195 orthopedic

procedures on their lower limbs at a mean age of 11.6 (6-19) years. On average, 5.7 (1-11) procedures per child were performed. Outcome measures were evaluation of gait quality using the gait profile score (GPS) and selected kinematic parameters, functional level using the functional mobility scale (FMS), and the degree of parental satisfaction. Results - The mean GPS improved from 20.7° (95% CI: 19-23) preoperatively to 15.4° (95% CI: 14-17) 5 years postoperatively. There was no significant change in GPS between 1 and 5 years. The individual kinematic parameters at the ankle, knee, and hip improved statistically significantly, as did gait function (FMS). The mean parental satisfaction, on a scale from 0 to 10, was 7.7 (2-10) points. There was a need for additional surgical procedures in 14 children; this was more frequent in those who had the index operation at an early age. Interpretation - The main finding was that orthopedic surgery based on preoperative GA gave marked improvements in gait function and quality, which were stable over a 5-year period. Nevertheless, additional orthopedic procedures were necessary in almost half of the children and further follow-up with GA for more than 1 year postoperatively is recommended in children with risk factors for such surgery.

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3. Brain. 2015 Jan 25. pii: awu399. [Epub ahead of print]

Gait training facilitates central drive to ankle dorsiflexors in children with cerebral palsy.

Willerslev-Olsen M1, Petersen TH2, Farmer SF3, Nielsen JB4.

Foot drop and toe walking are frequent concerns in children with cerebral palsy. The main underlying cause of these problems is early damage and lack of maturation of the corticospinal tract. In the present study we investigated whether 4 weeks of daily treadmill training with an incline may facilitate corticospinal transmission and improve the control of the ankle joint in children with cerebral palsy. Sixteen children with cerebral palsy (Gross Motor Classification System I:6, II:6, III:4) aged 5-14 years old, were recruited for the study. Evaluation of gait ability and intramuscular coherence was made twice before and twice after training with an interval of 1 month. Gait kinematics were recorded by 3D video analysis during treadmill walking with a velocity chosen by the child at the first evaluation. Foot pressure was measured by force sensitive foot soles during treadmill and over ground walking. EMG-EMG coherence was calculated from two separate electrode recordings placed over the tibialis anterior muscle. Training involved 30 min of walking daily on a treadmill with an incline for 30 days. Gait training was accompanied by significant increases in gait speed, incline on the treadmill, the maximal voluntary dorsiflexion torque, the number and amplitude of toe lifts late in the swing phase during gait and the weight exerted on the heel during the early stance phase of the gait cycle. EMG-EMG coherence in the beta and gamma frequency bands recorded from tibialis anterior muscle increased significantly when compared to coherence before training. The largest changes in coherence with training were observed for children <10 years of age. Importantly, in contrast to training-induced EMG increases, the increase in coherence was maintained at the follow-up measurement 1 month after training. Changes in the strength of coherence in the beta and gamma band were positively correlated with improvements in the subjects' ability to lift the toes in the swing phase. These data show that daily intensive gait training increases beta and gamma oscillatory drive to ankle dorsiflexor motor neurons and that it improves toe lift and heel strike in children with cerebral palsy. We propose that intensive gait training may produce plastic changes in the corticospinal tract, which are responsible for improvements in gait function.

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4. Clin Rehabil. 2015 Jan 30. pii: 0269215514565947. [Epub ahead of print]

Outcomes of gait trainer use in home and school settings for children with motor impairments: A systematic review.

Paleg G1, Livingstone R2.

