Background: Children with intellectual disabilities have high rates of behaviour problems. This study explored parents’ causal beliefs and attributions for general problematic child behaviour in children with different aetiologies of intellectual disabilities.

Materials and Methods: Ten parents of children with intellectual disabilities participated in interviews about their child’s problematic behaviour.

Results: Thematic analysis using NVivo revealed that parents viewed their child’s problematic behaviour not only as caused by the child’s intellectual disabilities but also by other causes unrelated to the intellectual disabilities, as well as by aspects of the social environmental context. Some causes were viewed as stable and uncontrollable and others as unstable and controllable. In addition, parents showed a strong sense of responsibility for child behaviour.

Conclusions: Parents of children with intellectual disabilities do not solely interpret their child’s problematic behaviour through the intellectual disabilities but incorporate the environment and causes and attributions that are not related to the intellectual disabilities, which may help to promote more effective parenting.
Differences in health-related quality of life and caregiver burden after hip and spine surgery in non-ambulatory children with severe cerebral palsy.

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AIM:
The aim of this study was to evaluate changes in caregivers' perceptions of health-related quality of life (HRQOL) and caregiver impact in children with severe, non-ambulatory cerebral palsy after orthopedic surgery to correct hip or spine deformities.

METHOD:
A prospective longitudinal cohort study (n=44) design was used to measure changes before and after surgery. Caregivers completed the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) and the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND). Data collection was between February 2011 and February 2014. Caregivers were included if their child was 3 to 25 years old, had cerebral palsy in Gross Motor Function Classification System levels IV and V, and was scheduled for orthopedic surgery. Analysis of variance with repeated measures was used to assess changes before and at four time points after surgery.

RESULTS:
Forty-four caregivers participated. Caregivers' perceptions of their child's HRQOL demonstrated an improvement from baseline to 12 months (p<0.001). Patients who had spine surgery demonstrated a steady improvement over time, whereas patients who had hip surgery had a decrease at 6 weeks followed by steady improvement. Improvements were noted in five of six of the CPCHILD domains, with no changes in the quality of life domain. No changes were noted in any of the ACEND domains.

INTERPRETATION:
Caregivers report an improvement in a variety of domains of HRQOL 1 year after orthopedic surgery.
Abstract

Aim
We studied ‘hip health’ in a population-based cohort of adolescents and young adults with cerebral palsy to investigate associations between hip morphology, pain, and gross motor function.

Method
Ninety-eight young adults (65 males, 33 females) from the birth cohort were identified as having developed hip displacement (migration percentage >30) and were reviewed at a mean age of 18 years 10 months (range 15–24y). Hip morphology was classified using the Melbourne Cerebral Palsy Hip Classification Scale (MCPHCS). Severity and frequency of pain were recorded using Likert scales. Gross motor function was classified by the Gross Motor Function Classification System (GMFCS).

Results
Hip pain was reported in 72% of participants. Associations were found between pain scores and both hip morphology and GMFCS. Median pain severity score for MCPHCS grades 1 to 4 was 2 (interquartile range [IQR] 1.0–3.0) compared to 7 (IQR 6.0–8.0) for grades 5 and 6 (severe subluxation or dislocation). Hip surveillance and access to surgery were associated with improved hip morphology and less pain.

Interpretation
Poor hip morphology at skeletal maturity was associated with high levels of pain. Limited hip surveillance and access to surgery, rather than GMFCS, was associated with poor hip morphology. The majority of young adults who had access to hip surveillance, and preventive and reconstructive surgery, had satisfactory hip morphology at skeletal maturity and less pain.
Deleterious mutation in GPR88 is associated with chorea, speech delay, and learning disabilities

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ABSTRACT

Objective: To identify the underlying molecular basis of a familial developmental disorder characterized by chorea, marked speech delay, and learning difficulties in 4 sisters from a consanguineous family.

Methods: Whole-exome analysis of DNA of the 2 older patients followed by Sanger sequencing of the mutated exon in all family members.

Results: A homozygous deleterious mutation, p.C291X, was identified in the GPR88 gene in both exome analyses. The mutation segregated with the disease in the family and was absent from a large cohort of controls.

