

Monday 15 March 2010

This free weekly bulletin lists the latest research on cerebral palsy (CP), as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "cerebral palsy".

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Interventions

1. *Acta Paediatr.* 2010 Mar 11. [Epub ahead of print]

Botulinum toxin A treatment in toddlers with cerebral palsy.

Tedroff K, Löwing K, Haglund-Åkerlind Y, Gutierrez-Farewik EM, Forssberg H.

Neuropediatric Unit, Astrid Lindgren Children's Hospital, Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden.

Aims: In this study the aim was to evaluate the effect of botulinum toxin A (BoNT-A) treatment on muscle tone, contracture development and gait pattern in young children with cerebral palsy (CP). **Method:** Fifteen children with spastic CP (mean age = 16 months) were included in a randomized control study. All received a daily stretching programme and children in the BoNT-A group additionally received two injections, 6 months apart in the gastrocnemius muscle. Outcomes were assessed at baseline, and after 1 and 3.5 years. A 3D gait-analysis was performed at 5 years of age. **Results:** Plantarflexor muscle tone in the BoNT-A group was significantly reduced after 3.5 years, while the muscle tone at the ankle and knee in the control group remained unchanged. The change-score in knee-flexion muscle tone between the groups was significantly different after 3.5 years. The knee joint ROM was significantly increased at 1 year in the BoNT-A group but reduced at the knee and ankle joints in the control group after 3.5 years. No group differences were found for gait analysis, GMFM-66 or PEDI. **Conclusion:** Early treatment of BoNT-A in children with spastic CP may decrease muscle tone and decelerate contracture development after 3.5 years. The effect on gait development remains inconclusive.

PMID: 20222884 [PubMed - as supplied by publisher]

2. *J Child Neurol.* 2010 Mar 10. [Epub ahead of print]

Evaluation of Spasticity in Children With Cerebral Palsy Using Ashworth and Tardieu Scales Compared With Laboratory Measures.

Alhusaini AA, Dean CM, Crosbie J, Shepherd RB, Lewis J.

Faculty of Health Science, The University of Sydney, Australia; and College of Applied Medical Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia.

The content validity of the Tardieu Scale and the Ashworth Scale was assessed in 27 independently ambulant children with cerebral palsy (gender: 17 males, 10 females; age: 5-9 years; Gross Motor Function Classification: level I and II). Ashworth and Tardieu Scale scores and laboratory measures of spasticity and contracture were collected from the plantarflexor muscles by 2 examiners who were blinded to the results. The Tardieu Scale was more effective than the Ashworth Scale in identifying the presence of spasticity (88.9%, kappa = 0.73; P = .000), the presence of contracture (77.8%, kappa = 0.503; P = .008) and the severity of contracture (r = 0.49; P = .009). How-

ever, neither scale was able to identify the severity of spasticity. The Tardieu Scale can provide useful information in children with cerebral palsy because it differentiates spasticity from contracture. However, a more comprehensive clinical method of testing neural and non-neural contributions to impairments and function is needed.

PMID: 20223745 [PubMed - as supplied by publisher]

3. Childs Nerv Syst. 2010 Mar 9. [Epub ahead of print]

Peripheral sensory neuropathy observed in children with cerebral palsy: is chronic afferent excitation from muscle spindles a possible cause?

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INTRODUCTION: Peripheral sensory neuropathy is known to be associated with several medical conditions; however, it has not been reported in patients with cerebral palsy. Authors have observed pathological changes in the sensory nerve rootlets taken during selective dorsal rhizotomy. This paper reports a possible novel cause of peripheral sensory neuropathy: the chronic afferent excitations from muscle spindles. **CASE REPORT:** Sensory nerve rootlets on L5 were taken for histological evaluation from two children with cerebral palsy during selective dorsal rhizotomy, performed for their leg spasticities. Rootlets with clonus reaction against intraoperative electrical stimulation show dysmyelination, and in one child, axonal degeneration can also be observed. Rootlets with normal reaction have only minimum changes on their myelin sheath. **CONCLUSION:** As cerebral palsy is a typical upper motor neuron disorder, peripheral sensory neuropathy is unexplained. Since observed neuropathy is mainly on the myelin sheath, the etiology is considered to be the chronic overload of afferent impulses from muscle spindles in the spastic muscle.

PMID: 20217095 [PubMed - as supplied by publisher]

4. Child Neuropsychol. 2010 Mar 5:1-20. [Epub ahead of print]

Children with Spastic Cerebral Palsy, Their Cognitive Functioning, and Social Participation: A Review.

