Cerebral Palsy ALLIANCE

NEWS
Cerebral Palsy Research

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## Interventions and Management

**1. Handb Clin Neurol. 2013;111:183-95. doi: 10.1016/B978-0-444-52891-9.00018-X.**

**Cerebral palsy: definition, assessment and rehabilitation.**

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Over the last 25 years the definition and classification of cerebral palsy (CP) have evolved, as well as the approach to rehabilitation. CP is a disorder of the development of movement and posture, causing activity limitations attributed to nonprogressive disturbances of the fetal or infant brain that may also affect sensation, perception, cognition, communication, and behavior. Motor control during reaching, grasping, and walking are disturbed by spasticity, dyskinesia, hyperreflexia, excessive coactivation of antagonist muscles, retained developmental reactions, and secondary musculoskeletal malformations, together with paresis and defective programing. Weakness and hypoextensibility of the muscles are due not only to inadequate recruitment of motor units, but also to changes in mechanical stresses and hormonal factors. Two methods, the General Movements Assessment and the Test of Infant Motor Performance, now permit the early detection of CP, while the development of valid and reliable outcome measures, particularly the Gross Motor Function Measure (GMFM), have made it possible to evaluate change over time and the effects of clinical interventions. The GMFM has further led to the development of predictive curves of motor function while the Gross Motor Classification System and the Manual Ability Classification System provide standardized means to classify the severity of the movement disability. With the emergence of the task-oriented approach, the focus of therapy in rehabilitation has shifted from eliminating deficits to enhancing function across all performance domains by emphasizing fitness, function, participation, and quality of life. There is growing evidence supporting selected interventions and interest for the therapy and social integration of adults with CP.



PMID: 23622163 [PubMed - in process]

**2. Handb Clin Neurol. 2013;112:1079-83. doi: 10.1016/B978-0-444-52910-7.00025-8.**

**Outcome and rehabilitation after childhood stroke.**

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In contrast to popular belief, the vascular stroke syndromes of childhood (arterial ischemic stroke, cerebral sinovenous thrombosis, and nontraumatic intracranial hemorrhage) result in appreciable mortality and significant morbidity in survivors. The specific nature and range of impairments is affected by the etiology and distribution of the lesion as well as the age of the child. However, no domain of function is universally spared. Impairments, in particular affecting cognitive function, may only emerge over time and therefore long-term vigilance is important. Current rehabilitation approaches in these children are rarely evidence based and are usually based on approaches used in management of congenital disorders such as cerebral palsy. The rehabilitation approach should be targeted to the observed pattern of impairment rather than the diagnosis - for example dystonia, rather than spasticity, is a far more common consequence of arterial ischemic stroke in children, whereas most conventional stroke rehabilitation approaches target spasticity. Age is likely to be an important factor in both determining the potential for natural recovery as well as the response to rehabilitation. New rehabilitation approaches such as constraint induced movement therapy and transcranial magnetic stimulation hold promise.



PMID: 23622313 [PubMed - in process]

**3. Handb Clin Neurol. 2013;111:197-202. doi: 10.1016/B978-0-444-52891-9.00019-1.**

**Treatment of movement disorders in dystonia-choreoathtosis cerebral palsy.**

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Symptomatic treatment of cerebral palsy (CP) is difficult, with variable beneficial effect. The choice of therapy is guided by the main clinical features (spasticity, dystonia/choreoathetosis), by the experience of experts, and by the results of open-label trials and a few controlled studies. Treatments of spasticity are not discussed in depth here. From open-label trials and a few controlled studies in dystonia/choreoathetosis CP, it appears that treatment should be started at a low dose and increased slowly, and that more beneficial effects are obtained on upper extremity function, face and jaw dystonia and drooling, and in children. L-Baclofen or antiepileptic drugs are rarely effective and poorly tolerated whereas benzodiazepines may be moderately helpful. Local injections of botulinum toxin help to reduce pain and limit the amplitude of some movements (violent neck movements with high risk of symptomatic radiculomyelopathy). In a rare subtype of dystonia-choreathetosis CP with little spasticity and MRI lesions, bilateral pallidal stimulation (GPi) has shown mild to moderate improvement of dystonia (in open-label small series and in one controlled study) with no cognitive or mood adverse effects. Optimal placement of the leads was a major (but not exclusive) factor for good outcome but results cannot be predicted on an individual basis and larger studies are needed.



