NEWS
Cerebral Palsy Research

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Interventions and Management

1. The Hand Assessment for Infants at risk for cerebral palsy.
Wallen M.

Dev Med Child Neurol. 2019 Feb 10. doi: 10.1111/dmcn.14183. [Epub ahead of print]

PMID: 30740667

2. Reliability and responsiveness of the Jebsen-Taylor Test of Hand Function and the Box and Block Test for children with cerebral palsy.
Araneda R, Ebner-Karestinos D, Paradis J, Saussez G, Friel KM, Gordon AM, Bleyenheuft Y.

Dev Med Child Neurol. 2019 Feb 14. doi: 10.1111/dmcn.14184. [Epub ahead of print]

AIM: To assess the reliability and to evaluate the responsiveness of both the Jebsen-Taylor Test of Hand Function (JTTHF) and the Box and Block Test (BBT) in children with cerebral palsy (CP). METHOD: In this retrospective study, the reliability analyses were conducted with paired t-tests considering a short (mean 14d) and a long (mean 120d) time in between two assessment periods. In addition, an intraclass correlation coefficient (ICC) was used to assess the level of congruency. The responsiveness to therapy was conducted with a paired t-test in the whole sample regarding the age, the manual ability level as classified with the Manual Ability Classification System (MACS), and the topography. RESULTS: Our main results confirmed the tests' reliability in a short time period for the JTTHF in both hands and for the BBT on the less affected hand. These results were consistent with the ICC. The responsiveness was confirmed, except on the less affected hand for the JTTHF, with similar results for age, MACS, and topography approach. INTERPRETATION: This study supports the use of the JTTHF and the BBT to examine changes after short-term interventions for children with CP. These results should be interpreted with association to normative values or with a control group when used over long assessment periods. WHAT THIS PAPER ADDS: The Box and Block Test (BBT) is reliable in a brief period of assessment in children with cerebral palsy (CP). The Jebsen-Taylor Test of Hand Function (JTTHF) is reliable in a brief period of assessment in children with CP. The JTTHF and BBT are responsive to changes in a brief period of intensive therapy in children with CP. The reliability and responsiveness of the JTTHF and BBT are weak over long assessment periods.

PMID: 30761528

3. Effectiveness of Modified Constraint-Induced Movement Therapy Compared With Bimanual Therapy Home Programs for Infants With Hemiplegia: A Randomized Controlled Trial.
Chamudot R, Parush S, Rigbi A, Horovitz R, Gross-Tsur V.

Am J Occup Ther. 2018 Nov/Dec;72(6):7206205010p1-7206205010p9. doi: 10.5014/ajot.2018.025981.

OBJECTIVE: We examined the effectiveness of modified constraint-induced movement therapy (mCIMT) in treating infants with hemiplegic cerebral palsy and compared therapy outcomes with a nonconstraining bimanual therapy (BIM) of equal intensity. METHOD: In a single-blinded randomized controlled trial, 33 infants with hemiplegia (mean corrected age = 11.1 mo, standard deviation = 2.2) received either mCIMT (n = 17) or BIM (n = 16). Both interventions included home programs encouraging the use of the affected hand during daily 1-hr play sessions for 8 wk. Outcome measures were administered pre- and posttreatment and included the Mini-Assisting Hand Assessment for babies and the Functional Inventory. At baseline, parents also filled out the Dimensions of Mastery Questionnaire. RESULTS: Both groups demonstrated a significantly large and equal improvement in hand and gross motor function posttreatment ($p < .001$) and high treatment compliance. CONCLUSION: mCIMT and BIM are equally effective methods for treating infants with hemiplegia.

PMID: 30760393

4. Outcome of hand surgery in children with spasticity, a 9-year follow-up study.
Pontén E, von Walden F, Lenke-Ekholm C, Zethraeus BM, Eliasson AC.

J Pediatr Orthop B. 2019 Feb 12. doi: 10.1097/BPB.0000000000000600. [Epub ahead of print]

To evaluate whether short-term positive effects on bimanual function after surgery of the paretic arm in cerebral palsy are maintained long term. Assisting Hand Assessment (AHA) and active range of motion was tested before surgery and at 7 month and 9-year follow-up (n=18). AHA improved significantly from 50 to 52 U at 7 months, but was not different from before surgery at the 9-year follow-up, 49 U. Surgery of wrist and elbow flexors significantly improved active extension. Improvement in wrist and elbow extension was maintained at the 9-year follow-up, but usefulness of the hand measured with AHA had returned to the same level as before surgery. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 30768582

5. Hip pain in children with cerebral palsy: a population-based registry study of risk factors.
Marcström A, Hägglund G, Alriksson-Schmidt AI.

BMC Musculoskelet Disord. 2019 Feb 8;20(1):62. doi: 10.1186/s12891-019-2449-8.