OBJECTIVE: To summarize and critically appraise evidence regarding use of gait trainers (walkers providing trunk and pelvic support) at home or school with children who are unable to walk independently or with hand-held walkers. DATA SOURCES: Searches were performed in seven electronic databases including EBM Reviews,

CINAHL, Medline and EMBASE for publications in English from database inception to November 2014. REVIEW METHODS: Included studies involved at least one child with a mobility limitation and measured an outcome related to gait trainer use. Articles were appraised using American Academy of Cerebral Palsy and Developmental Medicine criteria for group and single-subject designs and quality ratings completed for studies rated levels I-III. The PRISMA statement was followed with inclusion criteria set a priori. Two reviewers independently screened titles, s and full-text articles. RESULTS: Seventeen studies involving 182 children were included. Evidence from one small randomized controlled trial suggests a non-significant trend toward increased walking distance while the other evidence level II study (concurrent multiple baseline design) reports increased number of steps. Two level III studies (non-randomized two-group studies) report statistically significant impact on mobility level with one finding significant impact on bowel function and an association between increased intervention time and bone mineral density. Remaining descriptive level evidence provides support for positive impact on a range of activity outcomes, with some studies reporting impact on affect, motivation and participation with others. CONCLUSIONS: Evidence supporting outcomes for children using gait trainers is primarily descriptive and, while mainly positive, is insufficient to draw firm conclusions.

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5. Clin Rehabil. 2015 Jan 30. pii: 0269215514566249. [Epub ahead of print]

Over ground walking and body weight supported walking improve mobility equally in cerebral palsy: A randomised controlled trial.

Swe NN1, Sendhilnathan S2, van Den Berg M3, Barr C4.

OBJECTIVE: To assess partial body weight supported treadmill training versus over ground training for walking ability in children with mild to moderate cerebral palsy. DESIGN: Randomised controlled trial. SETTING: A Special Needs school in Singapore. SUBJECTS: Thirty children with cerebral palsy, aged 6-18, with a Gross Motor Function Classification System score of II-III. INTERVENTIONS: Two times 30 minute sessions of walking training per week for 8 weeks, progressed as tolerated, either over ground (control) or using partial body weight supported treadmill training (intervention). MAIN MEASURES: The 10 metre walk test, and the 6 minute walk test. Secondary measures were sub-sections D and E on the Gross Motor Function Measure. Outcomes were assessed at baseline, and after 4 and 8 weeks of training. RESULTS: There was no effect of group allocation on any outcome measure, while time was a significant factor for all outcomes. Walking speed improved significantly more in the intervention group by week 4 (0.109 (0.067)m/s vs 0.048 (0.071)m/s, P=0.024) however by week 8 the change from baseline was similar (intervention 0.0160 (0.069)m/s vs control 0.173 (0.109)m/s, P=0.697). All gains made by week 4 were significantly improved on by week 8 for the 10 metre walk test, 6 minute walk test, and the gross motor function measure. CONCLUSIONS: Partial body weight supported treadmill training is no more effective than over ground walking at improving aspects of walking and function in children with mild to moderate cerebral palsy. Gains seen in 4 weeks can be furthered by 8 weeks.

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6. Dev Med Child Neurol. 2015 Jan 27. doi: 10.1111/dmcn.12703. [Epub ahead of print]

Validity of the OMNI rating of perceived exertion scale for children and adolescents with cerebral palsy.

Fragala-Pinkham M1, O Neil ME, Lennon N, Forman JL, Trost SG.

AIM: This study evaluated the validity of the OMNI Walk/Run Rating of Perceived Exertion (OMNI-RPE) scores with heart rate and oxygen consumption (VO₂) for children and adolescents with cerebral palsy (CP). METHOD: Children and adolescents with CP, aged 6 to 18 years and Gross Motor Function Classification System (GMFCS) levels I to III completed a physical activity protocol with seven trials ranging in intensity from sedentary to moderate-to-vigorous. VO₂ and heart rate were recorded during the physical activity trials using a portable indirect calorimeter and heart rate monitor. Participants reported OMNI-RPE scores for each trial. Concurrent validity was assessed by