PMID: 23622164 [PubMed - in process]

**4. Arch Orthop Trauma Surg. 2013 Apr 30. [Epub ahead of print]**

**The use of a dual-mobility concept in total hip arthroplasty patients with spastic disorders : No dislocations in a series of ten cases at midterm follow-up.**

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INTRODUCTION: Total hip arthroplasty (THA) is one of the treatment options in patients with cerebral palsy (CP) with painful osteoarthritis of the hip. However, the risk of dislocation of the prosthesis is higher in patients with CP when compared with physically normal patients. In this retrospective study of ten consecutive cases, we hypothesized that the use of a dual-mobility cup could reduce this risk of dislocation combined with good functional results. MATERIALS AND METHODS: From January 2008 until October 2010, eight patients (ten hips) with CP who consecutively received a THA using a dual-mobility cup were identified. At the time of surgery, the average age of the patient group was 54 years (range 43-61). Latest follow-up took place after on average 39 months (range 22-56 months). All patients or their caregivers were interviewed by telephone. They were asked if dislocation of the prosthesis had occurred. To evaluate quality of life and health in general, patients completed the SF-36 questionnaire. RESULTS: None of the prostheses had dislocated at the latest follow-up. Reoperation was needed in one patient after a periprosthetic fracture. Radiologic evaluation showed a mean cup inclination of 46 (range 27-58). On average, the quality of life of patients in this study was found to be limited in particular on the domains of physical health and functioning, while a fair to good score was measured at the six other different domains. CONCLUSION: The use of a dual-mobility cup in THA in patients with CP can lead to favourable results with respect to dislocation and clinical outcome.

PMID: 23632783 [PubMed - as supplied by publisher]

**5. Am J Phys Med Rehabil. 2013 Apr 29. [Epub ahead of print]**

**Use of Rimabotulinum Toxin for Focal Hypertonicity Management in Children with Cerebral Palsy with Nonresponse to Onabotulinum Toxin.**

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OBJECTIVE: The aim of this study was to review the effect of rimabotulinum toxin (BoNT-B) for focal hypertonicity management in children with cerebral palsy and secondary nonresponse to onabotulinum toxin treated at the authors' tertiary care academic medical center. DESIGN: A retrospective review of the medical treatment of children was conducted at the authors' institution (March 16, 2001, to August 2, 2002) using the key words botulinum toxin B and Myobloc (Solstice Neurosciences Inc, South San Francisco, CA). Demographic information was analyzed using descriptive statistics (number [percentage] and mean [range]). The Pearson $\chi$ test was used to evaluate differences in incidence of adverse events. RESULTS: Eighty-two children had BoNT-B injections (116 treatments). Overall, 26.8% (19/71) of the children or their parents/guardians reported no or minimal response to the injections, with 89.5% (17/19) of these children having secondary nonresponse to onabotulinum toxin. Adverse events were frequent but did not require hospitalization of any patient. No significant differences were found in incidence of adverse events related to BoNT-B dosing, medical fragility, or Gross Motor Function Classification System level. CONCLUSIONS: More than one-fourth of the children receiving BoNT-B injections had nonresponse, with most having previous nonresponse to onabotulinum toxin. Adverse events related to BoNT-B injections were frequent and unpredictable but not severe.

PMID: 23636084 [PubMed - as supplied by publisher]

**6. Orthopade. 2013 May 2. [Epub ahead of print]**

**Spastic foot deformities in children : Surgical management [Article in German]**

Salzmann M, Berger N, Rechl H, Döderlein L.

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Although the neurological defects associated with cerebral palsy are not progressive, secondary musculoskeletal disorders due to growth and gravity are variable. In the clinical analysis of spastic foot deformities different mechanisms that produce a variety of deformities have to be analyzed. The goals of surgical treatment are correction of the deformity, reestablishment of stability of the foot and preservation of functionally important ranges of motion and muscle strength. The most common spastic foot deformities are equinus, planovalgus, equinovarus and calcaneus. For treatment soft tissue surgery, such as muscle lengthening and transfer together with bone surgery, such as osteotomy or arthrodesis are used and combinations of these methods are often required. Subsequently postoperative plasters are necessary followed by dynamic orthotic management.