BACKGROUND: Hip pain is prevalent in children with cerebral palsy (CP). Hip displacement is a known risk factor for hip pain. However, many children do not have displaced hips but still have hip pain and the aetiologies are poorly understood. The aims of this study were to investigate: 1. the prevalence of hip pain related to age, gender, gross motor function, degree of hip displacement and 2. the associations between hip pain and age, gender, gross motor function, degree of hip displacement, ranges of hip and knee motion (ROM) and degree of spasticity in the muscles around the hip. METHODS: This was a cross-sectional retrospective register study based on data from the Swedish follow-up programme and national healthcare registry CPUP, which includes > 95% of children with CP in Sweden. The participants were born in 2000 or later and 4-16 years of age. Data from the latest examination were used. In Aim 1, the prevalence of hip pain was calculated using frequencies and crosstabs. Differences between groups were calculated using chi-square tests and independent samples t-tests. In Aim 2, associations between hip pain and the variables were analysed using logistic regression. RESULTS: The overall prevalence of hip pain was 7%. No significant gender difference was found. Hip pain prevalence increased with age, lower gross motor function and higher degree of hip displacement. The median migration percentage (MP) in painful hips was 26%, compared to 21% in hips where pain was not reported. In the multivariable analysis, significant associations with hip pain were found for MP > 30% and decreased ROM in abduction, flexion and inwards rotation of the hip ($p < 0.05$). CONCLUSION: Hip displacement was associated with hip pain. However, hip displacement was not present in the majority of painful hips. In addition to hip displacement, decreased ROM was also associated with hip pain.

PMID: 30736784

6. Correction to: Locomotion and cadence detection using a single trunk-fixed accelerometer: validity for children with cerebral palsy in daily life-like conditions.
Paraschiv-Ionescu A, Newman CJ, Carcreff L, Gerber CN, Armand S, Aminian K.

J Neuroeng Rehabil. 2019 Feb 12;16(1):27. doi: 10.1186/s12984-019-0498-8.

The original article [1] contained a minor error whereby the middle initial of Christopher J. Newman's name was mistakenly omitted. Erratum for Locomotion and cadence detection using a single trunk-fixed accelerometer: validity for children with cerebral palsy in daily life-like conditions. [J Neuroeng Rehabil. 2019]

PMID: 30755215

7. Gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy: a randomized controlled trial.
Rasmussen HM, Pedersen NW, Overgaard S, Hansen LK, Dunkhase-Heinl U, Petkov Y, Engell V, Holsgaard-Larsen A.

Dev Med Child Neurol. 2019 Feb 10. doi: 10.1111/dmcn.14178. [Epub ahead of print]

AIM: To test the hypothesis that improvements in gait and function following individualized interdisciplinary interventions consisting of physical therapy, orthotics, spasticity management, and orthopaedic surgery using instrumented gait analysis are superior to 'usual care' in children with cerebral palsy (CP). METHOD: This was a prospective, single-blind, parallel-group, randomized controlled trial investigating the effectiveness of interventions based on the use of gait analysis. Primary outcome was gait (Gait Deviation Index) and secondary outcomes were walking and patient-reported outcome measures of function, disability, and health-related quality of life. Follow-ups were done at 26 weeks (questionnaires) and at the primary end point of 52 weeks (all outcomes). RESULTS: Sixty participants with CP (39 males, 21 females, mean age 6y 10mo, standard deviation 1y 3mo, range 5y-9y 1mo) in Gross Motor Function Classification System levels I or II, were randomized to interventions with or without gait analysis. No significant or clinically relevant between-group differences in change scores of the primary or secondary outcomes were found. The recommended categories of interventions were dominated by non-surgical interventions and were applied in 36% to 86% of the participants. INTERPRETATION: Interventions using gait analysis were not superior to 'usual care' on gait, walking, or patient-reported outcomes in a sample of relatively young and independently walking children with CP not expected to need surgery. WHAT THIS PAPER ADDS: Gait analysis in children with cerebral palsy in Gross Motor Function Classification System levels I or II recommends interdisciplinary interventions. Compliance to interventions recommended after gait analysis was low. No statistically significant advantages were identified for the intervention group versus the control group.

PMID: 30740658

8. Reliability of the Motor Learning Strategies Rating Instrument in physiotherapy intervention for children with cerebral palsy.
Ryan JL, Levac DE, Wright FV.

Dev Med Child Neurol. 2019 Feb 11. doi: 10.1111/dmcn.14177. [Epub ahead of print]

AIM: To evaluate the reliability of the Motor Learning Strategies Rating Instrument (MLSRI-20) in gait-based, video-recorded physiotherapy interventions for children with cerebral palsy (CP). METHOD: Thirty videos of 18 children with CP, aged 6 to 17 years, participating in either traditional or Lokomat-based physiotherapy interventions were rated using the MLSRI-20. Physiotherapist raters provided general and item-specific feedback after rating each video, which was used when interpreting reliability results. RESULTS: Both interrater and intrarater reliability of the MLSRI-20 total score was good. The interrater reliability intraclass correlation coefficient (ICC) was 0.78 with a 95% confidence interval (CI) of 0.53-0.89 and a coefficient of variation (CV) of 11.8%. The intrarater reliability ICC was 0.89 with a 95% CI of 0.76-0.95 and CV of 7.8%. Rater feedback identified task delineation and interpretation of therapist verbalizations as sources of interrater reliability-related scoring challenges. INTERPRETATION: The MLSRI-20 is a reliable tool for measuring the extent to which a physiotherapist uses motor learning strategies during a video-recorded intervention. These results have clinical and research implications for documenting and analyzing the motor learning content of physiotherapy interventions for children with CP. WHAT THIS PAPER ADDS: The Motor Learning Strategies Rating Instrument (MLSRI-20) is reliable for use by trained physiotherapist raters. Measuring motor learning strategies can identify active 'ingredients' in physiotherapy interventions for children with cerebral palsy. The MLSRI-20 promotes a common language in motor learning.

