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Professor Nadia Badawi AM
Macquarie Group Foundation Chair of Cerebral Palsy

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Interventions and Management

1. Dual mobility articulation total hip arthroplasty for displaced neck fracture in elderly with neuromuscular disorder
Hyung-Gon Ryu, Young Ju Roh, Kwang-Jun Oh, Ji-Hyo Hwang, Yeesuk Kim, Hyun-Woo Cho, Sang-Min Kim

Injury. 2021 Jan 7;S0020-1383(21)00021-8. doi: 10.1016/j.injury.2021.01.005. Online ahead of print.

Purpose: Neuromuscular disease is well known to be at increased risk of complications following hip replacement surgeries. This study is prospectively conducted to investigate clinical performance and survivorship of total hip arthroplasty (THA) using dual mobility articulation in femoral neck fractures of elderly with neuromuscular disease. Materials and methods: We prospectively enrolled 162 patients (162 hips) with displaced femoral neck fracture who gave informed consent for dual mobility articulation THA. Of the 162 patients, 35 patients had neuromuscular disease including cerebral palsy, poliomyelitis, hemiplegia, and Parkinson disease (NM group). The other 127 patients had no history of neuromuscular disease (non-NM group). The mean age was 76.5 years (range, 60 - 95) and female ratio was 71.0% (115/162). Clinical outcomes including Harris hip score (HHS), University of California Los Angles activity (UCLA) score were compared between the two groups. Computed tomography and serial radiographs were obtained after surgery. Postoperative complications and reoperation including revision were recorded. Results: Pain-VAS and all clinical scores of the NM group were comparable to those of the non-NM group. The incidence of dislocation in the NM group did not differ from that in Non-NM group (2/35, 5.7% versus 5/127, 3.9%, p = 0.645). Reoperation was performed in 3 hips (3/35, 8.6%) of the NM group and in 4 hips (4/127, 3.1%) of the non-NM group (p = 0.173). Kaplan-Meier survivorship with an end point of revision for any reason was 97.1% (95% confidence interval [CI], 0.92 to 1.03) in the NM group and 98.4% (95% CI, 0.96 to 1.01) in the non-NM group at 7.3 years after surgery. Conclusions: In elderly with neuromuscular disease, THA with dual mobility articulation is a reasonable option as a treatment for femoral neck fractures.

PMID: 33461769

2. Reliability of functional tests of the lower limbs and core stability in children and adolescents with cerebral palsy
Vanessa van Tittelboom, Ipek AlemdaroĞlu-GÜrbÜz, Britta Hanssen, Frank Plasschaert, Lieve Heyrman, Hilde Feys, Kaat Desloovere, Patrick Calders, Christine Van den Broeck

Eur J Phys Rehabil Med. 2021 Jan 20. doi: 10.23736/S1973-9087.21.06627-2. Online ahead of print.

Background: Muscle weakness in children and adolescents with cerebral palsy (CP) can affect daily life activities, even more if functional capabilities are poor. Also core stability plays an important role in distal force generation. Aim: The main purpose of this study was to investigate the reliability of functional tests of the lower limbs and the core stability in children and adolescents with bilateral spastic CP with Gross Motor Function Classification System (GMFCS) levels II and III. Secondary, associations within the functional tests and between the functional tests and gait capacity were analyzed. Design: Cross sectional study. Setting: CP reference center *blinded for reviewers*, pediatric physiotherapists and schools for children

and adolescents with motor impairments. Population: Twenty-four children and adolescents with CP (11.4±2.5 yrs, GMFCS II/III:13/11) participated in this study. Methods: Functional tests of the lower limbs (GMFCS II: Sit-To-Stand (STS), Lateral Step -Up (LSU), bilateral heel rise (BHR), high jump (HJ), long jump (LJ); GMFCS III: STS, LSU) and core stability (bridging and Rolling Like a Ball (RLB)) were tested twice. On the second test occasion, gait capacity (1-Minute Walk Test (1MWT) and modified Timed Up and Go (mTUG)) were also assessed. Results: Relative reliability of the functional tests ranged from good to excellent (Intraclass Correlation Coefficients (ICC), 0.88 - 0.96). Absolute reliability showed large variability with acceptable results for the BHR, HJ, LJ and RLB (Minimal Detectable Change % (MDC %) < 40%). Strong associations were found of the RLB test and the mTUG with the BHR, HJ and LJ tests. Conclusions: The functional tests of the lower limbs and core stability were found reliable. To measure change over time, the BHR, the HJ and LJ can be used for children and adolescents with GMFCS level II. The RLB test can be used for both GMFCS levels. Associations between the BHR, HJ and LJ tests in particular showed strong associations with the RLB test and with the mTUG. Clinical rehabilitation impact: this study highlighted the importance of developing functional tests for children and adolescents with lower motor function capacities and to integrate core stability tests in routine clinical assessments.

PMID: 33470579

3. Intramuscular psoas lengthening at the pelvic brim plus proximal lengthening of the rectus femoris as a treatment for fixed knee flexion deformity in cerebral palsy [Article in En, Spanish]
I Martínez Caballero, G Chorbadjian Alonso, R M Egea-Gámez, A Ramírez Barragán, M Fraga Collarte

Rev Esp Cir Ortop Traumatol. 2021 Jan 15;S1888-4415(20)30157-0. doi: 10.1016/j.recot.2020.09.002. Online ahead of print.

Although the correction of knee flexion by lengthening the hamstring musculature is traditionally contemplated in cerebral palsy, literature suggests that treatment of hip flexion also improves knee extension. The aim of the study was to first show the efficacy of the sequence of intrapelvic tenotomy of the psoas followed by intramuscular lengthening of the proximal rectus anterior and, later, that of both surgical soft tissue surgeries separately. For this, a prospective study was carried out in 10 patients with a mean age of 14 years, which presented 16 fixed knee flexes with a mean of deformity of 22°. The data was analyzed through means of an ANOVA of repeated measures and to determine the effect separately of each one of the techniques, the improvements obtained with respect to the previous level were contrasted. The mean extension achieved was 12°, 7° corresponding to the intrapelvic tenotomy of the psoas and, on the remaining knee flexion, a correction of 5° after intramuscular lengthening of the anterior rectus at the proximal level. Both the sequence of proposed gestures and those that form separately, showed statistically significant differences (P <0.001) in the correction of the deformity. In conclusion, the proposed techniques applied sequentially or separately are effective in reducing knee flexion in predominantly spastic cerebral palsy, facilitating or even being able to avoid the treatment that is directly needed.

