Reduced satellite cell population may lead to contractures in children with cerebral palsy

Aim: Satellite cells are the stem cells residing in muscle responsible for skeletal muscle growth and repair. Skeletal muscle in cerebral palsy (CP) has impaired longitudinal growth that results in muscle contractures. We hypothesized that the satellite cell population would be reduced in contractures muscle.

Method: We compared the satellite cell populations in hamstring muscles from participants with CP contracture (n=8; six males, two females; age range 6-15y; age range 6-15y; Gross Motor Function Classification Systems [GMFCS] levels II-4; 4 with hemiplegia, 4 with diplegia) and from typically developing participants (n=8; six males, two females, age range 15-18y). Muscle biopsies were extracted from the gracilis and semitendinosus muscles and mononuclear cells were isolated. Cell surface markers were stained with fluorescently conjugated antibodies to label satellite cells (neural cell adhesion molecule) and inflammatory and endothelial cells (CD34 and CD4 respectively). Cells were analyzed using flow cytometry to determine cell populations.

Results: After gating for intact cells a mean of 12.8% (SD 2.8%) were determined to be satellite cells in typically developing children, but only 5.3% (S.D 2.3%; p<0.05) in children with CP. Hematopoietic and endothelial cell types were equivalent in typically developing children and children with CP (p>0.05) suggesting the isolation procedure was valid.

Interpretation: A reduced satellite cell population may account for the decreased longitudinal growth of muscles in CP that develop into fixed contractures or the decreased ability to strengthen muscle in CP. This suggests a unique musculoskeletal disease mechanism and provides a potential therapeutic target for debilitating muscle contractures.

**Objectives:** To examine the effects of observed maternal sensitivity (MS), cognitive stimulation (CS), and linguistic stimulation on the 4-year growth of oral language in young, deaf children receiving a cochlear implant. Previous studies of cochlear implants have not considered the effects of parental behaviors on language outcomes.

**Study Design:** In this prospective, multisite study, we evaluated parent-child interactions during structures and unstructured play tasks and their effects on oral language development in 188 deaf children receiving a cochlear implant and 97 normal-hearing children as controls. Parent-child interactions were rated on a 7-point scale using the National Institute of Child Health and Human Development’s Early Childcare Study codes which have well-established psychometric properties. Language was assessed using the MacArthur Bates Communicative Developmental Inventories, the Reynell Developmental Language Scales, and the Comprehensive Assessment of Spoken Language (CASL).

**Results:** We used mixed longitudinal modeling to test our hypotheses. After accounting for early hearing experience and child and family demographics, MS and CS predicted significant increases in the growth of oral language. Linguistic stimulation was related to language growth only in the context of high MS.

**Conclusion:** The magnitude of effects of MS and CS on the growth of language was similar to that found for age at the time of cochlear implantation, suggesting that addressing parenting behaviors is a critical target for early language learning after implantation.
The authors compared the outcomes of 17 children aged 7 to 15 years with DYT1 dystonia or cerebral palsy following deep brain stimulation. While patients with cerebral palsy presented with significantly greater motor disability than the DYT1 cohort at baseline, both groups demonstrated improvement at 1 year (cerebral palsy = 24%; DYT1 = 6%). The group as a whole demonstrated significant improvement on the Barry-Albright Dystonia Scale across time. Gains in motor function were apparent in both axial and appendicular distribution involving both upper and lower extremities. Gains achieved by 6 months were sustained in the cerebral palsy group, whereas the DYT1 group demonstrated continued improvement with ongoing pallidal stimulation beyond 18 months. Young patients with dystonia due to cerebral palsy responded comparably to patients with DTY1 dystonia. The severity of motor impairment in patients with cerebral palsy at baseline and follow-up raises the issue of even earlier intervention with neuromodulation in this population to limit long-term impairments due to dystonia.
**Health risk behaviors among young adults with spina bifida.**
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**Aim:** Persons with spina bifida who adopt unhealthy lifestyles could be at increased risk of adverse health outcomes because of the presence of spina bifida may magnify this risk. We estimated overall and age-specific prevalence of selected health risk behaviors (HRBs) in young people with spina bifida and examined the association between HRBs and depression.

**Method:** We performed analyses on data obtained from individuals with spina bifida (n=130; mean age 23y SD 4yr 5mo; 64 males, 66 females; 64% lumbo-sacral lesion; 77% with shunt) who participated in a population based survey conducted by the Arkansas Spinal Cord Commission in 2005.

**Results:** Compared with national estimates, young people with spina bifida tend to eat less healthy diets, do less exercise, and engage in more sedentary activities. Respondents were less likely to use substances (alcohol, tobacco, illegal drugs), which peaked among 25-31 year olds. About 90% saw a doctor in the previous year. Nearly one half reported mild or major depressive symptoms. In the logistic regression analysis after controlling for potential confounders (age, sex, ethnic group, education, employment, marital status, living arrangement, level of lesion, presence of shunt, mobility, self-rated health and healthcare utilization) major depressive symptoms were associated with current alcohol drinking (adjusted odds ratio: 4.74; 95% CI 1.18-19.04).