PMID: 30740648

9. Quantifying motor learning strategies can translate to physiotherapy dose for children with cerebral palsy.
Dumas HM.

Dev Med Child Neurol. 2019 Feb 14. doi: 10.1111/dmcn.14196. [Epub ahead of print]

PMID: 30761519

10. Opening the Door to Physical Activity for Children With Cerebral Palsy: Experiences of Participants in the BeFAST or BeSTRONG Program.
Kahlon S, Brubacher-Cressman K, Caron E, Ramonov K, Taubman R, Berg K, Wright FV, Hilderley AJ.

Adapt Phys Activ Q. 2019 Feb 15:1-21. doi: 10.1123/apaq.2018-0048. [Epub ahead of print]

This study explored children's experiences of participating in one-to-one physical training programs to identify how programs can best promote physical activity participation for children with cerebral palsy. A qualitative descriptive design with self-determination theory was used. Semi-structured interviews were conducted with 6 children with cerebral palsy, age 8-14 years, who participated in a fundamental-movement-skills or lower-limb strength-training program. A hybrid approach of deductive and inductive analysis was used. Four themes developed: World around me (i.e., social/physical environments), Made for me (i.e., individualizing programs), Teach me how (i.e., teaching strategies facilitated skill learning), and I know me (i.e., sense of self). Results include recommendations for delivery of physical training programs. Using an individualized approach in a structured one-to-one program that employs skill-teaching strategies and self-reflection opportunities may provide a foundation to increase physical activity participation, related self-confidence, and desire to participate.

PMID: 30767562

11. High rates of malnutrition and epilepsy: two common comorbidities in children with cerebral palsy
Aydın K, Kartal A, Keleş Alp E.

Turk J Med Sci. 2019 Feb 11;49(1):33-37. doi: 10.3906/sag-1803-79.

BACKGROUND/AIM: The aim of this study was to evaluate the nutritional status of children with cerebral palsy and determine the particular characteristics of the disorder. MATERIALS AND METHODS: The nutritional status of the children was assessed by the Gomez classification using weight-for-age. The Gross Motor Function Classification System was used to determine the gross and fine motor functions. RESULTS: The study was conducted with 197 children (58.4% males) between the ages of 1 and 18 years old. Asphyxia (44.1%) was the primary etiological factor, and spastic quadriplegia (41.6%) was the most common type of cerebral palsy. Malnutrition was the most frequent comorbidity and the overall malnutrition rate was 76.6%. The most common type of malnutrition was severe malnutrition, which was seen in 70 patients (35.5%). Epilepsy was the second most common comorbidity, seen in 51.7% of the cases. CONCLUSIONS: Our results revealed a high rate of malnutrition and epilepsy in children with cerebral palsy. These two more common significant comorbidities that influence the outcomes of children with cerebral palsy should be carefully evaluated and successfully managed. Families of children with cerebral palsy and their physicians should be educated about the nutritional status in these children.

PMID: 30761843

12. Acute kwashiorkor in the setting of cerebral palsy and pancreatic insufficiency.
Marks RR, Burgy JR, Davis LS.

Cutis. 2019 Jan;103(1):E10-E12.

PMID: 30758347

13. Cardiovascular disease in cerebral palsy: shifting our focus from attention to prevention.
McPhee PG.

Dev Med Child Neurol. 2019 Feb 14. doi: 10.1111/dmcn.14198. [Epub ahead of print]

PMID: 30761526

14. A bio-psycho-social view of cerebral palsy: friendships reduce mental health disorders.
Paulus FW.

Dev Med Child Neurol. 2019 Feb 14. doi: 10.1111/dmcn.14200. [Epub ahead of print]

PMID: 30762227

15. Parent-reported sleep disorders in children with motor disabilities: a comparison with the Sleep Disturbance Scale for Children's new norms.
Jacquier D, Newman CJ.

Sleep Med. 2018 Dec 14;55:26-32. doi: 10.1016/j.sleep.2018.11.016. [Epub ahead of print]

OBJECTIVE: Children with motor disabilities such as cerebral palsy or neuromuscular diseases present more sleep disorders than their typically developing (TD) peers. However, research on these populations has always been performed using historical normative datasets or controls such as siblings. Therefore, we assessed the sleep quality of children with motor disabilities in comparison with a large, contemporary, general population sample. METHODS: Demographic, medical, and the Sleep Disturbance Scale for Children (SDSC) questionnaires were sent to parents of children aged 4-18 years and followed by our tertiary pediatric neurorehabilitation clinic, and to those of school-aged children in regional primary and secondary schools. TD participant data allowed us to set pathological sleep score thresholds (T score ≥70). RESULTS: We collected 245 responses for children with motor disabilities and 2891 for those from the general population (37% and 26% response rates, respectively). Cerebral palsy was the most frequent diagnosis (N = 109, 44.5%). Children with motor disabilities had significantly more frequent pathological sleep reported in their total SDSC score (7% vs 1.9%, odds ratio (OR) 3.98, 95% confidence interval (CI) 2.17-7.27, $p < 0.001$) and in five subscores. Single-parent households and drug-resistant epilepsy showed significant positive associations with pathological sleep among children with motor disabilities. For TD peers, parental unemployment and parental nationality were positively associated with pathological sleep. CONCLUSION: This population-based study robustly estimated the prevalence of sleep disorders in children with motor disabilities. Sleep disorders were significantly more frequent in children with motor disabilities, but at a lower frequency than previously reported.