calculating the average within-subject correlation between OMNI-RPE ratings and the two physiological indices. RESULTS: For the correlational analyses, 48 participants (22 males, 26 females; age 12y 6mo, SD 3y 4mo) had valid bivariate data for VO₂ and OMNI-RPE, while 40 participants (21 males, 19 females; age 12y 5mo, SD 2y 9mo) had valid bivariate data for heart rate and OMNI-RPE. VO₂ ($r=0.80$; 95% CI 0.66-0.88) and heart rate ($r=0.83$; 95% CI 0.70-0.91) were moderately to highly correlated to OMNI-RPE scores. No difference was found for the correlation of physiological data and OMNI-RPE scores across the three GMFCS levels. The OMNI-RPE scores increased significantly in a dose-response manner ($F_{6,258} = 116.1$, $p < 0.001$) as exercise intensity increased from sedentary to moderate-to-vigorous. INTERPRETATION: OMNI-RPE is a clinically feasible option to monitor exercise intensity in ambulatory children and adolescents with CP.

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7. Infect Immun. 2015 Jan 26. pii: IAI.00063-15. [Epub ahead of print]

The HC domain of Botulinum Neurotoxin A is Not the Only Site That Binds Neurons: HN also Plays a very Active Role in Toxin-Cell binding and Interactions.

Ayyar BV1, Aoki KR2, Atassi MZ3.

Botulinum neurotoxins (BoNT) possess unique specificity for nerve terminals. They bind to the presynaptic membrane then translocate intracellularly where the light chain endopeptidase cleaves the SNARE complex proteins, subverting synaptic exocytosis responsible for acetylcholine release to the synaptic cleft. This inhibits acetylcholine binding to its receptor causing paralysis. Binding, an obligate event for cell intoxication, is believed to occur through the heavy chain HC domain. It is followed by toxin translocation and entry into the cell cytoplasm which is thought to be mediated by the HN domain. Sub-molecular mapping analysis by synthetic peptides spanning BoNT/A, using mouse brain synaptosomes (snps) and protective antibodies against toxin, from mice and cervical dystonia patients undergoing BoNT/A treatment, revealed that not only regions of HC but also HN are involved in the toxin binding process. Based on these findings, we expressed a peptide corresponding to the BoNT/A region HN 729-845. HN729-845 bound directly to mouse brain synaptosomes (snps) and inhibited substantially BoNT/A binding to snps. The binding involved gangliosides GT1b, GD1a and few membrane lipids. The peptide bound to human or mouse neuroblastoma cells within 1 min. Peptide HN729-845 protected mice completely against a lethal BoNT/A dose (1.05 x LD₁₀₀). This protective activity was obtained at a comparable dose to that of peptide 967-1296 in the HC domain. These findings strongly indicate that HN729-845, and by extension the HN domain, is fully programmed and equipped to bind to neuronal cells and in the free state can even inhibit the binding of the toxin.

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8. Arch Phys Med Rehabil. 2015 Jan 20. pii: S0003-9993(14)01274-X. doi: 10.1016/j.apmr.2014.11.011. [Epub ahead of print]

Predicting the Response to Botulinum Toxin Treatment in Children With Cerebral Palsy.

Lin YC1.

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9. J Paediatr Child Health. 2015 Jan 26. doi: 10.1111/jpc.12789. [Epub ahead of print]

Bone density assessment in a tertiary paediatric centre over 13 years: Referral patterns and limitations.

Jones AR1, Zacharin MR, Cameron FJ, Simm PJ.