PMID: 23636790 [PubMed - as supplied by publisher]

**7. Foot (Edinb). 2013 Apr 29. pii: S0958-2592(13)00019-9. doi: 10.1016/j.foot.2013.03.002. [Epub ahead of print]**

**Hawkins Group I fracture of neck of talus and Salter Harris Type III tibial epiphyseal injury of medial malleolus.**

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We are reporting an unusual combination of Hawkins Group I fracture of the neck of left talus in association with Salter Harris Type III distal tibial epiphyseal injury of medial malleolus in a child with cerebral palsy and hemiplegia of contralateral limbs and discussed the possible mechanism as well as management. Fractures of medial malleolus usually occur in Hawkins Group III fracture-dislocations in adults. Forced dorsiflexion of talus against the anterior edge of tibia appears to be the accepted common mechanism, despite limited experimental and clinical evidence incriminating axial compression. Fracture of medial malleolus implicates supination. We managed this unusual pattern of injury conservatively. At 15 months, the child was asymptomatic with no radiological evidence of avascular necrosis of body of talus or growth disturbance of distal tibial epiphysis.



PMID: 23639364 [PubMed - as supplied by publisher]

**8. Assist Technol. 2013 Spring;25(1):39-48; quiz 49-50.**

**The positive effects of early powered mobility on children's psychosocial and play skills.**

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Powered mobility can have an important cognitive and psychosocial impact on young children who are unable to move independently. Twenty-three children with physical disabilities between the ages of 18 months and 6 years participated in this study. Data evaluating social skills, frequency of mobility play activities, frequency of interaction with toys/objects, and play/verbal developmental levels were collected at wheelchair evaluation, wheelchair delivery, and approximately 6 months later. Significant increases were found in parental perceptions of positive social skills for younger children after receiving a wheelchair; slightly older children showed improvements in social

skills before the wheelchair was received; no changes were found in negative social skills. Parental ratings also indicated a significantly greater difficulty remaining engaged in tasks after receiving a wheelchair. A significant increase was noted in the number of mobility activities during indoor free play but no difference was seen in interaction with toys or objects. Improvement in the qualitative level of outdoor interactive free play was reported but there was no change in verbal interactions. This article discusses the potential positive impact of early powered mobility. These findings may be helpful in justifying the recommendation of powered mobility to young children and in justifying medical necessity of powered mobility for reimbursement by third party payers.

PMID: 23527430 [PubMed - indexed for MEDLINE]

**9. Dev Neurorehabil. 2013 Apr 29. [Epub ahead of print]**

**Speech and language development in 2-year-old children with cerebral palsy.**

Hustad KC, Allison K, McFadd E, Riehle K.

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Objective: We examined early speech and language development in children who had cerebral palsy. Questions addressed whether children could be classified into early profile groups on the basis of speech and language skills and whether there were differences on selected speech and language measures among groups. Methods: Speech and language assessments were completed on 27 children with CP who were between the ages of 24 and 30 months (mean age 27.1 months; SD 1.8). We examined several measures of expressive and receptive language, along with speech intelligibility. Results: Two-step cluster analysis was used to identify homogeneous groups of children based on their performance on the seven dependent variables characterizing speech and language performance. Three groups of children identified were those not yet talking (44% of the sample); those whose talking abilities appeared to be emerging (41% of the sample); and those who were established talkers (15% of the sample). Group differences were evident on all variables except receptive language skills. Conclusion: 85% of 2-year-old children with CP in this study had clinical speech and/or language delays relative to age expectations. Findings suggest that children with CP should receive speech and language assessment and treatment at or before 2 years of age.

PMID: 23627373 [PubMed - as supplied by publisher]

**10. Disabil Rehabil. 2013 Apr 29. [Epub ahead of print]**

**Predictors of needs for families of children with cerebral palsy.**

Almasri NA, O'Neil M, Palisano RJ.

Physical Therapy Department, Rehabilitation Sciences Faculty, The University of Jordan, Amman, Jordan and.