PMID: 33461940

4. Efficacy of oral magnesium therapy in the treatment of chronic constipation in spastic cerebral palsy children: a randomized controlled trial
Sahar M A Hassanein, Shaymaa M Deifallah, Hend A Bastawy

World J Pediatr. 2021 Jan 22. doi: 10.1007/s12519-020-00401-0. Online ahead of print.

Background: Constipation is a common problem in children with spastic cerebral palsy (sCP) with a prevalence that reaches 75%. We hypothesized that treating constipation in those children will improve their health and shorten time spent in daily care. Our aim was to evaluate the efficacy and safety of oral magnesium sulfate for treating chronic constipation in children with sCP. Methods: A prospective, double-blinded randomized control trial was carried out involving 100 children aged 2-12 years with sCP (level III-V of the Gross Motor Functional Classification system) and chronic constipation. They were followed up in the Pediatric neurology clinic, Children's hospital, Ain Shams University, May 2017- January 2019. The intervention group (O-Mg) received oral magnesium sulfate 1 mL/kg/day daily for 1 month compared to the placebo. Outcome measures were constipation improvement and decrease in bowel evacuation time after 1 month. Results: Initially, weekly bowel movements, constipation scores and stool consistency were comparable in both groups. After 1 month of regular administration of oral magnesium sulfate, the constipation score, stool frequency and consistency improved compared to the placebo group (P < 0.001). Effective safe treatment was achieved in 31 (68%) and 4 (9.5%) patients in the O-Mg and placebo groups, respectively (RR, 2.95; 95% CI 2.0-4.5) (P < 0.001). Painful bowel evacuation attempts spent by mothers decreased from 25 (55.6%) of the cases initially to 10 (22%) cases after one month in the O-Mg group (P = 0.001). In contrast, in the placebo group, the decrease went from 21 (50%) cases initially to 18 (42.9%) after 1 month and was not significant (P = 0.5).

Conclusions: Oral magnesium sulfate seems effective in alleviating chronic constipation and pain experience in children with sCP. Consequently, saving maternal time spent in daily bowel evacuation attempts.

PMID: 33481179

5. [Sevoflurane sedation protocol in children with cerebral palsy undergoing botulinum toxin-A injections][Article in Spanish]
Ángel León-Valenzuela, Carmen Román Malo, Mercedes González López, Juan Sánchez Palacios, Pilar Sánchez Tarifa, Rogelio Del Pino Algarrada

Rehabilitacion (Madr). 2021 Jan 16;S0048-7120(20)30114-6. doi: 10.1016/j.rh.2020.09.005. Online ahead of print.

Objective: This study aimed to describe our experience with a protocol based on sevoflurane sedation to control pain and agitation during botulinum toxin-A (BoNT-A) infiltration in children with cerebral palsy (CP), especially in terms of safety and efficacy. Material and methods: We conducted a retrospective observational study of patients diagnosed with CP who underwent BoNT-A infiltration with sevoflurane sedation from November 2012 to December 2019. Demographic, clinical and functional characteristics, the effectiveness of sedation, adverse events (AE) and professional satisfaction were reviewed. Results: A total of 387 sedations were successfully performed in 74 patients. Effective sedation was achieved in 100% of procedures, facilitating collaboration during infiltration and improving professional satisfaction. AE were reported in 6.02% of the procedures, the most frequent being nausea and vomiting (3.88%) and transient hypoxemia (2.07%). There were no severe AE. No association was found between the incidence of AE and the clinical and functional variables or risk before anaesthesia. Conclusion: Sevoflurane sedation shows promising results in terms of safety and effectiveness for the management of agitation and pain during BoNT-A infiltration in our daily clinical practice. In addition, it can facilitate infiltration, allowing examination under sedation and multilevel infiltration with good tolerance.

PMID: 33468348

6. [Multilevel botulinum toxin treatment in severe spastic forms of cerebral palsy (GMFCS IV-V)] [Article in Russian]
A L Kurenkov, O A Klochkova, L M Kuzenkova, B I Bursagova, Kh M Karimova

Zh Nevrol Psikhiatr Im S S Korsakova. 2020;120(12):57-66. doi: 10.17116/jnevro202012012157.

Objective: To evaluate the most typical target muscles and dosages for the first and repeated botulinum toxin A (BTA) injections in cerebral palsy (CP) patients with severe motor deficit - GMFCS IV-V. Material and methods: A retrospective analysis of 677 protocols of the first and repeated Abobotulinumtoxin A (AboA) injections in 333 patients with CP GMFCS IV and V, aged 1 to 18 years, was carried out. Results: Ninety-seven percent of patients received multilevel injections. In the lower extremities the most typical target muscles were: m.gracilis - 221 (66.4%) patients, hip adductors - 164 (49.2%), medial hamstring - 144 (43.2%). In the upper extremities the most typical muscles were: m.pronator teres - 237 (71.2%) patients, m.biceps brachii+m.brachialis - 197 (59.2%). The total dosages of AboA and dosages for every target muscle were calculated. Several patients required high dosages (more than 30 U/kg of AboA). Higher dosages per kg were used in younger children and for repeated injections. The age-related evolution of spastic patterns was described. Adverse events were observed in 36 cases (5.3% of all injections). Conclusion: The majority of patients with GMFCS IV-V required multilevel BTA injections in high dosages, especially in young age. Described selection of target muscles and dosages of AboA could be taken into account as a practical experience and reference for the BTA therapy in GMFCS IV-V patients.

PMID: 33459542

7. Evaluation of the relationship between cranial magnetic resonance imaging findings and clinical status in children with cerebral palsy
Nİhan Şik, ÖzgÜr ÖztekİN, Fatma Ceren SarioĞlu, Berrak SarioĞlu

Turk J Med Sci. 2021 Jan 18. doi: 10.3906/sag-2010-187. Online ahead of print.

