Early intervention to improve hand function in hemiplegic cerebral palsy.

Basu AP1, Pearse J2, Kelly S3, Wisher V3, Kisler J1.

Children with hemiplegic cerebral palsy often have marked hand involvement with excessive thumb adduction and flexion and limited active wrist extension from infancy. Post-lesional aberrant plasticity can lead to progressive abnormalities of the developing motor system. Disturbances of somatosensory and visual function and developmental disregard contribute to difficulties with hand use. Progressive soft tissue and bony changes may occur, leading to contractures, which further limit function in a vicious cycle. Early intervention might help to break this cycle, however, the precise nature and appropriateness of the intervention must be carefully considered. Traditional approaches to the hemiplegic upper limb include medications and botulinum toxin injections to manage abnormalities of tone, and surgical interventions. Therapist input, including provision of orthoses, remains a mainstay although many therapies have not been well evaluated. There has been a recent increase in interventions for the hemiplegic upper limb, mostly aimed outside the period of infancy. These include trials of constraint-induced movement therapy (CIMT) and bimanual therapy as well as the use of virtual reality and robot-assisted therapy. In future, non-invasive brain stimulation may be combined with therapy. Interventions under investigation in the infant age group include modified CIMT and action observation therapy. A further approach which may be suited to the infant with thumb-in-palm deformity, but which requires evaluation, is the use of elastic taping. Enhanced cutaneous feedback through mechanical stimulation to the skin provided by the tape during movement has been postulated to modulate ongoing muscle activity. If effective, this would represent a low-cost, safe, widely applicable early intervention.

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Gatin L1, Khouri N2.

INTRODUCTION: Patients with neurological disorders often exhibit dislocation or subluxation of the hip. Anterior dislocation is rare, little known, and often associated with deformities. Its surgical treatment has rarely been studied.

HYPOTHESIS: Hip surgery (with open reduction, femoral and pelvic osteotomy, and adapted tenotomies) could provide a centered hip that is supple and painless. MATERIALS AND METHODS: Ten hips (seven dislocated, three subluxated) in six patients with a mean age of 8.3 years were operated between 1995 and 2009 and revised with a mean follow-up of 6.5 years. The deformities comprised four cases of abduction, extension, and external rotation and six cases of adduction, extension, and external rotation. Four patients had lost the ability to walk or maintain the sitting position. Intraoperative findings were an increased neck-shaft angle, anterosuperior acetabular dysplasia, and in only one case increased femoral anteversion. In all cases of dislocation, open reduction was necessary, and all hips underwent pelvic and femoral osteotomy. RESULTS: At the longest follow-up, hips were centered on X-rays. Five patients could walk or sit as they had done before and hips were supple, with no deformities.

DISCUSSION: The study of deformities and intraoperative findings is mandatory for surgical management, whose mid-term results are encouraging. Femoral anteversion does not seem to be excessive, but the increase of femoral valgus is constant, as is anterosuperior acetabular dysplasia. We propose a decision tree for the management of these patients. DESIGN OF STUDY: Retrospective.

LEVEL OF SCIENTIFIC EVIDENCE: IV.

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Sagittal gait patterns in cerebral palsy: The plantarflexor-knee extension couple index.

Sangeux M1, Rodda J2, Graham HK2.

The identification of gait patterns in cerebral palsy offers a common language for clinicians and contributes to management algorithms. We describe a quantitative classification of sagittal gait patterns based on the plantarflexor-knee extension couple index. This consists of a scatter plot based on ankle and knee scores, and allows objective identification of the sagittal gait pattern. Sagittal kinematic data from 200 limbs of 100 patients with bilateral spastic cerebral palsy were utilized to validate the algorithm against the assessment of a clinician with expertise in gait pattern identification. A dataset of 776 cerebral palsy patients, 1552 limbs, was used to compare the sagittal gait patterns against k-means statistical clustering. The classification was further explored with respect to the knee kinetics during the middle of stance and physical examination measurements of the gastrocnemius-soleus complex. Two supplementary materials (Appendices 2 and 3) provide in-depth discussion about statistical properties of the plantarflexor-knee extension couple index as well as its relationship with statistical clustering. The plantarflexor-knee extension index achieved 98% accuracy and may be suitable for the computational classification of large patient cohorts and multicentre studies. The sagittal gait patterns were strongly related to k-means statistical clustering and physical examination of the gastrocnemius-soleus complex. Patients in crouch gait had normal soleus and gastrocnemius lengths but spasticity in the gastrocnemius. Patients in jump gait exhibited a short gastrocnemius and soleus and gastrocnemius spasticity. Patients in true equinus presented with a moderately contracted soleus and gastrocnemius and gastrocnemius spasticity. Patients in apparent equinus did not show abnormal physical examination measurements for the gastrocnemius-soleus complex.