AIM: This study aims to examine the referral practices for the Royal Children's Hospital (RCH) bone density service over the past 13 years and to demonstrate referral patterns and possible limitations to accessing paediatric bone densitometry. **METHODS:** All patients attending the RCH Healthy Bones Unit for bone densitometry from 1 July 1999 to 30 June 2012, aged under 18 years of age, were included. Densitometry results were downloaded directly from the Hologic scanner into an Excel document. However, the referring unit and indication for referral were collected manually from either the referral card or the hospital's scanned medical records system. **RESULTS:** A total of 5767 bone densitometry scans were performed over the study period on 3004 patients. The majority of referrals were made by the Endocrinology department, followed by Adolescent Medicine, Gastroenterology and Neurology. Relatively few referrals were made by general paediatrics. The most common indication for bone density test overall was eating disorders, followed by steroid use, osteogenesis imperfecta and other collagen disorders and inflammatory bowel disease. The lowest lumbar spine z-scores by indication were for cerebral palsy and other causes of immobility. **CONCLUSIONS:** Multiple childhood diseases predispose to low bone density; however, paediatric bone densitometry is still underutilised and not appropriately supported by subsidies.

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10. Bone Joint J. 2015 Feb;97-B(2):270-6. doi: 10.1302/0301-620X.97B2.34280.

Avascular necrosis as a complication of the treatment of dislocation of the hip in children with cerebral palsy.

Koch A1, Jozwiak M1, Idzior M1, Molinska-Glura M2, Szulc A1.

We investigated the incidence and risk factors for the development of avascular necrosis (AVN) of the femoral head in the course of treatment of children with cerebral palsy (CP) and dislocation of the hip. All underwent open reduction, proximal femoral and Dega pelvic osteotomy. The inclusion criteria were: a predominantly spastic form of CP, dislocation of the hip (migration percentage, MP > 80%), Gross Motor Function Classification System, (GMFCS) grade IV to V, a primary surgical procedure and follow-up of > one year. There were 81 consecutive children (40 girls and 41 boys) in the study. Their mean age was nine years (3.5 to 13.8) and mean follow-up was 5.5 years (1.6 to 15.1). Radiological evaluation included measurement of the MP, the acetabular index (AI), the epiphyseal shaft angle (ESA) and the pelvic femoral angle (PFA). The presence and grade of AVN were assessed radiologically according to the Kruczynski classification. Signs of AVN (grades I to V) were seen in 79 hips (68.7%). A total of 23 hips (18%) were classified between grades III and V. Although open reduction of the hip combined with femoral and Dega osteotomy is an effective form of treatment for children with CP and dislocation of the hip, there were signs of avascular necrosis in about two-thirds of the children. There was a strong correlation between post-operative pain and the severity of the grade of AVN. Cite this article: Bone Joint J 2015;97-B:270-6.

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11. J Pediatr Orthop. 2015 Jan 28. [Epub ahead of print]

Postoperative Complications After Hip Surgery in Patients With Cerebral Palsy: A Retrospective Matched Cohort Study.

DiFazio R1, Vessey JA, Miller P, Van Nostrand K, Snyder B.

BACKGROUND: Little is known about the postoperative complications experienced by patients with severe cerebral palsy (CP) (GMFCS IV-V) compared with otherwise healthy patients with hip pathology requiring surgery. The purpose of this study was to determine whether differences exist between these 2 groups with respect to the incidence, type, and severity of complications. In addition, we evaluated the risk factors for complications and the number and cost of additional visits, hospital admissions, and repeat surgeries due to complications. **METHODS:** Retrospective matched cohort study of 55 patients aged 3 to 25 years with severe CP and 55 non-CP patients with hip dysplasia who underwent hip osteotomies (2000 to 2012). Postoperative complications were evaluated using

the adapted Clavien-Dindo classification system. Binary and ordinal logistic regressions were used to identify risk factors for complications. The number and cost of unplanned visits, admissions, and surgeries were calculated. RESULTS: CP patients experienced almost twice as many complications as the non-CP patients ($P=0.004$). All types of complications occurred in both groups except orthopaedic complications ($P<0.001$) were more frequent in the non-CP group. CP patients were 82% more likely to develop a complication compared with non-CP patients (relative risk=1.82; 95% confidence interval=1.21 to 2.76). The severity of complications was comparable with no significant differences in the relative distribution between the groups. There was a significant difference between groups for the number of unplanned clinic and emergency department visits ($P\leq 0.001$). The average cost for treating a complication was \$1857.00 for CP and \$1800.00 for non-CP ($P=0.72$). CONCLUSIONS: Although patients with severe CP requiring hip surgery have a 65% chance of experiencing at least 1 postoperative complication compared with 36% of non-CP patients, most of the complications were medical in the CP patients ($n=46$, 83%) as opposed to the non-CP patient who experienced predominantly orthopaedic complications (59%). When these complications occur the associated costs are greater for CP patients as a whole, but are relatively similar per patient.