Background: The objective of this study was to evaluate the relationship between cranial magnetic resonance imaging (MRI) findings and clinical features in cerebral palsy (CP). Methods: Children aged 3 to 18 years, who were followed with the diagnosis of CP between January 2012 and September 2015, were included. The type of CP was classified using the European Cerebral Palsy Monitoring Group?s classification system and then, patients were divided into two groups as spastic or non-spastic groups. The Gross Motor Function Classification System (GMFCS) was used to determine the level of mobility. According to the GMFCS, levels 1, 2, and 3 were grouped as mobile, and levels 4 and 5 were grouped as immobile. Cranial MRI findings were reevaluated by a voluntarily radiologist and grouped as periventricular leukomalacia (PVL) (grades 1, 2, and 3), cerebral atrophy, migration anomaly, cerebellar involvement, basal ganglion involvement, and normal MRI findings. Results: Sixty-two patients were enrolled. The rate of mobile patients did not differ between the spastic and non-spastic groups. The incidence of PVL was significantly higher in cases of prematurity and spastic CP ($p<0.05$). The rate of mobilization was significantly lower and the rate of epilepsy was significantly higher in patients with PVL. Immobile patients were more common among cases of grade 3 PVL ($p<0.05$). Conclusion: The most common cranial MRI pathology was PVL, and the presence of PVL and its grade might help clinically assess the patient?s CP type and level of mobilization. While pathology was observed mostly in cranial MRI in cases of CP with similar clinical features, the fact that cranial MRI was completely normal for 14.5% of the cases suggests that there may be some pathologies that we could not identify with today?s imaging technology.

PMID: 33460326

8. Prognostic value of cranial ultrasonography in comparison with magnetic resonance imaging in children with cerebral palsy: a population-based study
Sanja Delin, Katarina Bošnjak Nađ, Sunčica Martinec, Dunja Čokolić Petrović, Andrea Šimic Klarić, Vlatka Mejaški Bošnjak

Acta Clin Croat. 2020 Jun;59(2):260-269. doi: 10.20471/acc.2020.59.02.09.

The aim of this population-based study was to evaluate the characteristics of cerebral palsy (CP) in relation to the predominant pattern of the Magnetic Resonance Imaging Classification System (MRICS) that was analogously applied to the neonatal/early infant cranial ultrasound (CUS). The study included children born during the 2004-2007 period from the Croatian part (C28 RCP-HR) of the Surveillance of Cerebral Palsy in Europe (SCPE) CP register. Motor functions, accompanying impairments and brain MRI were evaluated in 227 children, 185 of which also had CUS. Concerning CP types, 56% of children had bilateral spastic, 34% unilateral spastic, 9% dyskinetic and 1% ataxic CP type. Gross Motor Function Classification System (GMFCS) revealed that 62.05% had mild (GMFCS I-III) and 37.85% had severe motor impairment (GMFCS IV-V). CUS showed white matter injury in 60%, gray matter injury in 12%, maldevelopments in 8%, miscellaneous changes in 14%, while 6% were normal; MRI showed significant agreement ($\kappa=0.675$, $p<0.001$). Neuroimaging findings of maldevelopments and predominant gray matter injury were associated with more severe CP, but 7% of children with CP had normal MRI. As we found very good agreement between CUS and MRI findings, CUS is recommended in children at an increased risk of CP if MRI is not available.

PMID: 33456113

9. Systematic review of clinical guidelines related to care of individuals with cerebral palsy as part of the World Health Organization efforts to develop a global Package of Interventions for Rehabilitation
Diane L Damiano, Egmar Longo, Ana Carolina deCampos, Hans Forssberg, Alexandra Rauch

Review Arch Phys Med Rehabil. 2021 Jan 13;S0003-9993(20)31337-X. doi: 10.1016/j.apmr.2020.11.015. Online ahead of print.

Objective: World Health Organization's (WHO) Rehabilitation 2030 initiative is developing a set of evidence-based interventions selected from clinical practice guidelines for Universal Health Coverage. As an initial step, WHO Rehabilitation Programme and Cochrane Rehabilitation convened global content experts to conduct systematic reviews of clinical practice guidelines for 20 chronic health conditions, including cerebral palsy. Data sources: Six scientific databases (Pubmed, EMBASE, Scopus, Web of Science, PEDro, CINAHL), Google Scholar, guideline databases and professional society websites were searched. Study selection: A search strategy was implemented to identify clinical practice guidelines for cerebral palsy across the lifespan published within 10 years in English. Standardized spreadsheets were provided for process documentation,

data entry and tabulation of the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool. Each step was completed by 2 or more group members with disagreements resolved by discussion. Initially, 13 guidelines were identified. Five did not meet AGREE II established threshold or criteria for inclusion. Further review by WHO eliminated 3 more, with 5 remaining. Data extraction: All 339 recommendations from the 5 final guidelines, with type (Assessment, Intervention or Service), strength and quality of evidence, were extracted and an ICF Functioning category assigned to each. Data synthesis: Most guidelines addressed mobility functions, with comorbid conditions and lifespan considerations also included; however, most were at the level of Body Functions. No guideline focused specifically on physical or occupational therapies to improve activity and participation despite their prevalence in rehabilitation. Conclusions: Despite the great need for high quality guidelines, this review demonstrated the limited number and range of interventions and lack of explicit use of the ICF during development of guidelines identified here. A lack of guidelines however does not necessarily indicate a lack of evidence. Further evidence review and development based on identified gaps and stakeholder priorities are needed.

PMID: 33453191

10. Caring-Related Chronic Low Back Pain and Associated Factors among Mothers of Children with Cerebral Palsy
Mehdi Ramezani, Jandark Eghlidi, Ehsan Pourghayoomi, Saeed Mohammadi

Rehabil Res Pract. 2020 Dec 30;2020:8854435. doi: 10.1155/2020/8854435. eCollection 2020.