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Department of Psychology, University of Copenhagen, Copenhagen, Denmark.

White matter lesions are often seen in children with spastic cerebral palsy (CP). Evidence points to specific impairment of attentional, visuospatial, and executive functions; although both attention and executive functions are relatively unexplored in spastic CP. The few recent studies on language functions in mild or moderate CP point to well-functioning language. The presence of specific cognitive impairments may, in part, explain why children with spastic CP have a higher risk of learning disabilities and problems in peer relations. However, to understand the development of cognitive impairments, it is necessary to include how social participation feeds back on cognitive processes.

PMID: 20209416 [PubMed - as supplied by publisher]

5. Int J Rehabil Res. 2010 Mar 4. [Epub ahead of print]**Feeding and gastrointestinal problems in children with cerebral palsy.**

Erkin G, Culha C, Ozel S, Kirbiyik EG.

Ankara Physical Medicine and Rehabilitation Education and Research Hospital, Ministry of Health, Ankara, Turkey.

The aim of our study was to identify feeding and gastrointestinal system (GIS) problems in children with cerebral palsy (CP), and to evaluate the relationship between these problems and the severity of CP. A total of 120 children with CP were enrolled consecutively into the study (67 males, 53 females; mean age: 6.0+/-2.4 years; range: 2-12 years). The children were classified according to the Swedish classification as diplegic, hemiplegic, or quadriplegic. Severity of CP was classified based on the Gross Motor Function Classification System. The amount of time that the caregiver allocated to mealtimes, modifications of the food, as well as feeding and GIS problems was evaluated. Feeding dysfunction was classified as mild, moderate, or severe. Comparisons of GIS and feeding disorders and the severity of CP were carried out using chi test. The results indicated lack of appetite in 46 of the 120 children (38.3%), sialorrhea in 37 (30.8%), constipation in 30 (25%), difficulty in swallowing in 23 (19.2%), and feeding dysfunction in 26 (21.7%). On the basis of the Gross Motor Function Classification System (GMFCS), the incidence of GIS problems and feeding dysfunction was found to be significantly higher in the children classified in the severe group. The time taken to consume meals was significantly longer among children with feeding dysfunction. Feeding and GIS problems are frequent in children with CP, and more marked in those with severe CP. Approximately one fourth of children with CP suffer from feeding dysfunction, and more time has to be allocated to consume meals.

PMID: 20216224 [PubMed - as supplied by publisher]

6. Dev Neurorehabil. 2010;13(2):120-8.**Virtual reality as a therapeutic modality for children with cerebral palsy.**

Snider L, Majnemer A, Darsaklis V.

McGill University, School of Physical & Occupational Therapy, Montreal, Canada.

Objective: The evidence for using virtual reality (VR) with children with cerebral palsy (CP) was examined. Methods: A search of 13 electronic databases identified all types of studies examining VR as an intervention for children with CP. The most recent article included was published in October 2008. For each study, the quality of the methods was assessed using the appropriate scale. A total of 19 articles were retrieved. Thirteen studies from 11 articles were included in the final analysis. Results: Outcomes documented brain reorganization/plasticity, motor capacity, visual-perceptual skills, social participation and personal factors. Two studies were randomized controlled trials. These reported conflicting results regarding motor outcomes. Twelve of the 13 studies presented positive outcomes in at least one domain. Conclusions: VR has potential benefits for children with CP. However, the current level of evidence is poor and empirical data is lacking. Future methodologically rigorous studies are required.

PMID: 20222773 [PubMed - in process]

7. Dev Neurorehabil. 2010;13(2):80-7.**Ambulant children with spastic cerebral palsy and their parents' perceptions and expectations prior to multilevel surgery.**

Capjon H, Bjørk IT.

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Purpose: This study explores the pre-operative situation of children accepted for multilevel surgery for cerebral palsy (CP) and their parents. Methods: Eight ambulatory children with varied severity of spastic CP and their parents were included. Qualitative, semi-structured interviews were carried out separately with the children and parents. Results: Everyday life of the children and their parents was vulnerable. The degree to which children strived

for social acceptance and normality increased their pain. Deteriorating physical capacity resulted in pain and fatigue and was the parents' and children's main motivation for the operation. Although the parents were ambivalent to the operation they mediated hope and cautious optimism about a better life for their children. Conclusion: Parents' and children's experiences imply the need for improvements to ensure facilitation for disabled children in schools and all levels of the health service, equality of communication and awareness-raising in the pre-operative phase of multi-level surgery.