Background: This study examined child, family and service characteristics that are predictors of family needs for community, financial, family support and services needs for families of children with cerebral palsy (CP). CP is a non-progressive neurological condition caused by lesions in the central nervous system resulting in limitations in motor function and associated co-morbid conditions. Children with CP often require multiple health, rehabilitation, and community services. Purpose: To identify risk and protective factors among predictors of needed resources and services (i.e. community, financial, family support) and to discuss implications for coordination of medical, rehabilitation, and community services for children with CP and their families. Methods: Secondary data analysis was conducted with a national dataset (n=441) of mothers of children with CP. The average age of children was 10.7 years (SD=4.5) and was distributed across the various Gross Motor Function Classification System levels. Four logistic regression models were conducted to examine predictive power of child, family and current service characteristics on needed resources and services. Results: Limited child gross motor function was a risk factor (odds ratio (OR): 1.30-1.70) while perception of family-centered services (FCS) was a protective factor (OR: 0.57-0.63) in having the needs met. Conclusion: Mothers of children with CP who are able to walk, reported strong family relationships, and perceived need-oriented and FCS expressed less needs for community, financial, family support and services' resources needs. Implications for service providers are provided. Implications for Rehabilitation Over 90% of participant mothers of children and youth with CP expressed needs for medical, rehabilitation, school-based

and community-based services for their children. Mothers of children and youth with CP who have severe limitation in functional mobility or might use wheeled mobility were at higher risk for expressing family needs related to locating community resources, paying for medical expenses and finding resources that support their family functioning. Mothers of children and youth with CP who perceived family-centered, respectful and supportive, and accessible services for their children were at lower risk of expressing needs for community, financial and family support resources.

PMID: 23627535 [PubMed - as supplied by publisher]

**11. Int J Qual Stud Health Well-being. 2013 Apr 30;8:1-13. doi: 10.3402/qhw.v8i0.20539.**

**Becoming a parent to a child with birth asphyxia-From a traumatic delivery to living with the experience at home.**

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The aim of this study is to describe the experiences of becoming a parent to a child with birth asphyxia treated with hypothermia in the neonatal intensive care unit (NICU). In line with the medical advances, the survival of critically ill infants with increased risk of morbidity is increasing. Children who survive birth asphyxia are at a higher risk of functional impairments, cerebral palsy (CP), or impaired vision and hearing. Since 2006, hypothermia treatment following birth asphyxia is used in many of the Swedish neonatal units to reduce the risk of brain injury. To date, research on the experience of parenthood of the child with birth asphyxia is sparse. To improve today's neonatal care delivery, health-care providers need to better understand the experiences of becoming a parent to a child with birth asphyxia. A total of 26 parents of 16 children with birth asphyxia treated with hypothermia in a Swedish NICU were interviewed. The transcribed interview texts were analysed according to a qualitative latent content analysis. We found that the experience of becoming a parent to a child with birth asphyxia treated with hypothermia at the NICU was a strenuous journey of overriding an emotional rollercoaster, that is, from being thrown into a chaotic situation which started with a traumatic delivery to later processing the difficult situation of believing the child might not survive or was to be seriously affected by the asphyxia. The prolonged parent-infant separation due to the hypothermia treatment and parents' fear of touching the infant because of the high-tech equipment seemed to hamper the parent-infant bonding. The adaption of the everyday life at home seemed to be facilitated by the follow-up information of the doctor after discharge. The results of this study underline the importance of family-centered support during and also after the NICU discharge.

PMID: 23639330 [PubMed - in process] Free full text

**12. Handb Clin Neurol. 2013;111:203-7. doi: 10.1016/B978-0-444-52891-9.00020-8.**

**Everyday life and social consequences of cerebral palsy.**

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The disclosure of diagnosis for a child with cerebral palsy (CP) is a highly stressful experience to the parents. The experience can be alleviated by clarity, empathy, and an emphasis on the child's resources and abilities. Despite chronic stress many families function well and manage to strengthen the child and family's resources through spousal and family support, maintenance of hope for further development, and active care taking. The caregiver burden can be divided into an objective burden (socio-structural constraints) and a subjective burden (emotional distress). The subjective burden of care seems less important, as illustrated by the quote: "We are tired, not sad." Quality of life is similar in 8- to 12-year-old European children with CP and controls, whereas participation in daily life was lower for children with CP. Participation varies significantly among countries implying that some countries can improve in this area. In a study from Denmark only 29% of adults with CP were employed (versus 88% of controls), 25% were cohabitating, and 20% had children. These long-term achievements could be predicted from development quotient, CP type, and motor impairment at age 5. The goal of habilitation is integration into society, which is not achieved for the majority.