Conclusions: Homozygous deleterious mutation in GPR88 in humans is associated with marked speech delay, learning disabilities, and chorea, which manifest at 8–9 years of age. The finding is consistent with the reported abundant expression of GPR88 in the striatum and the hyperkinetic activity and learning impairment observed in GPR88 knockout mice. Although further functional characterization is needed, the finding underscores the importance of GPR88 in movement control and learning.
Exome Sequencing and the Management of Neurometabolic Disorders


NEJM 374: 2246-55 Vancouver BC, Canada DOI: 10.1056/NEJMoa1515792

BACKGROUND: Whole-exome sequencing has transformed gene discovery and diagnosis in rare diseases. Translation into disease-modifying treatments is challenging, particularly for intellectual developmental disorder. However, the exception is inborn errors of metabolism, since many of these disorders are responsive to therapy that targets pathophysiological features at the molecular or cellular level.

METHODS: To uncover the genetic basis of potentially treatable inborn errors of metabolism, we combined deep clinical phenotyping (the comprehensive characterization of the discrete components of a patient’s clinical and biochemical phenotype) with whole-exome sequencing analysis through a semiautomated bioinformatics pipeline in consecutively enrolled patients with intellectual developmental disorder and unexplained metabolic phenotypes.

RESULTS: We performed whole-exome sequencing on samples obtained from 47 probands. Of these patients, 6 were excluded, including 1 who withdrew from the study. The remaining 41 probands had been born to predominantly nonconsanguineous parents of European descent. In 37 probands, we identified variants in 2 genes newly implicated in disease, 9 candidate genes, 22 known genes with newly identified phenotypes, and 9 genes with expected phenotypes; in most of the genes, the variants were classified as either pathogenic or probably pathogenic. Complex phenotypes of patients in five families were explained by coexisting monogenic conditions. We obtained a diagnosis in 28 of 41 probands (68%) who were evaluated. A test of a targeted intervention was performed in 18 patients (44%).

CONCLUSIONS: Deep phenotyping and whole-exome sequencing in 41 probands with intellectual developmental disorder and unexplained metabolic abnormalities led to a diagnosis in 68%, the identification of 11 candidate genes newly implicated in neurometabolic
disease, and a change in treatment beyond genetic counseling in 44%. (Funded by BC Children’s Hospital Foundation and others.)
ABSTRACT

Objective: To estimate the rate of psychotropic medication use in children and adolescents with Down syndrome (DS) and to describe age-related trends.

Methods: Data were obtained from electronic health records from 2010 to 2013 for a retrospective cohort of 832 children with DS, aged 5 to 21 years, including 5324 visits. The following medication classes: central nervous system (CNS) stimulants, selective serotonin reuptake inhibitors, atypical antipsychotics, and alpha adrenergic agonists were examined. The distribution of rates of medication use across ages was assessed graphically and with the Cochran-Armitage trend test. Between-group comparisons of medication classes were conducted using \( \chi^2 \). Repeated measures models with generalized estimating equations were used to assess changes in rates of medication use over time.

Results: Children aged 12 to 21 years were more likely to be on any medication at some point compared with children aged 5 to 11 years (25% vs 17%, respectively, \( p = .003 \)). For 5 to 11 year olds, the odds of being on a psychotropic medication increased with age for all medication classes studied. For 12 to 18 year olds, the odds of being on a CNS stimulant significantly decreased with increasing age (odds ratio: 0.73, 95% confidence intervals, 0.58–0.91), whereas the odds of being on a medication from one of the other classes was stable.

Conclusion: Changes in psychotropic medication use across the age span in children with DS suggest that the type and severity of neurobehavioral problems in this population likely also change over time. These findings will inform future research on the common mental health conditions and treatments for children with DS.

Guanfacine Use in Children With Down Syndrome and Comorbid Attention-Deficit Hyperactivity Disorder (ADHD) With Disruptive Behaviors

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The purpose of this study was to characterize children with Down syndrome and attention-deficit hyperactivity disorder (ADHD) with disruptive behaviors using the Aberrant Behavior
Checklist (ABC), and to measure the treatment effects of guanfacine on maladaptive behaviors. Subjects were enrolled from a group of outpatients who visited our clinic between 2002 and 2007. Subjects (N = 23) were children with Down syndrome ages 4 to 12 years (mean 7.4 + 4.1), who met criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The Aberrant Behavior Checklist Irritability and Hyperactivity subscales each showed a significant decrease (P < .0001) at follow-up. The mean decline on Hyperactivity was 25% (−7.8 points), and for Irritability, 25% (−3.5 points). The mean composite score also declined by 24% (−12 points). Effect size differences on Irritability were moderate, whereas differences on Hyperactivity and composite score appeared large. Clinically important target behaviors were reduced. Medication was generally well tolerated and the incidence of treatment emergent side effects remained low.
Injection frequency of botulinum toxin A for spastic equinus: a randomized clinical trial.