PMID: 30743207

16. Preoperative treatment of spasticity with botulinum neurotoxin A to reduce pain in cerebral palsy: is it worthwhile?
Gormley M.

Dev Med Child Neurol. 2019 Feb 14. doi: 10.1111/dmcn.14191. [Epub ahead of print]

PMID: 30761520

17. Safety and efficacy of a propofol and ketamine based procedural sedation protocol in children with cerebral palsy undergoing botulinum toxin A injections.
Louer R, McKinney RC, Abu-Sultaneh S, Lutfi R, Abulebda K.

PM R. 2019 Feb 13. doi: 10.1002/pmrj.12146. [Epub ahead of print]

BACKGROUND: Pediatric patients with cerebral palsy (CP) often undergo intramuscular botulinum toxin (BoNT-A) injections. These injections can be painful and may require procedural sedation. An ideal sedation protocol has yet to be

elucidated. OBJECTIVE: To investigate the safety and efficacy of a propofol and ketamine based sedation protocol in pediatric patients with cerebral palsy requiring BoNT-A injections. DESIGN: This is a retrospective chart review of children with CP undergoing propofol and ketamine based sedation for injections with botulinum toxin A. SETTING: The sedations took place in a procedural sedation suite at a tertiary children's hospital from Feb 2013 through Sept 2017. PATIENTS: 164 patients with diagnoses of cerebral palsy were included in this study. METHODS: An initial bolus of 0.5 mg/kg ketamine followed by a 2 mg/kg bolus of propofol was administered with supplemental boluses of propofol as needed to achieve deep sedation during the intramuscular BoNT-A injections. MAIN OUTCOME MEASUREMENTS: Propofol dosages, adverse events, serious adverse events, and sedation time parameters were reviewed. RESULTS: 345 sedations were successfully performed on 164 patients. The median total dose of propofol was 4.7 mg/kg (IQR 3.5, 6.3). Adverse events were encountered in 10.1% of procedures including hypoxemia responsive to supplemental oxygen (9.6%) and transient apnea (1.4%). The mean procedure time, recovery time and total sedation time were 10, 11 and 33 minutes, respectively. With regard to patient variables, including age, weight, dose of propofol, sedation time, and Gross Motor Function Classification System classification, there was no association with increased incidence of adverse events. CONCLUSION: Our sedation protocol of propofol and ketamine is safe and effective in children with cerebral palsy undergoing procedural sedation for intramuscular injections with BoNT-A. The adverse events encountered appeared to be related to airway and respiratory complications secondary to musculoskeletal deformities, emphasizing the importance of airway monitoring and management in these patients. Level III

PMID: 30761757

18. Emergent Prophylactic, Reparative and Restorative Brain Interventions for Infants Born Preterm With Cerebral Palsy.
Finch-Edmondson M, Morgan C, Hunt RW, Novak I.

Front Physiol. 2019 Jan 28;10:15. doi: 10.3389/fphys.2019.00015. eCollection 2019.

Worldwide, an estimated 15 million babies are born preterm (<37 weeks' gestation) every year. Despite significant improvements in survival rates, preterm infants often face a lifetime of neurodevelopmental disability including cognitive, behavioral, and motor impairments. Indeed, prematurity remains the largest risk factor for the development of cerebral palsy. The developing brain of the preterm infant is particularly fragile; preterm babies exhibit varying severities of cerebral palsy arising from reductions in both cerebral white and gray matter volumes, as well as altered brain microstructure and connectivity. Current intensive care therapies aim to optimize cardiovascular and respiratory function to protect the brain from injury by preserving oxygenation and blood flow. If a brain injury does occur, definitive diagnosis of cerebral palsy in the first few hours and weeks of life is difficult, especially when the lesions are subtle and not apparent on cranial ultrasound. However, early diagnosis of mildly affected infants is critical, because these are the patients most likely to respond to emergent treatments inducing neuroplasticity via high-intensity motor training programs and regenerative therapies involving stem cells. A current controversy is whether to test universal treatment in all infants at risk of brain injury, accepting that some patients never required treatment, because the perceived potential benefits outweigh the risk of harm. Versus, waiting for a diagnosis before commencing targeted treatment for infants with a brain injury, and potentially missing the therapeutic window. In this review, we discuss the emerging prophylactic, reparative, and restorative brain interventions for infants born preterm, who are at high risk of developing cerebral palsy. We examine the current evidence, considering the timing of the intervention with relation to the proposed mechanism/s of action. Finally, we consider the development of novel markers of preterm brain injury, which will undoubtedly lead to improved diagnostic and prognostic capability, and more accurate instruments to assess the efficacy of emerging interventions for this most vulnerable group of infants.

PMID: 30745876

19. The health of children conceived by ART: 'the chicken or the egg?'
Berntsen S, Söderström-Anttila V, Wennerholm UB, Laivuori H, Loft A, Oldereid NB, Romundstad LB, Bergh C, Pinborg A.