**Interpretation:** Young adults with spina bifida exhibit unhealthy behaviors that continue into their late 20’s. The findings highlight the need to increase awareness of their health risk profiles in the spina bifida community and show opportunities for mental health and health risk screening and counseling by healthcare providers.
Reduced Structural Connectivity of Frontolimbic Pathway in Generalized Anxiety Disorder.

Context: Emotion regulation deficits figure prominently in generalized anxiety disorder (GAD), as well as other anxiety and mood disorders. Research examining emotion regulation and top-down modulation has implicated reduced coupling of the amygdale with prefrontal and anterior cingulated cortex (ACC), suggesting frontolimbic white matter connectivity in GAD.

Objective: To investigate structural connectivity between ventral prefrontal/ACC areas and the amygdale in GAD, and to assess associations with functional connectivity between those areas.

Design: Participants underwent diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) scans.

Setting: University magnetic resonance imaging facility.

Participants: Forty-nine GAD patients and 29 healthy volunteers, including a subset of 21 patients without comorbid Axis I diagnoses and 21 healthy volunteers matched for age, sex, and education.

Main Outcome Measure: Mean fractional anisotropy (FA) values in the left and right uncinate fasciculus, as measured by tract-based analysis for DTI data.

Results: Lower mean FA values in bilateral uncinate fasciculus indicated reduced frontolimbic structural connectivity in GAD. This reduction in uncinate fasciculus integrity was most pronounced for patients without comorbidity and was not observed in other white matter tracts. Across all subjects, higher FA values were associated with more negative functional coupling between the pregenual ACC and amygdale during the anticipation of aversion.

Conclusion: Decrease frontolimbic structural connectivity suggests a neural basis for emotion regulation deficits in GAD. The functional significance of these structural differences is underscored by decreased functional connectivity between the ACC and amygdale in subjects with reduced structural integrity of the uncinate fasciculus.
Background: Cerebrospinal fluid (CSF) biomarkers reflecting neuronal and astroglial injury, such as total tau (T-tau), glial fibrillary acidic protein (GFAP), and neurofilament light (NFL), have been extensively investigated in neurologic diseases in adults, but no large study has investigated these biomarkers in children.

Methods: This study presents a detailed evaluation of CSF T-tau, GFAP, NFL, and CSF:albumin ratio in a large cohort of pediatric patients. This is a retrospective multicenter study on pediatric patients aged <16 years (n=607), where neuronal injury biomarkers T-tau, GFAP, NFL, and CSF albumin ratio were analyzed during 2000-2010 at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Sweden. The patients were grouped into eight categories: epilepsy, infectious and inflammatory central nervous system disorders, progressive encephalopathy, static encephalopathy, tumors, movement disorders, miscellaneous disorders, and a control group.

Results: T-tau, GFAP and NFL were increased in progressive encephalopathy (P<0.001), epilepsy (P<0.001), and infectious and inflammatory central nervous system disorders (P<0.001) compared with controls. T-tau was the biomarker with the highest diagnostic accuracy with the area under the curve of 0.83 (95% confidence interval (CI), 0.77-0.90; P<0.0001) for progressive encephalopathy followed by epilepsy 0.80 (95% CI, 0.75-.087; P<0.0001). The combination of all biomarkers further improved the area under the curve for progressive encephalopathy 0.87 (95% CI, 0.77-0.89; P<0.0001), followed by epilepsy 0.81(95% CI, 0.74-.080; P<0.030). The combination of the biomarkers also separated progressive from static encephalopathy 0.88 (95% CI, 0.83-.093; P<0.0001).

Conclusions: CSF T-tau, GFAP, and NFL are differently altered across different neurologic disease in children. Importantly, the biomarker pattern distinguishes between progressive and static neurologic disorders.
Background: Whole-exome sequencing is a diagnostic approach for the identification of molecular defects in patients with suspected genetic disorders.

Methods: We developed technical, bioinformatic, interpretive, and validation pipelines for whole-exome sequencing in a certified clinical laboratory to identify sequence variants underlying disease phenotypes in patients.

Results: We present data on the first 250 probands for whom referring physicians ordered whole-exome sequencing. Patients presented with a range of phenotypes suggesting potential genetic causes. Approximately 80% were children with neurologic phenotypes. Insurance coverage was similar to that for established genetic tests. We identified 86 mutated alleles that were highly likely to be causative in 62 of the 250 patients, achieving a 25% molecular diagnostic rate (95% confidence interval, 20-31). Among the 62 patients, 33 had autosomal dominant disease, 16 had autosomal recessive disease, and 9 had X-linked disease. A total of 4 probands received two nonoverlapping molecular diagnoses, which potentially challenged the clinical diagnosis that had been made on the basis of history and physical examination. A total of 83% of the autosomal dominant mutant alleles and 40% of the X-linked mutant alleles occurred de novo. Recurrent clinical phenotypes occurred in patients with mutations that were highly likely to be causative in the same genes and in different genes responsible for genetically heterogeneous disorders.