Background: Literature indicated some risk factors for low back pain; however, there is insufficient knowledge on the effect of caring-related physical activities and individual characteristics on Chronic Low Back Pain (CLBP) in mothers of children with Cerebral Palsy (CP). Objective: The main aim of the current study was to determine the association between caring-related physical activities, Body Mass Index (BMI), education level, and CLBP in mothers of children with CP. Design: Case-control observational study. Setting. Pediatric rehabilitation clinics. Participants. Mothers of children with CP. Main Outcome Measures. Measures is comprised of a self-administered questionnaire that included the demographic characteristics items, pain visual analog scale, and three items of the job-related physical demands questionnaire. The logistic regression model served to assess the association. Results: The control group included 81 healthy mothers, with a mean (SD) age of 39 (8.45) years, and the case group contained 90 mothers who suffered from CLBP, with a mean (SD) age of 37 (8.64) years. Performing lifting movements (OR 13.73, $\beta = 2.62$, $p < .001$), BMI (OR 11.85, $\beta = 2.47$, $p = .011$), repetitive bending (OR 7.67, $\beta = 2.04$, $p = .010$), forward-flexion (OR 6.71, $\beta = 1.91$, $p = .033$), and level of education (OR .21, $\beta = -1.53$, $p = .020$), in descending order of odds ratios, were found to be significant predictors of the CLBP in mothers of children with CP. Conclusion: Avoiding caring-related harmful physical activities, maintaining body weight within a healthy range, and increasing knowledge for accurate lifting/handling techniques can be helpful to prevent the CLBP in mothers of children with CP.

PMID: 33457016

11. Cerebral Palsy Grows Up
Mark D Peterson, Edward A Hurvitz

Mayo Clin Proc. 2021 Jan 9;S0025-6196(20)31184-8. doi: 10.1016/j.mayocp.2020.10.006. Online ahead of print.

PMID: 33451804

12. Mentally Fit: Negotiating the Boundaries of Cognitive Disability
Patrick McKearney, Anna Zogas

Editorial Med Anthropol. 2021 Jan 15;1-5. doi: 10.1080/01459740.2020.1858296. Online ahead of print.

Why do some people's minds seem conspicuous, disabled, and ill-fitting in some contexts and not others? This special issue presents articles about people in Jordan, Uganda, the United Kingdom and the United States who live with Down syndrome, autism, intellectual disabilities, cerebral palsy, or histories of brain injuries. We focus on the disjunctive encounters between these individuals' minds and the varied relational processes in their surrounding social world in order to understand why

different mental characteristics become points of concern and comparison at some points and not others - and thus to raise questions about how "fitting in" works altogether.

PMID: 33451257

13. Advances in cerebral palsy biomarkers
Zeynep Alpay Savasan, Sun Kwon Kim, Kyung Joon Oh, Stewart F Graham

Adv Clin Chem. 2021;100:139-169. doi: 10.1016/bs.acc.2020.04.006. Epub 2020 May 23.

Cerebral palsy (CP), defined as a group of nonprogressive disorders of movement and posture, is the most common cause of severe neurodisability in children. The prevalence of CP is the same across the globe, affecting approximately 17 million people worldwide. Cerebral Palsy is an umbrella term used to describe the disease due to its inherent heterogeneity. For instance, CP has multiple (1) causes; (2) clinical types; (3) patterns of neuropathology on brain imaging and (4) it's associated with several developmental pathologies such as intellectual disability, autism, epilepsy, and visual impairment. Understanding its physiopathology is crucial to developing protective strategies. Despite its importance, there is still insufficient progress in the areas of CP prediction, early diagnosis, treatment, and prevention. Herein we describe the current risk factors and biomarkers used for the diagnosis and prediction of CP. With the advancement in biomarker discovery, we predict that our understanding of the etiopathophysiology of CP will also increase, lending to more opportunities for developing novel treatments and prognosis.

PMID: 33453864

14. Assessment of mirror movements in children and adolescents with unilateral cerebral palsy: reliability of the Woods and Teuber scale
Victoria A Magne, Lars Adde, Brian Hoare, Katrijn Klingels, Cristina Simon-Martinez, Lisa Mailleux, Stian Lydersen, Ann-Kristin G Elvrum

Dev Med Child Neurol. 2021 Jan 19. doi: 10.1111/dmcn.14806. Online ahead of print.

Aim: To investigate the inter- and intrarater reliability of the Woods and Teuber scale to detect mirror movements in children and adolescents with unilateral cerebral palsy (CP). Method: A convenience sample of children and adolescents with unilateral CP (n=68; 31 males, 37 females; mean age 12y 2mo, SD 3y 6mo) in Manual Ability Classification levels I to III was recruited from Norway, Australia, and Belgium. Three therapists scored mirror movements according to the Woods and Teuber scale from three video-recorded tasks at two separate time points. A two-way, mixed model regression was used to calculate intraclass correlation coefficients (ICCs) reflecting overall inter- and intrarater reliability. In addition, ICCs for each hand and task were calculated separately. Results: The overall interrater reliability ICC was 0.90 and the corresponding intrarater reliability ICC was 0.92. The ICCs for each hand ranged from 0.86 to 0.92 and for each task from 0.63 to 0.89. Interpretation: The Woods and Teuber scale shows excellent reliability for scoring mirror movements in children and adolescents with unilateral CP. The assessment is easy to administer with no need for specific equipment and scoring can be determined from short video recordings, making it a feasible instrument in research and clinical practice.

PMID: 33469938

15. Associations Between Early Structural MRI, Hammersmith Infant Neurological Exam, and General Movements Assessment in Very Preterm Infants
Karen Harpster, Stephanie Merhar, Venkata Sita Priyanka Illapani, Colleen Peyton, Beth Kline-Fath, Nehal A Parikh

J Pediatr. 2021 Jan 13;S0022-3476(20)31566-3. doi: 10.1016/j.jpeds.2020.12.056. Online ahead of print.

Objective: To evaluate the prevalence and associations between structural MRI (sMRI) injury/abnormality at term equivalent age and absent fidgety General Movements Assessment (GMA) and abnormal Hammersmith Infant Neurological Examination

(HINE) scores among very preterm infants at 3-4 months corrected age. Study design: This prospective cohort study enrolled 392 infants born ≤32 weeks' gestation from five neonatal intensive care units in the greater Cincinnati area between September 2016 and October 2019. Infants completed sMRI at term-equivalent age and GMA and HINE at 3-4 months corrected age. All assessors were blinded. Results: Of 392 infants, 375 (96%) had complete data. Of these, 44 (12%) exhibited moderate or severe brain abnormalities, 17 (4.5%) had abnormal GMA, and 77 (20.3%) had abnormal HINE. Global and regional abnormality scores on sMRI were significantly correlated with GMA (R2 range: 0.05-0.17) and HINE at 3-4 months corrected age (R2 range: 0.01-0.17). These associations remained significant in multivariable analyses after adjusting for gestational age and sex. There was a significant but low correlation (R2 0.14) between GMA and HINE. Conclusion: We observed a low prevalence of moderate or severe brain abnormalities in very preterm survivors in this geographically-defined cohort. The much higher prevalence of abnormal motor exam on the HINE compared with GMA and their low correlation suggests that these tests evaluate different constructs, and thus, should be used in combination with sMRI rather than interchangeably.