Hum Reprod Update. 2019 Feb 12. doi: 10.1093/humupd/dmz001. [Epub ahead of print]

Worldwide, more than 7 million children have now been born after ART: these delivery rates are steadily rising and now comprise 2-6% of births in the European countries. To achieve higher pregnancy rates, the transfer of two or more embryos was previously the gold standard in ART. However, recently the practise has moved towards a single embryo transfer policy to avoid multiple births. The positive consequences of the declining multiple birth rates after ART are decreasing perinatal risks and overall improved health for the ART progeny. In this review we summarize the risks for short- and long-term health in ART singletons and discuss if the increased health risks are associated with intrinsic maternal or paternal factors related to subfertility or to the ART treatments per se. Although the risks are modest, singletons born after ART are more likely to have

adverse perinatal outcomes compared to spontaneously conceived (SC) singletons dependent on the ART method. Fresh embryo transfer is associated with a higher risk of small for gestational age babies (SGA), low birthweight and preterm birth (PTB), while frozen embryo transfer is associated with large-for-gestational age babies and pre-eclampsia. ICSI may be associated with a higher risk of birth defects and transferral of the poor semen quality to male progeny, while oocyte donation is associated with increased risk of SGA and pre-eclampsia. Concerning long-term health risks, the current evidence is limited but suggests an increased risk of altered blood pressure and cardiovascular function in ART children. The data that are available for malignancies seem reassuring, while results on neurodevelopmental health are more equivocal with a possible association between ART and cerebral palsy. The laboratory techniques used in ART may also play a role, as different embryo culture media give rise to different birthweights and growth patterns in children, while culture to blastocyst stage is associated with PTB. In addition, children born after ART have altered epigenetic profiles, and these alterations may be one of the key areas to explore to improve our understanding of adverse child outcomes after ART. A major challenge for research into adverse perinatal outcomes is the difficulty in separating the contribution of infertility per se from the ART treatment (i.e. 'the chicken or the egg'?). Choosing and having access to the appropriate control groups for the ART children in order to eliminate the influence of subfertility per se (thereby exploring the pure association between ART and child outcomes) is in itself challenging. However, studies including children of subfertile couples or of couples treated with milder fertility treatments, such as IUI, as controls show that perinatal risks in these cohorts are lower than for ART children but still higher than for SC indicating that both subfertility and ART influence the future outcome. Sibling studies, where a mother gave birth to both an ART and a SC child, support this theory as ART singletons had slightly poorer outcomes. The conclusion we can reach from the well designed studies aimed at disentangling the influence on child health of parental and ART factors is that both the chicken and the egg matter.

PMID: 30753453

20. Early Childhood Outcomes After Neonatal Encephalopathy in Uganda: A Cohort Study.
Tann CJ, Webb EL, Lassman R, Ssekyewa J, Sewegaba M, Musoke M, Burgoine K, Hagmann C, Deane-Bowers E, Norman K, Milln J, Kurinczuk JJ, Elliott AM, Martinez-Biarge M, Nakakeeto M, Robertson NJ, Cowan FM.

EClinicalMedicine. 2018 Dec;6:26-35. doi: 10.1016/j.eclinm.2018.12.001.

BACKGROUND: Neonatal encephalopathy (NE) is a leading cause of global child mortality. Survivor outcomes in low-resource settings are poorly described. We present early childhood outcomes after NE in Uganda. METHODS: We conducted a prospective cohort study of term-born infants with NE (n = 210) and a comparison group of term non-encephalopathic (non-NE) infants (n = 409), assessing neurodevelopmental impairment (NDI) and growth at 27-30 months. Relationships between early clinical parameters and later outcomes were summarised using risk ratios (RR). FINDINGS: Mortality by 27-30 months was 40·3% after NE and 3·8% in non-NE infants. Impairment-free survival occurred in 41·6% after NE and 98·7% of non-NE infants. Amongst NE survivors, 29·3% had NDI including 19·0% with cerebral palsy (CP), commonly bilateral spastic CP (64%); 10·3% had global developmental delay (GDD) without CP. CP was frequently associated with childhood seizures, vision and hearing loss and mortality. NDI was commonly associated with undernutrition (44·1% Z-score < - 2) and microcephaly (32·4% Z-score < - 2). Motor function scores were reduced in NE survivors without CP/GDD compared to non-NE infants (median difference - 8·2 (95% confidence interval; - 13·0, - 3·7)). Neonatal clinical seizures (RR 4.1(2.0-8.7)), abnormalities on cranial ultrasound, (RR 7.0(3.8-16.3), nasogastric feeding at discharge (RR 3·6(2·1-6·1)), and small head circumference at one year (Z-score < - 2, RR 4·9(2·9-5·6)) increased the risk of NDI. INTERPRETATION: In this sub-Saharan African population, death and neurodevelopmental disability after NE were common. CP was associated with sensorineural impairment, malnutrition, seizures and high mortality by 2 years. Early clinical parameters predicted impairment outcomes.

PMID: 30740596

21. Advanced Brain-Computer Interface for People With Paralysis.
Abbasi J.

JAMA. 2019 Feb 12;321(6):537. doi: 10.1001/jama.2019.0294.

PMID: 30747951

22. Current thinking in the health care management of children with cerebral palsy.
Graham D, Paget SP, Wimalasundera N.

Med J Aust. 2019 Feb 10. doi: 10.5694/mja2.12106. [Epub ahead of print]

Cerebral palsy is a developmental disorder of movement and posture which is often associated with comorbidities. While there is currently a limited range of evidence-based treatments that change the underlying pathology of cerebral palsy, there are many areas in which health care professionals can change the natural history of cerebral palsy and improve participation and quality of life for children with this condition. Early identification has become of paramount importance in the management of cerebral palsy, and it is hoped that it will allow earlier access to cerebral palsy interventions that may improve the natural history of the condition. Common challenges in the management of cerebral palsy include spasticity and dystonia, management of pain, hip surveillance, sleep and feeding, swallowing and nutrition. The six Fs framework (function, family, fitness, fun, friends and future) provides a guide to developing shared goals with families in the management of cerebral palsy.