PMID: 20222768 [PubMed - in process]

8. Disabil Rehabil. 2010;32(8):692-703.

An investigation of the factors affecting handwriting skill in children with hemiplegic cerebral palsy*.

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Purpose. This study investigated the effects of sensory-perceptual-motor and cognitive functions on handwriting skill in primary-school children with left-hemiplegic cerebral palsy, compared with that of their healthy peers. **Methods.** The study included 26 children aged 8-12 years with left hemiplegic cerebral palsy and 32 typically developing children of similar age with dominant right hand. The Minnesota Handwriting Assessment was used to evaluate handwriting skill. The Bruininks-Oseretsky Test of Motor Proficiency was used to assess motor performance. Cognitive function was assessed by the Lowenstein Occupational Therapy Cognitive Assessment. The Ayres Southern California Sensory Integration Tests were used to assess visual perception, kinaesthesia and graphesthesia. **Results.** Statistically significant differences were found between the two groups in sensory-perceptual-motor and cognitive function and handwriting skill ($p < 0.05$). There were also significant correlations between handwriting parameters and upper-extremity speed and dexterity, proprioception, bilateral coordination, visual and spatial perception and, visual-motor organisation in children with cerebral palsy ($p < 0.05$). **Conclusions.** The results showed that left-hemiplegic children with cerebral palsy whose right sides were dominant were significantly less competent at handwriting than their right-dominant, healthy peers. It was found that the impairment in proprioception seen in the non-hemiplegic side in children with cerebral palsy, and also the impairment in bilateral coordination, speed and dexterity of the upper extremities, visual and spatial perception, visual-motor organization, and tactile-sensory impairments negatively affected their handwriting skills. In the treatment approaches for children with hemiplegic cerebral palsy, comprehensive sensory-perceptual-motor assessments that involve both extremities must be performed in detail at the earliest possible stage, in order to minimize the existing problems with early-treatment policies. Developing the sensory-perceptual-motor and cognitive function of hemiplegic children would thus be possible, and they would be able to develop handwriting skill as a tool for their academic lives as healthy peers.

PMID: 20205584 [PubMed - in process]

9. Dev Neurorehabil. 2009;12(6):397-405.

Changes in gait following continuous intrathecal baclofen infusion in ambulant children and young adults with cerebral palsy.

Brochard S, Lempereur M, Filipetti P, Rémy-Néris O.

CHU Brest, Service Médecine Physique et de Réadaptation, Brest, France.

Objective: To assess the effect of continuous intrathecal baclofen infusion (ITB) on gait parameters of ambulant children with cerebral palsy (CP). **Methods:** The assessment before and 16 months after ITB on seven children with CP (mean age 15 years, SD 5.4) included: Ashworth scale score, range of motion (hip, knee, ankle), Gillette functional assessment questionnaire (FAQ), joint kinematics, spatiotemporal parameters and Gillette Gait Index (GGI). **Results:** Gillette FAQ significantly improved from 6.1 to 7.1. Mean GGI improved from 554.50 to 489.25, which was not significant although the improvement was large for three children. Parameters in the sagittal plane were significantly modified with a significant increase in step length (0.65 m to 0.74 m) and a significant increase in hip extension during stance phase (32.25 degrees to 21.6 degrees). These results were correlated to clinical assessments. **Conclusion:** ITB seems to improve sagittal gait parameters of children and young adults with CP.

PMID: 20205548 [PubMed - in process]

Epidemiology / Aetiology / Diagnosis & Early Treatment

Please note: This is not yet a comprehensive outline of cerebral palsy prevention literature. It is expected that more research will be included when the search terms are expanded to include key terms other than "cerebral palsy". It is a work-in-progress and it will be expanded in coming months.

10. J Child Neurol. 2010 Mar 11. [Epub ahead of print]

Neurodevelopmental Outcomes in Neonates With Seizures: A Numerical Score of Background Electroencephalography to Help Prognosticate.

Nagarajan L, Palumbo L, Ghosh S.