Conclusions: Whole-exome sequencing identified the underlying genetic defect in 25% of consecutive patients referred for evaluation of a possible genetic condition. (Funded by the National Human Genome Research Institute.)
Child coping, parent coping assistance, and post-traumatic stress following paediatric physical injury
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Background: Following a physical injury, many children exhibit long-term psychological reactions such as post-traumatic stress symptoms (PTSS). Children’s coping strategies, and the ways that others help them cope with injury (i.e. coping assistance), are understudied, potentially malleable variables that could be targeted in preventive interventions. The objectives of the current research were to describe child coping behavior and parent coping assistance following a child’s injury, and to investigate the relationships among coping, coping assistance and child PTSS.

Method: Participants included 82 children with injuries and one percent of each child. Children completed measures of coping and coping assistance 2 weeks after their injury (T1). Children also completed measures of coping and PTSS at 3-months follow-up (T2). Parents reported on the coping assistance they provided to their child at T1.

Results: Children reported using an average of six coping strategies (out of 10) with wishful thinking, social support, distraction, and cognitive restructuring endorsed most frequently. Child-reported social withdrawal and resignation 2 weeks after his or her injury (T1) were related to subsequent PTSS (T2). Social withdrawal at T2 was related to concurrent child PTSS (T2). Children were more likely to seek social support when their parents reported helping their child cope. No relationships were identified between active coping behaviors or parent coping assistance and PTSS outcomes.

Conclusions: Findings suggest that children’s coping strategies (particularly social withdrawal and resignation) play a possibly important, complex role in the development of traumatic stress symptoms. When parents help their child cope, children are more likely to seek out social support, suggesting that they will be more able to ask their parents for help as needed. Future research should identify effective strategies to prevent PTSS including how parents can best support their child following paediatric injury.
Medication for Attention Deficit-Hyperactivity Disorder and Criminality

Background: Attention deficit-hyperactivity disorder (ADHD) is a common disorder that has been associated with criminal behavior in some studies. Pharmacologic treatment is available for ADHD and may reduce the risk of criminality.

Methods: Using Swedish national registers, we gathered information on 25,656 patients with a diagnosis of ADHD, their pharmacologic treatment, and subsequent criminal convictions in Sweden from 2006 through 2009. We used stratified Cox regression analyses to compare the rate of criminality while the patients were receiving ADHD medication, as compared with the rate for the same patients while not receiving medication.

Results: As compared with non-medication periods, among patients receiving ADHD medication, there was a significant reduction of 32% in the criminality rate for men (adjusted hazard ratio, 0.68; 95% confidence interval [CI], 0.63 to 0.73) and 41% for women (hazard ratio, 0.59; 95% CI, 0.50 to 0.70). The rate reduction remained between 17% and 46% in sensitivity analyses among men, with factors that included different types of drugs (e.g., stimulant vs. non-stimulant) and outcomes (e.g., type of crime).

Conclusions: Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD.
Impact of Treatments for Depression on Comorbid Anxiety, Attentional, and Behavioral Symptoms in Adolescents With Selective Serotonin Reuptake Inhibitor-Resistant Depression

Objective: To assess the relative efficacy of antidepressant medication, alone and in combination with cognitive behavioral therapy (CBT), on comorbid symptoms of anxiety, attention, and disruptive behavior disorders in participants in the Treatment of Resistant Depression in Adolescents (TORDIA) trial.

Method: Adolescents with selective serotonin reuptake inhibitor (SSRI)-resistant depression (N=334) were randomly assigned to a medication switch alone (to another SSRI or to venlafaxine) or to a medication switch plus CBT. Anxiety, attention-deficit/hyperactivity disorder (ADHD), and disruptive behavior disorder (DBD) symptoms were assessed by psychiatric interview and self-report at regular intervals between baseline and 24 weeks. The differential effects of medication and of CBT, and the impact of remission on the course of comorbid symptoms and diagnoses, were assessed using generalized linear mixed models.

Result: Remission was associated was a greater reduction in scalar measures of anxiety, ADHD, and DBDs, and a greater decrease in the rate of diagnosed anxiety disorders. The correlations between the changes in symptoms of depression on the CDRS-R and anxiety, ADHD, and oppositional symptoms were modest, ranging from r=0.28. There were no significant differential treatment effects on diagnoses, or corresponding symptoms.

Conclusion: The achievement of remission had a beneficial effect on anxiety, ADHD, and DBD symptoms, regardless of the type of treatment received. There were no differential effects of medication or CBT on outcome, except for a nonsignificant trend that those adolescents treated with SSRIs showed a greater decrease in rates of comorbid DBDs relative to those treated with venlafaxine.