PMID: 23622165 [PubMed - in process]

**13. Int J Ophthalmol. 2013 Apr 18;6(2):204-10. doi: 10.3980/j.issn.2222-3959.2013.02.19. Print 2013.**

**Ocular disorders in children with spastic subtype of cerebral palsy.**

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AIM: To document common ocular abnormalities in children with spastic subtype of cerebral palsy (CP) and to find out whether any correlation exists between their occurance and etiologic factors. METHODS: Totally 194 patients with the diagnosis of spastic type CP were enrolled in this retrospective study. Detailed ophthalmic examinations were performed. Demographic data and neuroradiological findings were documented. Kruskal-Wallis, Mann Whitney U, Pearson Chi-square tests and Student's t tests were used in the statistical analysis. RESULTS: The mean age was 64.7±44.2 months on the first ophthalmic examination. Prevalences of diplegia (47.4%) and tetraplegia (36.1%) were found to be higher than the frequency of hemiplegia (16.5%) in our study population. Etiologic factor was asphyxia in 60.8% of the patients. Abnormal ocular findings were present in 78.9% of the patients. Statistically significant poor vision was detected in tetraplegia group among all the spastic ubtypes of CP (P=0.000). Anisometropia and significant refractive error were found in 14.4% and 70.1% of the patients, respectively. Thirty-six children (18.6%) had nystagmus and 107 children (55.2%) had strabismus. Lower gestational age and birth weight were statistically higher in patients with esotropia than exotropia (P=0.009 and P=0.024, respectively). Abnormal morphology of the optic disc was present in 152 eyes (39.2%). Severe periventricular leukomalacia (PVL) was found in 48 patients and statistically significant poor vision was detected in the presence of PVL (P=0.000). CONCLUSION: Spastic diplegic or tetraplegic CP patients with positive neuroradiological symptoms, younger gestational age and lower birth weight ought to have detailed ophthalmic examinations as early as possible to provide best visual rehabilitation.

PMID: 23638425 [PubMed] free PMC Article

**14. Int J Pediatr Otorhinolaryngol. 2013 Apr 29. pii: S0165-5876(13)00152-3. doi: 10.1016/j.ijporl.2013.03.034. [Epub ahead of print]**

**Performance after timely cochlear implantation in prelingually deaf children with cerebral palsy.**

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OBJECTIVES: To investigate auditory perception, speech production, and language ability of prelingually deaf toddlers with cerebral palsy (CP) who were implanted within a sensitive period and who received proper speech therapy. Comparison of their outcomes with age- and sex-matched CI recipients without additional disabilities was also performed. METHODS: We retrospectively reviewed a cohort of pediatric CI in Samsung Medical Center. Eight CP subjects who received CI before 3 years of age and age-sex matched control recipients who had no additional disabilities except idiopathic sensorineural hearing loss (SNHL) were included for the analysis. Preoperative evaluation included the Categories of Auditory Performance (CAP) score, Korean Version of the Ling's Stage (K-Ling), Sequenced Language Scale for Infants (SELSI), Bailey Scales of Infant Development II assessment, Social Maturity Scale test, and grading of CP severity using severity level and Gross Motor Function Classification System for CP (GMFCS). To measure the outcome, the CAP scores, K-Ling, and SELSI were performed at 3, 6, 12, and 24 months after implantation. RESULTS: Four CP children with outstanding performances showed comparable achievement with matched control recipients. These patients had less severe motor disabilities (mild-moderate severity, GMFCS level 1-3), better social quotient, and better cognitive abilities. Although the others showed poor language abilities and hardly produced meaningful speech, their CAP scores reached 1 or 2 in 24 months after

implantation. CONCLUSIONS: Deaf children with CP could have various ranges of benefits up to the levels of normal peers whose only disability was hearing loss, when CI was performed within a critical period. Especially, children with mild or moderate CP had a favorable outcome after CI, equivalent to that of normal peers.