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Long-term outcome in selective dorsal rhizotomy in spastic cerebral palsy: differentiation in mobility levels is needed.
Vermeulen RJ1, Becher JG.

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Effects of anodal transcranial direct current stimulation combined with virtual reality for improving gait in children with spastic diparetic cerebral palsy: A pilot, randomized, controlled, double-blind, clinical trial.
Collange Grecco LA1, de Almeida Carvalho Duarte N2, Mendonça ME3, Galli M4, Fregni F5, Oliveira CS2.

OBJECTIVE: To compare the effects of anodal vs. sham transcranial direct current stimulation combined with virtual reality training for improving gait in children with cerebral palsy.
DESIGN: A pilot, randomized, controlled, double-blind, clinical trial.
SETTING: Rehabilitation clinics.
SUBJECTS: A total of 20 children with diparesis owing to cerebral palsy.
INTERVENTIONS: The experimental group received anodal stimulation and the control group received sham stimulation over the primary motor cortex during virtual reality training. All patients underwent the same training programme involving a virtual reality (10 sessions). Evaluations were performed before and after the intervention as well as at the one-month follow-up and involved gait analysis, the Gross Motor Function Measure, the Pediatric Evaluation Disability Inventory and the determination of motor evoked potentials.
RESULTS: The experimental group had a better performance regarding gait velocity (experimental group: 0.63 ±0.17 to 0.85 ±0.11?m/s; control group: 0.73 ±0.15 to 0.61 ±0.15?m/s), cadence (experimental group: 97.4 ±14.1 to 116.8 ±8.7?steps/minute; control group: 92.6 ±10.4 to 99.7 ±9.7?steps/minute), gross motor function (dimension D experimental group: 59.7 ±12.8 to 74.9 ±13.8; control group: 58.9 ±10.4 to 69.4 ±9.3; dimension E experimental group: 59.0 ±10.9 to 79.1 ±8.5; control group: 60.3 ±10.1 to 67.4 ±11.4) and independent mobility (experimental group: 34.3 ±5.9 to 43.8 ±7.53; control group: 34.4 ±8.3 to 37.7 ±7.7). Moreover, transcranial direct current stimulation led to a significant increase in motor evoked potential (experimental group: 1.4 ±0.7 to 2.6 ±0.4; control group: 1.3 ±0.6 to 1.6 ±0.4). CONCLUSION: These preliminary findings support the hypothesis that anodal transcranial direct current stimulation combined with virtual reality training could be a useful tool for improving gait in children with cerebral palsy.

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Dexmedetomidine suppressed involuntary movement in a patient with cerebral palsy.
Dayton D1, Kowalczyk AK.

Involuntary movements in patients with cerebral palsy can interfere with invasive procedures performed under sedation. We present a case of a 58-year-old man with cerebral palsy, who successfully underwent a cardiac catheterization while sedated with IV dexmedetomidine. The patient's involuntary movements were suppressed, which allowed the cardiologist to perform the procedure on an immobile, cooperative patient, all while maintaining patient comfort, stable hemodynamics, as well as adequate oxygenation and ventilation. This novel use of dexmedetomidine might facilitate monitored anesthesia care in patients otherwise requiring general anesthesia.

PMID: 25611139 [PubMed - in process]

**Treatment of spasticity in children with cerebral palsy with botulinum toxin A.**[Article in Danish]

Madsen ES1, Sonne-Holm S, Wong C, Curtis D, Bencke J.

Over the latest 30 years there has been an increasing use of botulinum toxin A injections in the lower limbs in children with cerebral palsy. However, the conclusions regarding effect of treatment in both randomized controlled and non-controlled trials have been inconclusive. One explanation may be that children with cerebral palsy do not always exhibit pure spasticity and/or dystonia of the affected muscles. Furthermore, the dose, injection volume and injection technique may vary from study to study. The evidence for the effect is so small that careful consideration on whether to continue this treatment regimen or not is needed.

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**Laparoscopic watson fundoplication is effective and durable in children with gastrooesophageal reflux.**

Dunckley MG1, Rajwani KM1, Mahomed AA1.