PMID: 30739332

23. Hereditary spastic paraplegia: a clinical and epidemiological study of a Brazilian pediatric population.
Ortega RPM, Rosemberg S.

Arq Neuropsiquiatr. 2019 Jan;77(1):10-18. doi: 10.1590/0004-282X20180153.

AIMS: To investigate hereditary spastic paraplegia (HSP) in a pediatric Brazilian sample. METHODS: Epidemiological, clinical, radiological and laboratory data were analyzed in 35 patients. RESULTS: Simple HSP (HSP-S) was detected in 12 patients, and complicated HSP (HSP-C) was detected in 23 patients. The mean age of onset of symptoms was 2.9 years in HSP-S and 1.6 years in HSP-C ($p = 0.023$). The disease was more severe in HSP-C. There were no differences in sex, ethnic background, or family history between groups. Intellectual disability was the most frequent finding associated with HSP-C. Peripheral axonal neuropathy was found in three patients. In the HSP-C group, MRI was abnormal in 13 patients. The MRI abnormalities included nonspecific white matter lesions, cerebellar atrophy, thinning of the corpus callosum and the "ear of the lynx sign". CONCLUSIONS: In children with spastic paraplegia, HSP must be considered whenever similar pathologies, mainly diplegic cerebral palsy, are ruled out.

PMID: 30758437

24. Compensating cerebral palsy cases: Problems in court litigation and the no-fault alternative.
Kassim PNJ, Ushiro S, Najid KM.

Med Law. 2015 Sep;34(1):335-355.

Children having cerebral palsy will incur life-long disabilities, which require high costs of medical and nursing care. This imposes a tremendous burden on the families of the affected children, whether financially or emotionally. It is understandable for the affected families to initiate court litigation in order to alleviate the financial burden and at the same time to overcome the emotional pain associated with the permanent and lifetime implications which cerebral palsy entails. However, suing for such injuries in court and identification of medical malpractice is not an easy task for the families. Further, court litigation tends to be tedious, lengthy and unpleasant. The hazards of litigation have prompted several countries to find an available alternative to court litigation, such as the implementation of a no-fault compensation system, to settle these types of claims. Thus, it is much applauded that the Japan Obstetric Compensation System for Cerebral Palsy was established in January 2009, with the aim of helping children with such disabilities to improve their quality of life and to provide monetary compensation in order to lessen the economic burden on the family. The system features two vital pillars; that is, compensation and causal analysis prevention. The system aims at improving the quality of maternity care and analyzing the causes of accidents in order to prevent similar cases from happening in the future. Overall, the system clearly depicts social solidarity in encouraging collective responsibility for the mishaps suffered by the community.

PMID: 30759941

25. Diethylstilbestrol (DES): also harms the third generation.
[No authors listed]

Prescrire Int. 2016 Dec;25(177):294-298.

Diethylstilbestrol(DES) is a synthetic nonsteroidal oestrogen and endocrine disruptor that was used in the 1950s-1970s to

prevent spontaneous abortion, despite its lack of proven efficacy. Millions of women worldwide took DES during pregnancy. In France, between 1951 and 1981, about 160 000 children were exposed to DES during the first trimester of their intrauterine life, and in some cases almost throughout the entire pregnancy. They are referred to as "DES daughters" and "DES sons". In 2010, in France, about 25 000 DES daughters were aged 33 to 40 years: pregnancies among these women are foreseeable until about 2020. In utero exposure to DES can have harmful effects. In particular, DES daughters have an increased risk of cancer and structural abnormalities of the uterus that can adversely affect their pregnancies. What are the consequences of taking DES during pregnancy for the third generation, i.e. the children of DES children? To answer this question, we reviewed the available data in mid- 2016 using the standard Prescrire methodology. According to a retrospective study conducted in France by Réseau DES France, published in 2016, which included 4409 DES grandchildren (2228 girls and 2181 boys) and about 6000 controls, about one-quarter of DES grandchildren are born prematurely. Preterm delivery exposes neonates to serious neonatal complications, including neurosensory disorders, disabilities and increased neonatal mortality. The more premature the baby, the greater the risk of complications. In the Réseau DES France study, cerebral palsy was more frequent in the DES grandchildren group: 59/10 000, versus 6/10 000 in the control group. A study conducted in the United States in about 4500 DES daughters found that preterm delivery occurred at a frequency of about 26%, much higher than that reported in controls. Neonatal mortality was 8 times higher among DES grandchildren, and the risk of stillbirth was twice as high. Other smaller studies have also shown an increased risk of preterm birth. A cohort study conducted in about 5000 DES grandchildren found that the risk of malformations of any type was higher than in the unexposed control group. Epidemiological studies, conducted in several countries, found an increased frequency of hypospadias in DES grandsons. The relative risk was about 5 in the largest study. Other, less robust studies found no statistically significant difference. Several studies in several countries have shown a twofold increase in the risk of oesophageal atresia or trachea-oesophageal fistula in DES grandchildren. The data on congenital heart defects or musculoskeletal malformations are limited and uninformative. Epidemiological studies have not identified a significant increase in the risk of gynaecological anomalies or cancers in DES granddaughters. Limited data are available on the risk of malformations in the children of DES sons. The data obtained in rodents exposed to DES (and other endocrine disruptors) make it entirely plausible that in utero exposure to DES, in humans too, provokes epigenetic effects that are passed on to future generations not directly exposed to DES. In practice, these data should be discussed with DES daughters, their partners and healthcare teams so that appropriate monitoring, clinical management and follow-up can be arranged for both mother and baby. The harms of taking DES during pregnancy last for decades and affect future generations.