PMID: 23639338 [PubMed - as supplied by publisher]

**15. R I Med J (2013). 2013 Apr 1;96(4):38-40.**

**Neurogenic detrusor overactivity: an update on management options.**

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Neurogenic detrusor overactivity (NDO) affects a variety of patients with storage and voiding dysfunction including those with multiple sclerosis, spinal cord injuries, Parkinson's disease, cerebral palsy, and myelomeningocele, and includes symptoms of urinary frequency, urgency, and incontinence. Primary treatment goals are 1) preventing renal injury, and 2) improving quality of life. First-line therapies include behavioral and anticholinergic agents, with onabotulinum toxin-A as the only FDA- approved second-line therapy, and non-FDA approved second-line therapies including neuromodulation, and intravesical vanilloids. Surgical intervention is reserved for those at risk for upper-tract deterioration and with persistent incontinence. In select individuals an indwelling catheter may be necessary.

PMID: 23641451 [PubMed - in process]

**16. Arch Dis Child Educ Pract Ed. 2013 Apr 26. [Epub ahead of print]**

**Hyperbaric oxygen did not improve symptoms in children with cerebral palsy.**

Pérez-Gaxiola G.

PMID: 23625161 [PubMed - as supplied by publisher]

# Prevention and Cure

**17. Handb Clin Neurol. 2013;111:169-76. doi: 10.1016/B978-0-444-52891-9.00016-6.**

**Pathophysiology of cerebral palsy.**

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Cerebral palsy (CP), defined as a group of nonprogressive disorders of movement and posture, is the most common cause of severe neurodisability in children. Understanding its physiopathology is crucial to developing some protective strategies. Interruption of oxygen supply to the fetus or brain asphyxia was classically considered to be the main causal factor explaining later CP. However several ante-, peri-, and postnatal factors could be involved in the origins of CP syndromes. Congenital malformations are rarely identified. CP is most often the result of environmental factors, which might interact with genetic vulnerabilities, and could be severe enough to cause the destructive injuries visible with standard imaging (i.e., ultrasonographic study or MRI), predominantly in the white matter in preterm infants and in the gray matter and the brainstem nuclei in full-term newborns. Moreover they act on an immature brain and could alter the remarkable series of developmental events. Biochemical key factors originating in cell death or cell process loss, observed in hypoxic-ischemic as well as inflammatory conditions, are excessive production of proinflammatory cytokines, oxidative stress, maternal growth factor deprivation, extracellular matrix modifications, and excessive release of glutamate, triggering the excitotoxic cascade. Only two strategies have succeeded in decreasing CP in 2-year-old children: hypothermia in full-term newborns with moderate neonatal encephalopathy and administration of magnesium sulfate to mothers in preterm labor.



PMID: 23622161 [PubMed - in process]

**18. Handb Clin Neurol. 2013;111:163-7. doi: 10.1016/B978-0-444-52891-9.00015-4.**

**Epidemiology of cerebral palsy.**

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PMID: 23622160 [PubMed - in process]

**19. Handb Clin Neurol. 2013;111:177-81. doi: 10.1016/B978-0-444-52891-9.00017-8.**

**Imaging cerebral palsy.**

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Neuroimaging in children with (suspected) cerebral palsy is useful for contributing to or corroborating the diagnosis, clarifying the etiology and the "timing" of the underlying brain lesion, establishing a prognosis and, in some cases, as a basis for genetic counseling. Therefore, each child with cerebral palsy should undergo at least one neuroimaging procedure. While cranial ultrasound is often the first and least invasive technique applied in newborns

and infants, and computed tomography is beneficial especially in emergency situations, the "gold standard" technique for imaging children with cerebral palsy is magnetic resonance imaging, ideally performed after the age of 2 years. Underlying brain lesions can be subdivided into brain malformations (including disorders of neuronal proliferation and cellular lineage, disorders of neuroblast migration, and disorders of neocortical organization) and defective lesions. Defective lesions, which typically occur only during the 3rd trimester of pregnancy or peri-/postnatally, are subdivided into lesions affecting primarily the periventricular white matter ("early 3rd trimester lesions") and those affecting primarily structures of cortical/deep gray matter ("late 3rd trimester lesions"). The understanding of the functional consequences of such lesions can be enhanced by diffusion tensor tractography; cortical (re-)organization can be visualized using functional magnetic resonance imaging (fMRI).