Gastroesophageal reflux (GOR) affects 2-8% of children over 3 years of age and is associated with significant morbidity. The disorder is particularly critical in neurologically impaired children, who have a high risk of aspiration. Traditionally, the surgical antireflux procedure of choice has been Nissen's operation. However, this technique has a significant incidence of mechanical complications and has a reoperation rate of approximately 7%, leading to the development of alternative approaches. Watson's technique of partial anterior fundoplication has been shown to achieve long-lasting reflux control in adults with few mechanical complications, but there is limited data in the paediatric population. We present here short- and long-term outcomes of laparoscopic Watson fundoplication in a series of 76 children and infants, 34% of whom had a degree of neurological impairment including severe cerebral palsy and hypoxic brain injury. The overall complication rate was 27.6%, of which only 1 was classified as major. To date, we have not recorded any incidences of perforation and no revisions. In our experience, Watson's laparoscopic partial fundoplication can be performed with minimal complications and with durable results, not least in neurologically compromised children, making it a viable alternative to the Nissen procedure in paediatric surgery.

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**Stability of Executive Functioning Measures in 8-17-Year-Old Children With Unilateral Cerebral Palsy.**

Piovesana AM1, Ross S, Whittingham K, Ware RS, Boyd RN.

The study investigated the stability of executive functioning (EF) measures in children and adolescents aged 8-17 years with unilateral cerebral palsy (CP). Here 44 participants with unilateral CP (mean age = 11 years, 11 months; Manual Abilities Classification Scale Level I = 6 and Level II = 37; Gross Motor Function Classification Scale Level I = 22 and Level II = 22) were randomized into the wait-list control group of a large randomized controlled trial. Participants had baseline testing with Wechsler Intelligence Scale for Children - Fourth Edition Short Form (WISC-IV-SF) and Delis-Kaplan Executive Function System (D-KEFS) subtests. Parents completed the Behavior Rating Inventory of Executive Functioning (BRIEF). Participants were re-assessed 20 ±2 weeks later with a shortened test battery including the D-KEFS subtests; Digit Span, Coding and Symbol Search (WISC-IV); and BRIEF. Pearson's test-retest reliabilities and Reliable change scores were calculated. Results indicated excellent to fair test-retest reliabilities ($r = 0.91\text{-}0.74$) for all measures except Digit Span Backwards ($r = 0.62$), Inhibition ($r = 0.69$), and Initiate ($r = 0.68$). Reliable change scores applying 90% confidence intervals for estimating reliable change while accounting for practice effects were provided for all measures. The data support the stability of EF measures in this population.

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11. CNS Neurol Disord Drug Targets. 2015 Jan 16. [Epub ahead of print]

Quality of Life of Children with Cerebral Palsy: A cross-sectional KIDSCREEN study in the Southern part of the Netherlands.

Vles GF1, Hendriksen RG, Hendriksen JG, van Raak EP, Soudant D, Vles JS, Gavilanes AW.

Objective: To compare the quality of life (QoL) of 8-18 year old children with cerebral palsy (CP) in the Southern part of the Netherlands to a sample of European children from the general population and to investigate factors associated with possible differences. Design: A cross-sectional KIDSCREEN-52 (by-proxy version) study. Subjects / patients: The parents of 80 out of 81 children (mean age 13.4 years, SD 2.98; 49 boys, 31 girls; Gross Motor Function Classification System (GMFCS) level 1: 21, 2: 5. 3: 16, 4: 18, 5: 20) agreed to participate. Methods: Two-sample T-tests were used to compare domain scores between groups. Regression analysis was used to identify factors associated with deviant QoL scores. Results: Parents reported significantly higher QoL for the domains of parent relation & home life and school environment. On the other hand significantly lower QoL was reported for the domains of psychical well-being, social support & peers, and social acceptance. Factors associated with deviant QoL scores were lower cognitive levels, less communication skills, and higher GMFCS levels. Conclusion: This study exposed several problem domains of QoL in children with CP living in the Southern part of the Netherlands. Several possible explanations for these findings are given. This information can be used to inform caregivers and service-providers.

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Unestablished indications for hyperbaric oxygen therapy.

Mitchell S1, Bennett M2.