PMID: 33453201

16. Predicting long-term neurodevelopmental outcomes in very preterm neonates by umbilical cord gas parameters
Sima H Baalbaki, S Lindsay Wood, Alan T Tita, Jeff M Szychowski, William W Andrews, Akila Subramaniam

Am J Obstet Gynecol MFM. 2021 Jan;3(1):100248. doi: 10.1016/j.ajogmf.2020.100248. Epub 2020 Oct 6.

Background: The predictive value of acidemia at birth on long-term neurodevelopmental outcomes remains poorly understood, especially in preterm neonates. Objective: This study aimed to assess the relationship between the umbilical artery acid-base status and major neurodevelopmental disability at an age of between 5 and 8 years among children born very prematurely. Study design: We performed a secondary analysis of the data from a follow-up study of a prospective cohort of 457 children aged between 23 weeks and 31 weeks and 6 days from 1996 to 2001. Arterial cord gas parameters that were <10th percentile in the original cohort of 457 neonates (ie, pH of <7.1, base deficit of <-8.6 mEq/L, and a partial pressure of CO2 of >77 mm Hg) were considered abnormal. Sensitivity analyses considered alternative definitions for abnormal cord gases including a pH of <7.0 or base deficit of <-12 mEq/L. The primary outcome was a composite of major neurodevelopmental disability, including an intelligence quotient score of <70, cerebral palsy, blindness, deafness, abnormal balance, impaired cognition, dystonia, and seizure disorder. A logistic regression analysis was used to adjust for race and caregiver intelligence quotient score and, in an additional analysis, for gestational age. Results: A total of 259 of 261 maternal-infant dyads were evaluated at a mean child age of 6.8 years, with complete umbilical cord gas data for 228 of those. Infants with an abnormal pH and a base deficit (defined above) were over 4-fold more likely to have the composite disability and an intelligence quotient score of <70. These increased odds persisted after adjusting for age and caregiver intelligence quotient score, but when considering gestational age as well, none of the umbilical cord gas parameters significantly predicted the presence of the composite disability or an intelligence quotient score of <70. However, when using the stricter umbilical cord gas criteria (ie, pH of <7.0 and a base deficit of <-12 mEq/L), a base deficit of <-12 mEq/L was independently associated with both neurodevelopmental disability and an intelligence quotient score of <70. Conclusion: When defined more strictly, abnormal umbilical cord gases, specifically a base deficit of <-12 mEq/L, are associated with an increased risk for major long-term neurodevelopmental disability and an intelligence quotient score of <70 in children born very prematurely.

PMID: 33451600

17. Mortality and neurological outcomes in extremely and very preterm infants born to mothers with hypertensive disorders of pregnancy
Noriyuki Nakamura, Takafumi Ushida, Masahiro Nakatochi, Yumiko Kobayashi, Yoshinori Moriyama, Kenji Imai, Tomoko Nakano-Kobayashi, Masahiro Hayakawa, Hiroaki Kajiyama, Fumitaka Kikkawa, Tomomi Kotani, Neonatal Research Network of Japan

Sci Rep. 2021 Jan 18;11(1):1729. doi: 10.1038/s41598-021-81292-7.

To evaluate the impact of maternal hypertensive disorders of pregnancy (HDP) on mortality and neurological outcomes in extremely and very preterm infants using a nationwide neonatal database in Japan. This population-based retrospective study was based on an analysis of data collected by the Neonatal Research Network of Japan from 2003 to 2015 of neonates weighing 1,500 g or less at birth, between 22 and 31 weeks' gestation. A total of 21,659 infants were randomly divided into two groups, HDP (n = 4,584) and non-HDP (n = 4,584), at a ratio of 1:1 after stratification by four factors including maternal age, parity, weeks of gestation, and year of delivery. Short-term (neonatal period) and medium-term (3 years of age) mortality and

neurological outcomes were compared between the two groups by logistic regression analyses. In univariate analysis, HDP was associated with an increased risk for in-hospital death (crude odds ratio [OR], 1.31; 95% confidence interval, 1.04-1.63) and a decreased risk for severe intraventricular haemorrhage (0.68; 0.53-0.87) and periventricular leukomalacia (0.60; 0.48-0.77). In multivariate analysis, HDP was significantly associated with a lower risk for in-hospital death (adjusted OR, 0.61; 0.47-0.80), severe intraventricular haemorrhage (0.47; 0.35-0.63), periventricular leukomalacia (0.59; 0.45-0.78), neonatal seizures (0.40; 0.28-0.57) and cerebral palsy (0.70; 0.52-0.95) at 3 years after adjustment for covariates including birth weight. These results were consistent with those of additional analyses, which excluded cases with histological chorioamnionitis and which divided the infants into two subgroups (22-27 gestational weeks and 28-31 gestational weeks). Maternal HDP was associated with an increased risk for in-hospital death without adjusting for covariates, but it was also associated with a lower risk for mortality and adverse neurological outcomes in extremely and very preterm infants if all covariates except HDP were identical.

PMID: 33462302

18. Randomised trial of dobutamine versus placebo for low superior vena cava flow in preterm infants: Long-term neurodevelopmental outcome
María Carmen Bravo, Paloma López-Ortego, Laura Sánchez, Jesús Díez, Fernando Cabañas, Adelina Pellicer

J Paediatr Child Health. 2021 Jan 19. doi: 10.1111/jpc.15344. Online ahead of print.