PMID: 23622162 [PubMed - in process]

**20. Am J Hum Genet. 2013 Apr 24. pii: S0002-9297(13)00129-8. doi: 10.1016/j.ajhg.2013.03.021. [Epub ahead of print]**

**ZC4H2 Mutations Are Associated with Arthrogryposis Multiplex Congenita and Intellectual Disability through Impairment of Central and Peripheral Synaptic Plasticity.**

Hirata H, Nanda I, van Riesen A, McMichael G, Hu H, Hambrock M, Papon MA, Fischer U, Marouillat S, Ding C, Alirol S, Bienek M, Preisler-Adams S, Grimme A, Seelow D, Webster R, Haan E, Maclennan A, Stenzel W, Yap TY, Gardner A, Nguyen LS, Shaw M, Lebrun N, Haas SA, Kress W, Haaf T, Schellenberger E, Chelly J, Viot G, Shaffer LG, Rosenfeld JA, Kramer N, Falk R, El-Khechen D, Escobar LF, Hennekam R, Wieacker P, Hübner C, Ropers HH, Gecz J, Schuelke M, Laumonnier F, Kalscheuer VM.

Center for Frontier Research, National Institute of Genetics, Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, Mishima 411-8540, Japan.

Arthrogryposis multiplex congenita (AMC) is caused by heterogeneous pathologies leading to multiple antenatal joint contractures through fetal akinesia. Understanding the pathophysiology of this disorder is important for clinical care of the affected individuals and genetic counseling of the families. We thus aimed to establish the genetic basis of an AMC subtype that is associated with multiple dysmorphic features and intellectual disability (ID). We used haplotype analysis, next-generation sequencing, array comparative genomic hybridization, and chromosome breakpoint mapping to identify the pathogenic mutations in families and simplex cases. Suspected disease variants were verified by cosegregation analysis. We identified disease-causing mutations in the zinc-finger gene ZC4H2 in four families affected by X-linked AMC plus ID and one family affected by cerebral palsy. Several heterozygous females were also affected, but to a lesser degree. Furthermore, we found two ZC4H2 deletions and one rearrangement in two female and one male unrelated simplex cases, respectively. In mouse primary hippocampal neurons, transiently produced ZC4H2 localized to the postsynaptic compartment of excitatory synapses, and the altered protein influenced dendritic spine density. In zebrafish, antisense-morpholino-mediated zc4h2 knockdown caused abnormal swimming and impaired a-motoneuron development. All missense mutations identified herein failed to rescue the swimming defect of zebrafish morphants. We conclude that ZC4H2 point mutations, rearrangements, and small deletions cause a clinically variable broad-spectrum neurodevelopmental disorder of the central and peripheral nervous systems in both familial and simplex cases of both sexes. Our results highlight the importance of ZC4H2 for genetic testing of individuals presenting with ID plus muscle weakness and minor or major forms of AMC.



PMID: 23623388 [PubMed - as supplied by publisher]

**21. Early Hum Dev. 2013 Apr 25. pii: S0378-3782(13)00069-8. doi: 10.1016/j.earlhumdev.2013.03.014. [Epub ahead of print]**