PMID: 30758926

26. DCX-Related Disorders.
Hehr U, Uyanik G, Aigner L, Couillard-Despres S, Winkler J.
EditorsIn: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors.
SourceGeneReviews® [Internet].

Seattle (WA): University of Washington, Seattle; 1993-2019. 2007 Oct 19 [updated 2019 Feb 7].

CLINICAL CHARACTERISTICS: DCX-related disorders include the neuronal migration disorders: Classic thick lissencephaly (more severe anteriorly), usually in males. Subcortical band heterotopia (SBH), primarily in females. Males with classic DCX-related lissencephaly typically have early and profound cognitive and language impairment, cerebral palsy, and epileptic seizures. The clinical phenotype in females with SBH varies widely with cognitive abilities that range from average or mild cognitive impairment to severe intellectual disability and language impairment. Seizures, which frequently are refractory to antiepileptic medication, may be either focal or generalized and behavioral problems may also be observed. In DCX-related lissencephaly and SBH the severity of the clinical manifestation correlates roughly with the degree of the underlying brain malformation as observed in cerebral imaging. DIAGNOSIS/TESTING: The diagnosis of a DCX-related disorder is established in a proband by identification of a DCX pathogenic variant on molecular genetic testing. MANAGEMENT: Treatment of manifestations: Antiepileptic drugs for epileptic seizures; deep brain stimulation may improve the seizure disorder in individuals with SBH; special feeding strategies in newborns with poor suck; physical therapy to promote mobility and prevent contractures; special adaptive chairs or positioners as needed; occupational therapy to improve fine motor skills and oral-motor control; participation in speech therapy, educational training, and enrichment programs. Surveillance: Regular neurologic examination and monitoring of seizure activity, EEG, and antiepileptic drug levels; regular measurement of height, weight, and head circumference; evaluation of feeding and nutrition status; assessment of psychomotor, speech, and cognitive development; prompt consultation in the event of novel neurologic findings or deterioration, aspiration, or infections; monitoring for orthopedic complications such as foot deformity or scoliosis. GENETIC COUNSELING: DCX-related disorders are inherited in an X-linked manner. Up to10% of unaffected mothers of children with a DCX pathogenic variant are presumed to have germline mosaicism with or without somatic mosaicism. A woman who is heterozygous for a DCX pathogenic variant has a 50% chance of transmitting the pathogenic variant in each pregnancy. Hemizygous male offspring usually manifest DCX-related classic lissencephaly, while heterozygous female offspring may be asymptomatic or more frequently manifest a wide phenotypic spectrum of SBH. If the pathogenic variant has been identified in the family, testing to determine the genetic status of at-risk family members and prenatal testing for pregnancies at increased risk are possible.

PMID: 20301364

27. High prevalence of pituitary hormone deficiency in both unilateral and bilateral optic nerve hypoplasia.
Dahl S, Kristoffersen Wiberg M, Teär Fahnehjelm K, Sävendahl L, Wickström R.

Acta Paediatr. 2019 Feb 11. doi: 10.1111/apa.14751. [Epub ahead of print]

AIM: This study examined the prevalence of neurological impairment and pituitary hormone deficiency (PHD) in patients with unilateral and bilateral optic nerve hypoplasia (ONH). METHODS: A population-based cross-sectional cohort study of 65 patients (51% female) with ONH was conducted in Stockholm. Of these were 35 bilateral and 30 unilateral. The patients were below 20 years of age, living in Stockholm in December 2009 and found through database searching. The median age at the analysis of the results in January 2018 was 16.1 years (range 8.1-27.5 years). Neurological assessments and blood sampling were conducted, neuroradiology was reviewed and growth curves were analysed. Diagnoses of PHDs were based on clinical and biochemical evidence of hormone deficiency. RESULTS: Neurological impairments were identified in 47% of the patients and impairments in gross and fine motor function were more prevalent in bilateral ONH ($p < 0.001$). In addition, 9% had cerebral palsy and 14% had epilepsy. The prevalence of PHD was 29% and 19% had multiple PHD. CONCLUSION: Children with ONH had a high risk of neurological impairment, especially in bilateral disease. Both unilateral and bilateral ONH signified an increased prevalence of PHD and all these children should be endocrinologically followed up until completed puberty.

PMID: 30740788

Prevention and Cure

28. MicroRNA Profile Differences in Neonates at Risk for Cerebral Palsy.
Chapman SD, Farina L, Kronforst K, Dizon M.

Phys Med Rehabil Int. 2018;5(3). pii: 1148. Epub 2018 May 31.