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There is a high incidence of mortality and neurodevelopmental sequelae in babies with neonatal seizures. The electroencephalography (EEG) background has been shown to be an excellent predictor of outcome by most studies, with a few suggesting limited value in prognostication. Previous studies suggest poor prognosis with severely abnormal backgrounds, but prediction was difficult with moderate abnormalities. The proposed numerical scoring system for the EEG background provides an objective method of evaluation with improved reproducibility, categorization, and prognostication. Our study showed that the numerical score of EEG background was a good predictor of outcome. Higher numerical scores reflecting greater abnormality of background EEG were associated with increasing incidence of mortality, neurodevelopmental impairment, cerebral palsy, vision and hearing impairment, and epilepsy. The numerical score also correlated with neuroimaging abnormalities. A numerical EEG score can help target interventional strategies for neonatal seizures.

PMID: 20223749 [PubMed - as supplied by publisher]

11. J Child Neurol. 2010 Mar 11. [Epub ahead of print]

A Registry-Based Assessment of Cerebral Palsy and Cerebral Malformations.

Self L, Shevell MI.

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Cerebral malformations are 1 of the many possible causes of cerebral palsy. In this study, a population-based comprehensive cerebral palsy registry was used to identify children whose cerebral palsy could be attributed to a cerebral malformation. The clinical features of these children were then compared with other children with cerebral palsy. Children with cerebral palsy and cerebral malformation did not differ from those without in terms of the neurological subtype of cerebral palsy or its functional severity as measured by the Gross Motor Function Classification System. There was a difference in the number of cumulative comorbidities experienced by the children with cerebral malformation. In addition, children with cerebral malformation tended to be of greater gestational age and birth weight, or the product of a twin gestation. Children with cerebral palsy attributable to a cerebral malformation represent a distinct clinical pathologic entity with respect to predisposing clinical features and associated comorbidities.

PMID: 20223748 [PubMed - as supplied by publisher]

12. Reprod Sci. 2010 Mar 10. [Epub ahead of print]**Human C-Reactive Protein Enhances Vulnerability of Immature Rats to Hypoxic-Ischemic Brain Damage: A Preliminary Study.**

Kinugasa-Taniguchi Y, Tomimatsu T, Mimura K, Kanagawa T, Shimoya K, Murata Y, Kimura T.

In utero exposure to infection or inflammation is a strong and independent predictor of cerebral palsy. Using a rat model of neonatal hypoxic-ischemic (HI) encephalopathy, we investigated the hypothesis that C-reactive protein (CRP), which is not specific for infection, aggravates vulnerability of the immature brain to HI. Seven-day-old rats were divided into human CRP treated and control groups. After injection of each solution, they underwent left common carotid artery ligation and exposure to 8% hypoxia for 40 minutes. Human CRP, rat CRP, and interleukin 6 (IL-6) concentrations in serum were measured by enzyme-linked immunosorbent assay 30 to 60 minutes after injection of each solution. Four days later, microtubule-associated protein 2 (MAP-2) immunostaining was used to examine the brains for neuronal damage. Human CRP treatment significantly reduced the MAP-2 positive area ratio, compared with control group ($P < .05$), suggesting that human CRP-enhanced susceptibility to HI-induced brain damage. Mean serum human CRP concentration in the human CRP group was 1823 +/- 520 ng/mL (range: 365-3964 ng/mL). Interleukin 6 concentrations in serum were moderately elevated in both groups, without significant differences, and rat CRP concentrations were within normal range. C-reactive protein makes the immature brain susceptible to HI insult, even if the insult causes little or no injury by itself.

PMID: 20220110 [PubMed - as supplied by publisher]

13. Pediatr Infect Dis J. 2010 Mar 6. [Epub ahead of print]**Continuing Impact of Infectious Diseases on Childhood Deaths in England and Wales, 2003-2005.**

Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M.

From the *Centre for Infections, Health Protection Agency, London, United Kingdom; and daggerPaediatric Infectious Diseases Unit, St George's Hospital, London, United Kingdom.