**General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm.**

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BACKGROUND: Extremely preterm (EPT) birth is a major risk factor for brain injury and neurodevelopmental impairment. Reliable tools for early prediction of outcome are warranted. AIM: To investigate the predictive value of general movements (GMs) at "fidgety age" for neurological outcome at age 30months in EPT infants, both in comparison and in combination with structural magnetic resonance imaging (MRI) at term equivalent age (TEA). STUDY DESIGN: Fifty-three infants born <27 weeks of gestation were included prospectively. MRI was performed at TEA and images were evaluated for white and grey matter abnormalities. GMs were assessed at age 3 months corrected ("fidgety age"). OUTCOME MEASURES: Neuromotor outcome was assessed at age 30 months corrected. Children were classified as having a normal neurological status, unspecific signs, or cerebral palsy (CP). RESULTS: Abnormal GMs were a common finding, seen in 32% (17/53) of infants. Of these, six infants (11%) had definitely abnormal GMs. Four infants (8%) had a diagnosis of CP at follow up. Definitely abnormal GMs were significantly associated to CP at 30months (Fisher's Exact test p=0.03, sensitivity 50%, specificity 92%). Moderate-severe white matter abnormalities on MRI were more strongly associated with CP (Fisher's Exact test p<0.001, sensitivity 100%, specificity 98%) than GMs. Combining GMs with MRI-findings at TEA increased the predictive specificity to 100% (Fisher's Exact test, p=0.005), whereas sensitivity remained unchanged. CONCLUSIONS: The presence of definitely abnormal GMs was predictive of CP: prediction was significantly enhanced when the GMs assessment was combined with findings from MRI obtained at TEA.



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**22. Evid Based Nurs. 2013 May 1. [Epub ahead of print]**

**In infants born extremely preterm, aspirin or NSAID use during pregnancy are associated with increased risk of quadriparetic cerebral palsy.**

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**21. Handb Clin Neurol. 2013;113:1667-73. doi: 10.1016/B978-0-444-59565-2.00034-4.**

**Disorders of pyruvate metabolism.**

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Pyruvate dehydrogenase and pyruvate carboxylase deficiency are the most common disorders in pyruvate metabolism. Diagnosis is made by enzymatic and DNA analysis after basic biochemical tests in plasma, urine, and CSF. Pyruvate dehydrogenase has three main subunits, an additional E3-binding protein and two complex regulatory enzymes. Most frequent are deficiencies in PDH-E1a. There is a spectrum of clinical presentations in E1a deficiency, ranging in boys from severe neonatal lactic acidosis, Leigh encephalopathy, to later onset of neurological disease such as intermittent ataxia or dystonia. Females tend to have a more uniform presentation

resembling nonprogressive cerebral palsy. Neuroradiological abnormalities such as corpus callosum agenesis are seen more frequently in girls, basal ganglia and midbrain disturbances in boys. Deficiencies in the other subunits have also been described, but in a smaller number of patients. Pyruvate carboxylase deficiency has three clinical phenotypes. The infantile type is characterized mainly by severe developmental delay, failure to thrive, and seizures. The second type is characterized by neonatal onset of severe lactic acidosis with rigidity and hypokinesia. A third form is rarer with intermittent episodes of lactic acidosis and ketoacidosis. Neuroradiological findings such as cystic periventricular leukomalacia have been described.



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**22. Obstet Gynecol. 2013 Apr;121(4):789-97. doi: 10.1097/AOG.0b013e3182878b43.**

**Consequences of a primary elective cesarean delivery across the reproductive life.**

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OBJECTIVE: To estimate cumulative risks of morbidity associated with the choice of elective cesarean delivery for a first delivery. METHODS: A decision analytic model was designed to compare major adverse outcomes across a woman's reproductive life associated with the choice of elective cesarean delivery compared with a trial of labor at a first delivery. Maternal outcomes assessed included maternal transfusion, hysterectomy, thromboembolism, operative injury, and death. Neonatal outcomes assessed included cerebral palsy and permanent brachial plexus palsy in the offspring. RESULTS: Choosing an initial cesarean delivery resulted in a 0.3% increased risk of a major adverse maternal outcome in the first pregnancy. In each subsequent pregnancy, the difference in composite maternal morbidity increased such that by the fourth pregnancy, the cumulative risk of a major adverse maternal outcome was nearly 10% in the elective primary cesarean delivery group, three times higher than women who initially underwent a trial of labor. Although the choice of an initial cesarean delivery resulted in 2.4 and 0.41 fewer cases of cerebral palsy and brachial plexus palsy, respectively, per 10,000 women in the first pregnancy, by a fourth pregnancy, the risk of a adverse neonatal outcome was higher among offspring of women who had chosen the initial elective cesarean delivery (0.368% compared with 0.363%). CONCLUSION: Maternal morbidity associated with the choice of primary elective cesarean delivery increases in each subsequent pregnancy and is greater in magnitude than that associated with the choice of a trial of labor. These increased risks are not offset by a substantive reduction in the risk of neonatal morbidity.

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