BACKGROUND: MicroRNAs; miRs are used as biomarkers in the diagnosis of several diseases. Cerebral palsy; CP, resulting from perinatal brain injury, cannot be diagnosed until 18-24 months old. Biomarkers to predict CP and assess response to investigational therapies are needed. We hypothesized that miRs expressed in neonates with the CP risk factors of abnormal tone and/or intraventricular hemorrhage; IVH differ from those without risk factors. METHODS: This was a cohort study of neonates at risk for CP. Subjects <32 weeks gestation and <1500 grams were recruited from neonatal intensive care units at a large urban delivery hospital and an adjacent children's hospital. Thirty-one plasma samples were evaluated. An unbiased examination was performed by locked nucleic acid quantitative real time - polymerase chain reaction; qRT-PCR. Results were evaluated in the context of IVH and abnormal tone. RESULTS: Plasma miR profiles in neonates at risk for CP differ when comparing those with and without IVH, and with and without abnormal tone. Restricted profiles were found in each condition with greater differences in the tone comparison than the IVH comparison. CONCLUSION: Plasma miR profiles show potential in predicting CP. This study also suggests biologically plausible candidates for future studies.

PMID: 30740584

29. Could the inhibitor of DNA binding 2 and 4 play a role in white matter injury?
Gou X, Tang Y, Qu Y, Xiao D, Ying J, Mu D.

Rev Neurosci. 2019 Feb 9. pii: /j/revneuro.ahead-of-print/revneuro-2018-0090/revneuro-2018-0090.xml. doi: 10.1515/revneuro-2018-0090. [Epub ahead of print]

White matter injury (WMI) prevents the normal development of myelination, leading to central nervous system myelination disorders and the production of chronic sequelae associated with WMI, such as chronic dyskinesia, cognitive impairment and cerebral palsy. This results in a large emotional and socioeconomic burden. Decreased myelination in preterm infant WMI is associated with the delayed development or destruction of oligodendrocyte (OL) lineage cells, particularly oligodendrocyte precursor cells (OPCs). The development of cells from the OL lineage involves the migration, proliferation and different stages of OL differentiation, finally leading to myelination. A series of complex intrinsic, extrinsic and epigenetic factors regulate the OPC cell cycle withdrawal, OL lineage progression and myelination. We focus on the inhibitor of DNA binding 2 (ID2), because it is widely involved in the different stages of OL differentiation and genesis. ID2 is a key transcription factor for the

normal development of OL lineage cells, and the pathogenesis of WMI is closely linked with OL developmental disorders. ID4, another family member of the IDs protein, also plays a similar role in OL differentiation and genesis. ID2 and ID4 belong to the helix-loop-helix family; they lack the DNA-binding sequences and inhibit oligodendrogenesis and OPC differentiation. In this review, we mainly discuss the roles of ID2 in OL development, especially during OPC differentiation, and summarize the ID2-mediated intracellular and extracellular signaling pathways that regulate these processes. We also discuss ID4 in relation to bone morphogenetic protein signaling and oligodendrogenesis. It is likely that these developmental mechanisms are also involved in the myelin repair or remyelination in human neurological diseases.

PMID: 30738015

30. The role of microglial inflammasome activation in pyroptotic cell death following penetrating traumatic brain injury.
Lee SW, de Rivero Vaccari JP, Truettner JS, Dietrich WD, Keane RW.

J Neuroinflammation. 2019 Feb 8;16(1):27. doi: 10.1186/s12974-019-1423-6.

BACKGROUND: Traumatic brain injury remains a significant cause of death and disability in the USA. Currently, there are no effective therapies to mitigate disability except for surgical interventions necessitating a need for continued research into uncovering novel therapeutic targets. In a recent study, we used a rodent model of penetrating traumatic brain injury known as penetrating ballistic-like brain injury (PBBI) to examine the role of innate immunity in post-traumatic secondary injury mechanisms. We previously reported that the inflammasome, a multiprotein complex composed of apoptosis-associated speck-like protein containing card and caspase-1, plays a role in secondary cell death mechanisms after PBBI, including inflammatory cell death (pyroptosis). METHODS: In the current study, we used flow cytometry analysis to evaluate activated microglia and CD11b-positive leukocytes after PBBI and assessed inflammasome activation and pyroptosis of specific cellular populations. Sprague-Dawley male rats underwent PBBI or sham-operated procedures and ipsilateral cortical regions processed for flow cytometry and cellular analysis. Flow cytometry results were compared using one-way ANOVA followed by Tukey's multiple comparisons. RESULTS: At 48 h following PBBI, there was an increase in activated microglia and infiltrating leukocytes compared to sham controls that were associated with increased caspase-1 activity. Using a florescent probe to identify caspase-1 activity and a fluorescent assay to determine cell viability, evidence for pyroptosis in CD11b+ cells was also determined. Finally, while post-traumatic treatment with an anti-ASC antibody had no effect on the number of activated microglia and infiltrating leukocytes, antibody treatment decreased caspase-1 activity in both resident microglia and infiltrating leukocytes and reduced pyroptotic CD11b+ cell death. CONCLUSIONS: These results provide evidence for inflammasome activation in microglia and infiltrating leukocytes after penetrating traumatic brain injury and a role for pyroptotic cell death in the pathophysiology. In addition to inhibiting neuronal cell death, therapeutic treatments targeting inflammasome activation may also provide beneficial effects by reducing the potentially detrimental consequences of activated microglia and infiltrating CD11b+ leukocytes following penetrating traumatic brain injury.

PMID: 30736791