BACKGROUND: Data on the contribution of specific infections to childhood deaths in developed countries are limited. **METHODS:** Infection-related deaths in children aged 28 days to 14 years who died in England and Wales between 2003 and 2005 were identified from routine anonymized death certificate dataset provided by the Office for National Statistics to the Health Protection Agency, using predefined International Classification of Diseases codes for infection. **RESULTS:** There were 1368 infection-related deaths documented, constituting 20% of all childhood deaths. An underlying medical condition was recorded in 50% (676 cases), the most common being prematurity in infants (322/660, 52%), cerebral palsy in 1 to 4 year olds (46/190, 24%), and malignancy (46/163, 28%) in 5 to 14 year olds. Of the 837 deaths where a pathogen was coded, 494 (59%) specified bacterial infection, 256 (31%) viral infection, and 69 (8%) fungal infection. Among deaths with recorded bacterial infections, a lower proportion of meningococcal and pneumococcal infections (14% [22/155] vs. 60% [205/339], $P < 0.0001$) and a higher proportion of Gram-negative enteric bacilli (78/155 cases [50%] vs. 17/339 cases [5%], $P < 0.0001$) were reported in children with and without documented underlying medical conditions, respectively. **CONCLUSIONS:** Infections continue to make a major contribution to deaths in children, particularly among those with underlying conditions. Identification of the pathogens associated with childhood deaths should help prioritize the development of intervention strategies for reducing pediatric mortality. Linkage of death registrations to national infectious disease surveillance systems should be undertaken to strengthen monitoring of infectious deaths and evaluate the effect of interventions.

PMID: 20216475 [PubMed - as supplied by publisher]

14. Semin Fetal Neonatal Med. 2010 Mar 6. [Epub ahead of print]**Hypothermia: a systematic review and meta-analysis of clinical trials.**

Shah PS.

Department of Paediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada; Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada; Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

Hypothermia is a potential neuroprotective intervention to treat neonatal post-asphyxial (hypoxic-ischemic) encephalopathy (HIE). In this meta-analysis of 13 clinical trials published to date, therapeutic hypothermia was associated with a highly reproducible reduction in the risk of the combined outcome of mortality or moderate-to-severe neurodevelopmental disability in childhood. This improvement was internally consistent, as shown by significant reductions in the individual risk for death, moderate-to-severe neurodevelopmental disability, severe cerebral palsy, cognitive delay, and psychomotor delay. Patients in the hypothermia group had higher incidences of arrhythmia and thrombocytopenia; however, these were not clinically important. This analysis supports the use of hypothermia in reducing the risk of the mortality or moderate-to-severe neurodevelopmental disability in infants with moderate HIE. Copyright © 2010. Published by Elsevier Ltd.

PMID: 20211588 [PubMed - as supplied by publisher]

15. Acta Paediatr. 2010 Mar 5. [Epub ahead of print]**Health and the use of health care services in 5-year-old very-low-birth-weight infants.**

Rautava L, Häkkinen U, Korvenranta E, Andersson S, Gissler M, Hallman M, Korvenranta H, Leipälä J, Peltola M, Tammela O, Lehtonen L; for PERFECT Preterm Infant Study Group.

Department of Pediatrics, Turku University Hospital, Turku, Finland.

Aim: We aimed to study the effect of prematurity, time of birth and level of birth hospital on morbidity and the use of health care services at age 5. **Methods:** This national study included all very-low-birth-weight infants (VLBWI, <32 gestational weeks or birth weight \leq 1500 g) born in Finnish level II or III hospitals in 2001-2002 (n = 918), and full-term controls (n = 381). Parental questionnaires and register data were used to compare morbidity, and the use of health care services between VLBWI and full-term controls, and within VLBWI according to the time of birth and birth hospital level. **Results:** Cerebral palsy, retinopathy of prematurity, other ophthalmic problems, respiratory infections, asthma or chronic lung disease, and inguinal hernia were overrepresented in VLBWI compared with the controls. VLBWI had more outpatient and inpatient days than the controls. The time of birth and birth hospital level were not associated with the use of services or with prematurity-related morbidity. **Conclusion:** Although morbidity and the use of health care services were increased in the surviving VLBWI, the average use of services was relatively small at age 5. In surviving VLBWI, the time of birth and the birth hospital level did not affect morbidity or the use of services.

PMID: 20219051 [PubMed - as supplied by publisher]

16. Neurochem Int. 2010 Mar 5. [Epub ahead of print]**Neuroprotective effects of the drug GVT (monosodium luminol) is mediated by the stabilization of Nrf2 in astrocytes.**

Reddy PV, Lungu G, Kuang X, Stoica G, Wong PK.