LEVEL OF EVIDENCE: Prognostic, case-control study-Level III.

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12. J Spec Pediatr Nurs. 2015 Jan 29. doi: 10.1111/jspn.12106. [Epub ahead of print]

Children with cerebral palsy: why are they awake at night? A pilot study.

Petersen S1, Harvey A, Reddihough D, Newall F.

PURPOSE: The purpose of this study was to assess acceptability of study design and utility of assessment tools for determining causes of sleep disturbance in children with cerebral palsy (CP) and their caregivers. DESIGN AND METHODS: This pilot study explored parental report ($n = 8$) of the child's sleep using a validated sleep questionnaire, a survey, and a time use diary. RESULTS: The selected tools were appropriate. Study design provided challenges for recruitment. Future research should include qualitative data. PRACTICE IMPLICATIONS: Although further research is required to confirm results, sleep problems for children with CP and resulting sleep disturbances for caregivers may be an important part of clinical assessment.

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Prevention and Cure

13. *Curr Med Chem.* 2015 Jan 14. [Epub ahead of print]

Neonatal Brain Hemorrhage (NBH) of Prematurity: Translational Mechanisms of the Vascular-Neural Network.

Lekic T, Klebe D, Poblete R, Krafft PR, Rolland WB, Tang J, Zhang JH1.

Neonatal brain hemorrhage (NBH) of prematurity is an unfortunate consequence of preterm birth. Complications result in shunt dependence and long-term structural changes such as post-hemorrhagic hydrocephalus, periventricular leukomalacia, gliosis, and neurological dysfunction. Several animal models are available to study this condition, and many basic mechanisms, etiological factors, and outcome consequences, are becoming understood. NBH is an important clinical condition, of which treatment may potentially circumvent shunt complication, and improve functional recovery (cerebral palsy, and cognitive impairments). This review highlights key pathophysiological findings of the neonatal vascular-neural network in the context of molecular mechanisms targeting the post-hemorrhagic hydrocephalus affecting this vulnerable infant population.

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14. *Front Neurol.* 2015 Jan 9;5:284. doi: 10.3389/fneur.2014.00284. eCollection 2014.

Movement recognition technology as a method of assessing spontaneous general movements in high risk infants.

Marcroft C1, Khan A2, Embleton ND3, Trenell M4, Plötz T2.

Preterm birth is associated with increased risks of neurological and motor impairments such as cerebral palsy. The risks are highest in those born at the lowest gestations. Early identification of those most at risk is challenging meaning that a critical window of opportunity to improve outcomes through therapy-based interventions may be missed. Clinically, the assessment of spontaneous general movements is an important tool, which can be used for the prediction of movement impairments in high risk infants. Movement recognition aims to capture and analyze relevant limb movements through computerized approaches focusing on continuous, objective, and quantitative assessment. Different methods of recording and analyzing infant movements have recently been explored in high risk infants. These range from camera-based solutions to body-worn miniaturized movement sensors used to record continuous time-series data that represent the dynamics of limb movements. Various machine learning methods have been developed and applied to the analysis of the recorded movement data. This analysis has focused on the detection and classification of atypical spontaneous general movements. This article aims to identify recent translational studies using movement recognition technology as a method of assessing movement in high risk infants. The application of this technology within pediatric practice represents a growing area of interdisciplinary collaboration, which may lead to a greater understanding of the development of the nervous system in infants at high risk of motor impairment.