Unestablished indications are conditions in which systematic clinical use of hyperbaric oxygen treatment (HBOT) is not supported by adequate proof of benefit. HBOT is vulnerable to use in many such conditions for various reasons, perhaps the most important being that a placebo or participation effect may create an impression of efficacy. The systematic use of HBOT in unestablished indications raises ethical concerns about provision of misleading information, giving false hope, and taking payment for therapy of doubtful benefit. Any practice perceived as unethical or unscientific has the potential to draw the wider field into disrepute. Of substantial contemporary relevance is the use of HBOT in treatment of various forms of chronic brain injury; in particular, cerebral palsy in children and the sequelae of mild traumatic brain injury in adults. There are now multiple, randomised, blinded, sham-controlled trials of HBOT in both indications. None of these studies showed benefit of HBOT when compared to sham control, though the sham and HBOT groups often both improved, indicating that a placebo or participation effect influenced outcomes. These results almost certainly explain those of open-label trials (lacking sham controls) in which HBOT frequently seems beneficial. Advocates for HBOT in chronic brain injury claim that the sham treatments (usually 1.3 ATA pressure exposure whilst air breathing) in the blinded trials are actually active treatments; however, the same dose of oxygen can be achieved at 1 ATA breathing 27% oxygen. To counter this argument, advocates also claim that the extra 0.3 ATA of pressure is somehow independently beneficial, but this notion has limited biological plausibility and there is little supporting evidence. Chronic brain injuries remain unestablished indications at this time and, in our opinion, should not be systematically treated with HBOT.

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Prevention and Cure


Stoknes M1, Lien E2, Andersen GL3, Bao Y4, Blackman JA5, Lie RT6, Vik T2.

OBJECTIVE: To use case-parent triad data to investigate if cerebral palsy (CP) is associated with variants of the APOE gene, the rs59007384 SNP of the TOMM40 gene or combined haplotypes of the two genes. STUDY DESIGN: DNA was analyzed in buccal swabs from 235 children with CP, their parents and a sibling. The relative risks (RR) with 95% confidence intervals (CI) that the children would have a distribution of APOE genotypes, rs59007384 variants or combined haplotypes deviating from Mendelian inheritance were estimated. RESULTS: Children with CP were more likely than expected to carry the APOEe3 allele (RR 7.5; CI: 0.99-53.7 for heterozygotes and 10.3; CI: 1.4-79.6 for homozygotes), and to have the haplotype of APOEe3 and rs59007384 G (RR 2.4; CI: 1-5.7 for heterozygotes, RR 3.7; CI: 1.4-9.5 for homozygotes) whereas the distribution was as expected for rs59007384 alone. In the subgroup analyses the findings were confined to children born preterm. Among siblings the distribution of these genes was as expected according to Mendelian inheritance.

CONCLUSION: We speculate that children with APOEe2/APOEe4 alleles are more likely to die following cerebral injury in utero, resulting in a higher than expected proportion of children with CP carrying the APOEe3 allele.

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Cerebral palsy: Phenotypes and risk factors in term singletons born small for gestational age.

Freire G1, Shevell M2, Oskoui M3.

BACKGROUND AND OBJECTIVES: Children born small for gestational age (SGA) are at increased risk of developing cerebral palsy (CP). The pathophysiology behind this association remains unclear. We compare the clinical profile of children with CP born SGA to other children with CP. We hypothesize that differences noted will support antenatal causes of CP in children born SGA. METHODS: We conducted a retrospective cohort study of term singletons with CP, extracting data from the Canadian Cerebral Palsy Registry. SGA was determined as birth weight for gestational age and sex below the tenth percentile. RESULTS: Mothers of children with CP born SGA were more likely to be of African-American ethnicity (RR 2.54, 95% CI 1.20-5.39), have intrauterine infections (RR 2.22, 95% CI 1.09-4.50) and have gestational hypertension (RR 1.78, 95% CI 1.06-3.00). Children with CP born SGA had smaller head circumferences at birth (p < 0.001) and higher frequencies of emergency cesarean-section (RR 1.53, 95% CI 1.22-1.92), birth asphyxia (RR 1.53, 95% CI 1.0-2.32), and placental abnormalities (RR 1.45, 95% CI 1.00-2.10). Children with CP born SGA had greater fine motor (RR 1.46, 95% CI 1.02-2.11), gross motor (RR 1.53, 95% CI 1.12-2.10) and communication impairment (RR 1.24, 95% CI 1.10-1.40), and a higher frequency of cognitive impairment (RR 1.33, 95% CI 1.06-1.69). CONCLUSION: Children with CP born SGA have different clinical factors and phenotypic profiles than other children with CP. These differences support the hypothesis of antenatal and perinatal causes of CP in children born SGA. Future case control studies would be desired to further define this causal pathway.

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A dual role for AMP-activated kinase (AMPK) during neonatal hypoxic-ischaemic brain injury in mice.

Rousset CI1, Leiper FC, Kichev A, Gressens P, Carling D, Hagberg H, Thornton C.