Aim: Although circulatory impairment during the transitional circulation associates morbidity and mortality, its treatment remains controversial. In a pilot trial on circulatory impairment defined as low superior vena cava (SVC) flow, dobutamine (Db) versus placebo (PL) showed a trend towards improved short-term outcomes. The purpose of this study was to report on the long-term outcome of the infants who were observed for SVC flow patterns. Methods: Among the 126 infants <31 weeks of gestation prospectively scanned from birth, 28 presented low SVC flow within the first 24 h after birth and received Db (n = 16) or PL (n = 12). Follow-up of survivors included motor assessment and Bayley Scales II or III at 2 years, and the Reynolds Intellectual Assessment Scale at 6 years. Neurodevelopmental impairment (NDI) was defined as: cerebral palsy (Gross Motor Function Classification System ≥ level 2), or a cognitive function score < -2 standard deviations; or moderate or severe hearing or visual impairment. Db group, PL group and normal-flow group were compared. Results: Eighteen infants died (Db: 5; PL: 2; normal flow group: 11, P = 0.1). Follow-up in survivors was accomplished in 80% and 55% of the cohort at 2 years and 6 years, respectively. No significant difference in the combined outcome (mortality or NDI) was found between the groups (42% Db, 36% PL, 30% normal flow group). Conclusions: This exploratory analysis did not show any differences in the long-term outcome of infants according to SVC flow patterns or its treatment early after birth.

PMID: 33464688

19. Outcomes of a uniformly active approach to infants born at 22-24 weeks of gestation
Fanny Söderström, Erik Normann, Maria Jonsson, Johan Ågren

Arch Dis Child Fetal Neonatal Ed. 2021 Jan 15;fetalneonatal-2020-320486. doi: 10.1136/archdischild-2020-320486. Online ahead of print.

Objective: To determine survival and outcomes in infants born at 22-24 weeks of gestation in a centre with a uniformly active approach to management of extremely preterm infants. Study design: Single-centre retrospective cohort study including infants born 2006-2015. Short-term morbidities assessed included retinopathy of prematurity, necrotising enterocolitis, patent ductus arteriosus, intraventricular haemorrhage, periventricular malacia and bronchopulmonary dysplasia. Neurodevelopmental outcomes assessed included cerebral palsy, visual impairment, hearing impairment and developmental delay. Results: Total survival was 64% (143/222), ranging from 52% at 22 weeks to 70% at 24 weeks. Of 133 (93%) children available for follow-up at 2.5 years corrected age, 34% had neurodevelopmental impairment with 11% classified as moderately to severely impaired. Treatment-requiring retinopathy of prematurity, severe bronchopulmonary dysplasia, visual impairment and developmental delay correlated with lower gestational age. Conclusions: A uniformly active approach to all extremely preterm infants results in survival rates that are not distinctly different across the gestational ages of 22-24 weeks and more than 50% survival even in infants at 22 weeks. The majority were unimpaired at 2.5 years, suggesting that such an approach does not result in higher rates of long-term adverse neurological outcome.

PMID: 33452221

20. Neurodevelopmental outcomes after ventriculoperitoneal shunt placement in children with non-infectious hydrocephalus: a meta-analysis
Mirna Sobana, Danny Halim, Jenifer Kiem Aviani, Uni Gamayani, Tri Hanggono Achmad

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Background: Hydrocephalus is diagnosed when an accumulating amount of cerebrospinal fluid (CSF) fails to circulate and/or absorbed in the ventricular system. Based on its etiology, hydrocephalus can be classified into infectious and non-infectious hydrocephalus. In children, non-infectious hydrocephalus includes congenital hydrocephalus, posthemorrhagic hydrocephalus, neural tube defect-related hydrocephalus, and tumor-related hydrocephalus. Regardless of the cause, a CSF diversion device is placed to divert the excess fluid from the ventricles into peritoneal cavity. Among all, ventriculoperitoneal (VP) shunt is arguably the most commonly used CSF diversion device to date. Until now, the long-term neurodevelopmental impact of VP shunt placement in non-infectious hydrocephalus patients remained unclear. Objective: This study aims to evaluate the neurodevelopmental outcomes in children with non-infectious hydrocephalus who had VP shunt placement. Materials and methods: Systematic searches were performed using PubMed, Google Scholar, Scopus databases, and reference lists. Publications that fulfilled the inclusion criteria were included in the meta-analysis. Calculation of Mantel-Haezel risk ratio (RR) was applied, and heterogeneity index (I2) test was used to evaluate the existence of heterogeneity in all studies. Risk of bias was assessed based on the criteria from the Newcastle-Ottawa Scale (NOS). Results: Of the 1929 studies identified, 12 publications were concluded to have fulfilled the inclusion criteria. Results from the meta-analysis showed that the risks of cerebral palsy, visual and hearing impairment, epilepsy, or seizures are significantly higher in children with non-infectious hydrocephalus who already had VP shunt placement (shunted non-infectious hydrocephalus, S-NIH) compared to that of the healthy control. The meta-analysis on intelligent quotient (IQ) and mental development index (MDI) showed that S-NIH children tend to score lower IQ and acquire risk of having mental development delay. On motoric development, S-NIH children scored lower motoric score and have significantly higher risk of motor development delay compared to control. Although normal children tend to have more internalizing behavior compared to S-NIH children, overall assessment on the risk of behavioral abnormalities showed that the differences between these two groups are insignificant. Conclusion: S-NIH children have significantly higher risks of disabilities and mental and motoric development delays; thus, planning on continuous rehabilitation for children with non-infectious hydrocephalus who already had placement of VP shunt is important to acquire their optimum potentials and quality of life.

PMID: 33479825

21. Cytomegalovirus infection in pregnancy - An update
Osric B Navti, Mariam Al-Belushi, Justin C Konje, FRCOG

Eur J Obstet Gynecol Reprod Biol. 2020 Dec 11;258:216-222. doi: 10.1016/j.ejogrb.2020.12.006. Online ahead of print.

Cytomegalovirus (CMV) is a ubiquitous DNA virus with a global seroprevalence of 83 %. It is the most common pathogen causing teratogenic congenital infection. It is therefore a major public health concern. Maternal infection is associated with congenital CMV (cCMV), the leading cause of non-genetic sensorineural hearing loss. cCMV also causes impairment of cognitive development and cerebral palsy. Transmission of CMV occurs through direct contact with bodily fluids such as saliva, urine or semen from someone who is actively shedding the virus. Transmission rates are higher after primary infection with the rate of transmission increasing with gestational age. Severe fetal effects are however more common when infection occurs before 20weeks. Past infection does not confer immunity to mother or protect the fetus. cCMV may present with cerebral or extracerebral abnormalities on ultrasound, fetal growth restriction and fetal loss. Diagnosis of primary maternal CMV in pregnancy should be based on seroconversion in pregnancy (de novo appearance of virus-specific immunoglobulin G (IgG) in the serum of pregnant women who were previously seronegative) or on detection of specific immunoglobulin M (IgM) and IgG antibodies in association with low IgG avidity. Prenatal diagnosis of fetal CMV is imperfect and based on amniocentesis performed at least 8 weeks after presumed maternal infection and after 17 weeks of gestation. Hygiene information and education of pregnant women is currently the most effective strategy for prevention of CMV infection. The role of vaccines, antiviral drugs and immunoglobulins remains unproven.