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Oxidative stress is implicated in various kinds of neurological disorders, including human immunodeficiency virus (HIV) associated dementia (HAD). Our laboratory has been studying the murine retrovirus ts1, a pathogenic mutant

of the Moloney murine leukemia virus (MoMuLV), as a model for HAD. Like HIV in humans, ts1 induces oxidative stress and progressive neurodegeneration in mice. We have shown previously that an antioxidant and anti-inflammatory drug GVT or MSL (monosodium luminol) suppresses ts1-induced oxidative stress, attenuates the development of spongiform encephalopathy, and delays hind limb paralysis in infected mice. It is known that upregulation of the nuclear transcription factor NF-E2-related factor 2 (Nrf2) is involved in upregulating cellular antioxidant defenses. Since Nrf2 is associated with elevation of antioxidant defenses in general, and since GVT suppresses ts1-induced neurodegeneration, our aim in this study was to determine whether GVT neuroprotection is linked to Nrf2 upregulation in the brain. We report here that GVT upregulates the levels of Nrf2, both in primary astrocyte cultures and in brainstem of ts1-infected mice. Significant upregulation of Nrf2 expression by GVT occurs in both the cytosolic and nuclear fractions of cultured astrocytes and brainstem cells. Notably, although GVT treatment increases Nrf2 protein levels in cultured astrocytes and brainstem tissues, Nrf2 mRNA levels are not altered. This suggests that the neuroprotective effects of GVT may be mediated by the stabilization of the Nrf2 protein, allowing continuous upregulation of Nrf2 levels in the astrocytes. Copyright © 2010. Published by Elsevier Ltd.

PMID: 20211212 [PubMed - as supplied by publisher]

17. Am J Obstet Gynecol. 2010 Mar;202(3):292.e1-292.e9.

Magnesium sulfate reduces inflammation-associated brain injury in fetal mice.

Burd I, Breen K, Friedman A, Chai J, Elovitz MA.

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OBJECTIVE: The purpose of this study was to investigate whether magnesium sulfate (MgSO₄) prevents fetal brain injury in inflammation-associated preterm birth (PTB). **STUDY DESIGN:** Using a mouse model of PTB, lipopolysaccharide (LPS) or normal saline solution (NS)-exposed mice were randomized to intraperitoneal treatment with MgSO₄ or NS by intrauterine injection. From the 4 treatment groups (NS + NS; LPS + NS; LPS + MgSO₄ (4); and NS + MgSO₄), fetal brains were collected for quantitative polymerase chain reaction studies and primary neuronal cultures. Messenger RNA expression of cytokines, cell death, and markers of neuronal and glial differentiation were assessed. Immunocytochemistry and confocal microscopy were performed. **RESULTS:** There was no difference between the LPS + NS and LPS + MgSO₄ groups in the expression of proinflammatory cytokines, cell death markers, and markers of prooligodendrocyte and astrocyte development ($P > .05$ for all). Neuronal cultures from the LPS + NS group demonstrated morphologic changes; this neuronal injury was prevented by MgSO₄ ($P < .001$). **CONCLUSION:** Amelioration of neuronal injury in inflammation-associated PTB may be a key mechanism by which MgSO₄ prevents cerebral palsy. Copyright © 2010 Mosby, Inc. All rights reserved.

PMID: 20207246 [PubMed - as supplied by publisher]

PMCID: PMC2835629 [Available on 2011/3/1]

18. Proc Natl Acad Sci U S A. 2010 Jan 26;107(4):1636-41. Epub 2010 Jan 4.

Ubiquitin carboxyl-terminal hydrolase L1 is required for maintaining the structure and function of the neuromuscular junction.

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The enzyme ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) is one of the most abundant proteins in the mammalian nervous system. In humans, UCH-L1 is also found in the ubiquitinated inclusion bodies that characterize neurodegenerative diseases in the brain, suggesting its involvement in neurodegeneration. The physiologic role of UCH-L1 in neurons, however, remains to be further elucidated. For example, previous studies have provided evidence both for and against the role of UCH-L1 in synaptic function in the brain. Here, we have characterized a line of knockout mice deficient in the UCH-L1 gene. We found that, in the absence of UCH-L1, synaptic transmission at the neuromuscular junctions (NMJs) is markedly impaired. Both spontaneous and evoked synaptic activity are re-

duced; paired pulse-facilitation is impaired, and synaptic transmission fails to respond to high-frequency, repetitive stimulation at the NMJs of UCH-L1 knockout mice. Morphologic analyses of the NMJs further revealed profound structural defects-loss of synaptic vesicles and accumulation of tubulovesicular structures at the presynaptic nerve terminals, and denervation of the muscles in UCH-L1 knockout mice. These findings demonstrate that UCH-L1 is required for the maintenance of the structure and function of the NMJ and that the loss of normal UCH-L1 activity may result in neurodegeneration in the peripheral nervous system.

PMID: 20080621 [PubMed - indexed for MEDLINE]