Perinatal hypoxic-ischaemic encephalopathy (HIE) occurs in 1-2 in every 1000 term infants and the devastating consequences range from cerebral palsy, epilepsy and neurological deficit to death. Cellular damage post-insult occurs after a delay and is mediated by a secondary neural energy failure. AMP-activated protein kinase (AMPK) is a sensor of cellular stress resulting from ATP depletion and/or calcium dysregulation, hallmarks of the neuronal cell death observed after HIE. AMPK activation has been implicated in models of adult ischaemic injury but, as yet, there have been no studies defining its role in neonatal asphyxia. Here we find that in an in vivo model of neonatal hypoxia-ischaemic and in oxygen/glucose deprivation in neurons there is pathological activation of the calcium/calmodulin-dependent protein kinase kinase (CaMKK)β-AMPKα1 signalling pathway. Pharmacological inhibition of AMPK during the insult promotes neuronal survival but, conversely, inhibiting AMPK activity prior to the insult sensitises neurons, exacerbating cell death. Our data have pathological relevance for neonatal HIE as prior sensitisation such as exposure to bacterial infection (reported to reduce AMPK activity) produces a significant increase in injury. This article is protected by copyright. All rights reserved.

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Brain structural connectivity increases concurrent with functional improvement: Evidence from diffusion tensor MRI in children with cerebral palsy during therapy.

Englander ZA1, Sun J2, Laura Case3, Mikati MA4, Kurtzberg J2, Song AW5.

Cerebral Palsy (CP) refers to a heterogeneous group of permanent but non-progressive movement disorders caused by injury to the developing fetal or infant brain (Bax et al., 2005). Because of its serious long-term consequences, effective interventions that can help improve motor function, independence, and quality of life are critically needed. Our ongoing longitudinal clinical trial to treat children with CP is specifically designed to meet this challenge. To maximize the potential for functional improvement, all children in this trial received autologous cord blood transfusions (with order randomized with a placebo administration over 2 years) in conjunction with more standard physical and occupational therapies. As a part of this trial, magnetic resonance imaging (MRI) is used to improve our understanding of how these interventions affect brain development, and to develop biomarkers of treatment efficacy. In this report, diffusion tensor imaging (DTI) and subsequent brain connectome analyses were performed in a subset of children enrolled in the clinical trial (n = 17), who all exhibited positive but varying degrees of functional improvement over the first 2-year period of the study. Strong correlations between increases in white matter (WM) connectivity and functional improvement were demonstrated; however no significant relationships between either of these factors with the age of the child at time of enrollment were identified. Thus, our data indicate that increases in brain connectivity reflect improved functional abilities in children with CP. In future work, this potential biomarker can be used to help differentiate the underlying mechanisms of functional improvement, as well as to identify treatments that can best facilitate functional improvement upon un-blinding of the timing of autologous cord blood transfusions at the completion of this study.


Corticopontocerebellar Connectivity Disruption in Congenital Hemiplegia.

Fiori S1, Pannek K2, Pasquariello R3, Ware RS4, Cioni G5, Rose SE6, Boyd RN7, Guzzetta A5.

Background. Crossed cerebellar diaschisis is the disruption of functional connectivity between cerebrum and cerebellum after hemispheric unilateral brain lesions. In adults and to a lesser extent in children, crossed cerebellar
Diaschisis has been largely investigated by functional connectivity and demonstrated to influence paretic hand function. Objective. We aim to demonstrate a disruption in structural corticopontocerebellar (CPC) connectivity in children with congenital brain lesions and examine its correlation with paretic hand motor function. Methods. Thirty-six children (Manual Ability Classification System: I, n = 21; II, n = 15) with unilateral brain lesions and 18 controls were analyzed in a case-control study, and diffusion magnetic resonance imaging data were acquired at 3T. High angular resolution diffusion imaging probabilistic tractography was employed for the region of interest-based reconstruction of CPC tracts. To identify statistical differences in structural cerebrocerebellar connectivity between case and control groups, an asymmetry index based on the number of streamlines of CPC tracts was used. In the case group, the correlation between asymmetry index and hand function measures was also determined. Results. Projections through the middle cerebellar peduncle to the contralateral cerebral cortex showed greater asymmetry in children with congenital unilateral brain lesion compared to controls (P = .03), thus indicating a disruption of structural cerebrocerebellar connectivity. The degree of asymmetry index showed a correlation (P < .03; r = -0.31) with impaired hand abilities in bimanual tasks. Conclusions. Disruption of structural cerebrocerebellar connectivity is present in patients with congenital unilateral brain injury and might be related to impaired hand function in bimanual skills, with potential implication in tailoring early intervention strategies.

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Multifactoral causes of cerebral palsy [Article in French]

Péluchon R.

Comment on: Familial risk of cerebral palsy: population based cohort study. [BMJ. 2014]

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