PMID: 33454510

22. Maternal hepatitis B or C carrier status and long-term risk for offspring neurological morbidity: a population-based cohort study
Israel Yoles, Eyal Sheiner, Naim Abu-Freha, Tamar Wainstock

J Dev Orig Health Dis. 2021 Jan 21;1-5. doi: 10.1017/S2040174420001397. Online ahead of print.

Hepatitis B and hepatitis C (HBV/HCV) are important global public health concerns. We aimed to evaluate the association between maternal HBV/HCV carrier status and long-term offspring neurological hospitalisations. A population-based cohort analysis compared the risk for long-term childhood neurological hospitalisations in offspring born to HBV/HCV carrier vs. non-carrier mothers in a large tertiary medical centre between 1991 and 2014. Childhood neurological diseases, such as cerebral palsy, movement disorders or developmental disorders, were pre-defined based on ICD-9 codes as recorded in hospital medical files. Offspring with congenital malformations and multiple gestations were excluded from the study. A Kaplan-Meier survival curve was constructed to compare cumulative neurological hospitalisations over time, and a Cox proportional hazards model was used to control for confounders. During the study period (1991-2014), 243,682 newborns met the inclusion criteria, and 777 (0.3%) newborns were born to HBV/HCV mothers. The median follow-up was 10.51 years (0-18 years). The offspring from HBV/HCV mothers had higher incidence of neurological hospitalisations (4.5 vs. 3.1%, hazard ratio (HR) = 1.91, 95% CI 1.37-2.67). Similarly, the cumulative incidence of neurological hospitalisations was higher in children born to HBV/HCV carrier mothers (Kaplan-Meier survival curve log-rank test $p < 0.001$). The increased risk remained significant in a Cox proportional hazards model, which adjusted for gestational age, mode of delivery and pregnancy complications (adjusted HR = 1.40, 1.01-1.95, $p = 0.049$). We conclude that maternal HBV or HCV carrier status is an independent risk factor for the long-term neurological hospitalisation of offspring regardless of gestational age and other adverse perinatal outcomes.

PMID: 33472720

23. Protocol for a cost-utility analysis of neurostimulation and intensive camp-based therapy for children with perinatal stroke and hemiparesis based on a multicentre clinical trial
Patrick Berrigan, Jacquie Hodge, Adam Kirton, Myla E Moretti, Wendy J Ungar, Jennifer D Zwicker

BMJ Open. 2021 Jan 19;11(1):e041444. doi: 10.1136/bmjopen-2020-041444.

Introduction: Perinatal stroke leads to cerebral palsy (CP) and lifelong disability for thousands of Canadian children. Hemiparesis, referring to impaired functionality in one side of the body, is a common complication of perinatal stroke. Standard long-term care for hemiparetic CP focuses on rehabilitation therapies. Early research suggests that patients with hemiparesis may benefit from adjunctive neuromodulation treatments such as transcranial direct current stimulation (tDCS). tDCS uses electric current to stimulate targeted areas of the brain non-invasively, potentially enhancing the effects of motor learning therapies. This protocol describes an economic evaluation to be conducted alongside a randomised controlled trial (RCT) to assess the incremental cost of tDCS added to a camp-based therapy compared with camp-based therapy alone per quality-adjusted life year (QALY) gained in children with hemiparetic CP. Methods and analysis: The Stimulation for Perinatal Stroke Optimising Recovery Trajectories (SPORT) trial is a multicentre RCT evaluating tDCS added to a 2-week camp-based therapy for children aged 6-18 years with perinatal ischaemic stroke and disabling hemiparetic CP affecting the upper limb. Outcomes are assessed at baseline, 1 week, 2 months and 6 months following intervention. Cost and quality of life data are collected at baseline and 6 months and results will be used to conduct a cost-utility analysis (CUA). The evaluation will be conducted from the perspectives of the public healthcare system and society. The CUA will be conducted over a 6-month time horizon. Ethics and dissemination: Ethical approval for the SPORT trial and the associated economic evaluation has been given by the research ethics boards at each of the study sites. The findings of the economic evaluation will be submitted for publication in a peer reviewed academic journal and submitted for presentation at conference. Trial registration number: NCT03216837; Post-results.

PMID: 33468454

24. Cost-effectiveness of influenza vaccination during pregnancy
Sarina R Chaiken, Alyssa R Hersh, Marguerite S Zimmermann, Britta M Ameel, Vanessa R Layoun, Aaron B Caughey

J Matern Fetal Neonatal Med. 2021 Jan 21;1-17. doi: 10.1080/14767058.2021.1876654. Online ahead of print.