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15. *Glia.* 2015 Jan 27. doi: 10.1002/glia.22788. [Epub ahead of print]

The thrombin receptor is a critical extracellular switch controlling myelination.

Yoon H1, Radulovic M, Drucker KL, Wu J, Scarisbrick IA.

Hemorrhagic white matter injuries in the perinatal period are a growing cause of cerebral palsy yet no neuroprotective strategies exist to prevent the devastating motor and cognitive deficits that ensue. We demonstrate that the thrombin receptor (protease-activated receptor 1, PAR1) exhibits peak expression levels in the spinal cord at term and is a critical regulator of the myelination continuum from initiation to the final levels achieved. Specifically, PAR1 gene deletion resulted in earlier onset of spinal cord myelination, including substantially more

Olig2-positive oligodendrocytes, more myelinated axons, and higher proteolipid protein (PLP) levels at birth. In vitro, the highest levels of PAR1 were observed in oligodendrocyte progenitor cells (OPCs), being reduced with differentiation. In parallel, the expression of PLP and myelin basic protein (MBP), in addition to Olig2, were all significantly higher in cultures of PAR1^{-/-} oligodendroglia. Moreover, application of a small molecule inhibitor of PAR1 (SCH79797) to OPCs in vitro increased PLP and MBP expression. Enhancements in myelination associated with PAR1 genetic deletion were also observed in adulthood as evidenced by higher amounts of MBP and thickened myelin sheaths across large, medium, and small diameter axons. Enriched spinal cord myelination in PAR1^{-/-} mice was coupled to increases in extracellular-signal-regulated kinase 1/2 and AKT signaling developmentally. Nocturnal ambulation and rearing activity were also elevated in PAR1^{-/-} mice. These studies identify the thrombin receptor as a powerful extracellular regulatory switch that could be readily targeted to improve myelin production in the face of white matter injury and disease. *GLIA* 2015.

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16. *J Neurochem.* 2015 Jan 27. doi: 10.1111/jnc.13036. [Epub ahead of print]

Exosome-mediated inflammasome signaling after central nervous system injury.

de Rivero Vaccari JP¹, Brand F 3rd, Adamczak S, Lee SW, Barcena JP, Wang MY, Bullock MR, Dietrich WD, Keane RW.

Neuroinflammation is a response against harmful effects of diverse stimuli and participates in the pathogenesis of brain and spinal cord injury (SCI). The innate immune response plays a role in neuroinflammation following central nervous system (CNS) injury via activation of multi-protein complexes termed inflammasomes that regulate the activation of caspase-1 and the processing of the pro-inflammatory cytokines IL-1 β and IL-18. We report here that the expression of components of the nucleotide-binding-and-oligomerization domain (NOD)-like receptor protein-1 (NLRP-1) inflammasome, apoptosis speck-like protein containing a caspase recruitment domain (ASC) and caspase-1 are significantly elevated in spinal cord motor neurons and cortical neurons after CNS trauma. Moreover, NLRP1 inflammasome proteins are present in exosomes derived from cerebrospinal fluid (CSF) of SCI and traumatic brain- injured patients following trauma. To investigate whether exosomes could be used to therapeutically block inflammasome activation in the CNS, exosomes were isolated from embryonic cortical neuronal cultures and loaded with short-interfering RNA (siRNA) against ASC and administered to spinal cord-injured animals. Neuronal-derived exosomes crossed the injured blood-spinal cord barrier, and delivered their cargo in vivo, resulting in knock down of ASC protein levels by approximately 76% when compared to SCI rats treated with scrambled siRNA. Surprisingly, siRNA silencing of ASC also led to a significant decrease in caspase-1 activation and processing of IL-1 β after SCI. These findings indicate that exosome-mediated siRNA delivery may be a strong candidate to block inflammasome activation following CNS injury. This article is protected by copyright. All rights reserved.

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