Objective: To assess the cost-effectiveness of influenza vaccination for all pregnant patients in the United States. Methods: We designed a cost-effectiveness model to compare outcomes and costs in pregnant patients who received the inactivated, trivalent influenza vaccine to those who did not. We used a theoretical cohort of 4 million patients, the number of individuals giving birth in the United States per year. We assumed that H1N1 and A or B type influenza were of equal incidence based on seasonal variation from the past ten years. Our outcomes include acquiring H1N1, acquiring A or B type influenza, maternal death, stillbirth, infant death, preterm birth, and cerebral palsy in addition to cost and quality-adjusted life years (QALYs). Probabilities were derived from the literature and QALYs generated at a discount rate of 3%. Sensitivity analyses were performed to assess the robustness of our model. Results: In our theoretical cohort of 4 million pregnant patients, the influenza vaccination strategy was associated with 1632 fewer stillbirths (24,332 in the vaccine strategy vs. 25,964 in the no vaccine strategy), 120 fewer maternal deaths (284 vs. 404), 340 fewer infant deaths (5608 vs. 5948), 32,856 fewer preterm births (403,896 vs. 436,752), and 641 fewer cases of moderate cerebral palsy (12,388 vs. 13,029). Additionally, the vaccination strategy corresponded to savings of $3.7 billion ($63.3 billion vs. $67.0 billion) and increased QALYs of 81,696 (226,852,076 vs 226,770,380). Therefore, it was considered a dominant strategy. Univariate sensitivity analysis demonstrated that the vaccine is cost saving until vaccine cost passes $900, far above the current cost of $12.16. In addition, we used sensitivity analysis to vary seasonal proportions of H1N1 to A or B type influenza. The vaccine was cost saving and increased QALYs for any proportion of H1N1 to A or B type influenza including when H1N1 was absent. Conclusion: We demonstrate that in a cohort of 4 million patients, the influenza vaccine may save $3.7 billion per year, improve maternal and infant outcomes, and reduce morbidity and mortality. Our study provides further evidence that providers should strongly recommend that pregnant patients receive their annual influenza vaccine.

PMID: 33478281

25. [Changes and clinical significance of serum NSE and MBP levels in children with cerebral palsy at high altitude during comprehensive rehabilitation][Article in Chinese]
S Z Chen, J L Liu, X R A, P L Ren, Y Yang

Randomized Controlled Trial Zhonghua Yu Fang Yi Xue Za Zhi. 2021 Jan 6;55(1):84-88. doi: 10.3760/cma.j.cn112150-20200520-00761.

Objective: To explore the changes of serum neuron-specific enolase (NSE) and myelin basic protein (MBP) in children with cerebral palsy at high altitude during comprehensive rehabilitation and their clinical significance. Methods: A clinical randomized controlled study design was used to select 144 children with cerebral palsy who were diagnosed and treated in the Rehabilitation Center of Xining Traditional Chinese Medicine Hospital of Qinghai Province from June 2018 to October 2019, including 83 males and 61 females, aged 3-5 years old. According to the order of admission, the random number table was used to divide into a conventional treatment group (n=72, 40 males and 32 females) and a comprehensive treatment group (n=72, 43 males and 29 females). The conventional treatment group was treated with conventional rehabilitation. The comprehensive treatment group was treated with monosialotetrahexose ganglioside sodium on the basis of conventional rehabilitation. In addition, 30 healthy children aged 3-5 years, 16 males and 14 females, were selected as the control group during the physical examination of the Pediatrics Department of Xining Hospital of Traditional Chinese Medicine, Qinghai Province. The serum levels of NSE and MBP in each group were detected, and the children's GMFM-88 scores were evaluated before and after treatment. The SPSS19.0 software was used for statistical analysis, the count data was tested by $\chi 2$. Results: The serum NSE and MBP levels of the control group were (5.96±0.80), (0.71±0.15) μg/L. Before treatment, the serum NSE and MBP levels of children with severe, moderate, and mild cerebral palsy were [(21.63±1.92), (3.63±0.49) μg/L], [(17.86±1.43) μg/L, (2.21±0.07) μg/L] and [(15.14±0.95), (1.76±0.30) μg/L], respectively. After treatment, the serum NSE and MBP levels of the conventional treatment group and the comprehensive treatment group were [(13.54±2.41), (2.07±0.85) μg/L] and [(12.09±2.37), (1.81±0.69) μg/L], respectively, and the GMFM-88 score was (116.75±27.41) points and (125.94±24.93) points. The levels of NSE and MBP in the serum of children with cerebral palsy were significantly higher than those of normal children in the control group, and their levels increased with the degree of disease, and the corresponding gross motor function scores were lower. After treatment, the GMFM-88 scale assessment scores of the two groups of children were significantly improved (t values were 310.97 and 70.86, P values were both<0.05), and serum NSE and MBP levels decreased to varying degrees compared with before treatment. The decline in the comprehensive treatment group was greater than that in the conventional treatment group. Conclusions: Serum NSE and MBP levels in children with cerebral palsy at high altitude are significantly higher than those in healthy children, and their levels are closely related to the degree of impairment and GMFM-88 scores in children with cerebral palsy. Dynamic monitoring of changes in NSE and MBP levels may be responsible for the condition and treatment effects of children with cerebral palsy judgments based.

PMID: 33455137

Prevention and Cure

26. Amniotic fluid stem cells as a novel strategy for the treatment of fetal and neonatal neurological diseases
Yushi Abe, Daigo Ochiai, Yu Sato, Toshimitsu Otani, Marie Fukutake, Satoru Ikenoue, Yoshifumi Kasuga, Mamoru Tanaka

Review Placenta. 2021 Jan 12;104:247-252. doi: 10.1016/j.placenta.2021.01.009. Online ahead of print.

Even in the context of modern medicine, infants with fetal and neonatal neurological diseases such as cerebral palsy and myelomeningocele suffer serious long-lasting impairment due to the irreversible neuronal damage. The promotion of neurologically intact survival in patients with perinatal intractable neurological diseases requires the development of novel strategies. One promising strategy involves the use of human amniotic fluid stem cells (hAFSCs), which have attracted much attention in recent years and are known to exert anti-inflammatory and neuroprotective effects. In recent years, the therapeutic effects of hAFSCs on fetal-neonatal neurological diseases have become evident as per intense research efforts by our group and others. Specifically, hAFSCs administered into the nasal cavity migrated to the brain and controlled local inflammation in a rodent model of neonatal hypoxic-ischemic encephalopathy. In contrast, hAFSCs administered intraperitoneally did not migrate to the brain; they rather formed spheroids in the abdominal cavity, resulting in the suppression of systemic inflammation (including in the brain) via the secretion of anti-inflammatory cytokines in concert with peritoneal macrophages in a rodent model of periventricular leukomalacia. Moreover, studies in a rat model of myelomeningocele suggested that hAFSCs administered in utero secreted hepatocyte growth factor and protected the exposed spinal cord during pregnancy. Importantly, autologous hAFSCs, whose use for fetal-neonatal treatment does not raise ethical issues, can be collected during pregnancy and prepared in sufficient numbers for therapeutic use. This article outlines the results of preclinical research on fetal stem cell therapy, mainly involving hAFSCs, in the context of perinatal neurological diseases.

PMID: 33461069