Abstract
AIM:
We compared two botulinum toxin A (BoNT-A) injection frequency regimens, 12-monthly versus 4-monthly, for spastic equinus in a randomized clinical trial. The primary outcome measure was passive ankle dorsiflexion.

METHOD:
Forty-two ambulant children with spastic equinus, secondary to cerebral palsy (23 males and 19 females; mean age 3y 6mo, SD 13mo; GMFCS levels I [n=20], II [n=19], III [n=3]) were randomized to receive either 12-monthly or 4-monthly BoNT-A injections to the calf, over a 26-month period. Twenty-one children had spastic hemiplegia, 21 children had spastic diplegia. A fixed 6U/kg dose of Botox was injected into the gastrocnemius muscle of both limbs in children with diplegia and the gastrocsoleus of the affected limb in children with hemiplegia, under mask anaesthesia.

RESULTS:
Forty-two children entered the trial with 21 participants randomized to each group. There were three withdrawals and two children received serial casting midway through the trial. There was no significant difference in passive dorsiflexion between 12-monthly and 4-monthly regimens (p=0.41). There were also no significant between group differences on secondary outcome measures. There were no serious adverse events - the rate was 1.2 adverse events per child per year in the 12-monthly group and 2.2 adverse events per child per year in the 4-monthly group. Subgroup analysis revealed a significant difference in passive dorsiflexion between children with hemiplegia and diplegia (p=0.01).

INTERPRETATION:
There was no significant difference between 12-monthly and 4-monthly injection regimens on passive dorsiflexion or secondary outcome measures. BoNT-A injections for spastic equinus may be recommended on a 12-monthly basis.
Investigating the impact of pain, age, Gross Motor Function Classification System, and sex on health-related quality of life in children with cerebral palsy.

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Abstract
AIM:
To explore whether health-related quality of life (HRQOL) can be predicted by pain, age, Gross Motor Function Classification System (GMFCS) level, and sex in children with cerebral palsy (CP) and whether different pain etiologies have varying effects on HRQOL.

METHODS:
Children with CP aged 3 to 19 years and their caregivers were consecutively recruited. Caregivers reported their child's pain (Health Utilities Index 3 [HUI3] pain subset) and HRQOL (DISABKIDS questionnaires). Physicians identified pain etiologies. A multiple linear regression model determined whether pain, GMFCS level, sex, and age predicted HRQOL. An ANOVA evaluated the effects of pain etiologies on HRQOL.

RESULTS:
Three hundred and forty-four participants were approached and 87\% (n=300) participated. Sufficient data were available on 248 (72\% of total sample). Sixty-six participants (27\%) formed the pain group with HUI3 pain scores of at least 3. The presence of pain and increasing age significantly negatively predicted HRQOL (p<0.001, R\textsuperscript{2} =0.141), while GMFCS and sex did not. Musculoskeletal deformity (24\%) and hypertonia (18\%) were the most frequent pain causes. HRQOL statistically differed depending on the pain etiology (p=0.028) with musculoskeletal deformity showing the lowest mean HRQOL.

INTERPRETATION:
The presence of pain and increasing age negatively predict HRQOL in CP. Musculoskeletal deformity has the greatest negative impact on HRQOL.
OBJECTIVE: To determine safety of intramuscular botulinum toxin A (BoNT-A) injections to reduce abstract spasticity and improve care and comfort of nonambulatory children with cerebral palsy (CP).

METHODS: Nonambulatory children with CP were randomly allocated to receive either BoNT-A (n = 23) or sham procedure (n = 18) in Cycle 1. In Cycle 2, the BoNT-A group received a second episode of BoNT-A (n = 20) and sham group received their first episode of BoNT-A (n = 17). A pediatric rehabilitation specialist masked to group allocation graded each adverse event (AE) according to system, severity (mild, moderate, serious, sentinel) and causality (unlikely/unrelated; possible; probable/definite).

RESULTS: There was no difference for all moderate/serious AEs between the BoNT-A and sham/control groups in either Cycle 1 (incident rate ratio = 1.30, 95% confidence interval = 0.43–4.00; P = .64) or Cycle 2 (incident rate ratio = 0.72, 95% confidence interval = 0.30–1.75; P = .47). In Cycle 2, 1 serious, 3 moderate (single-episode group), and 24 mild (single-episode group n = 10; 2 episode group n = 14) AEs were probably/definitely related to BoNT-A.

CONCLUSIONS: Children receiving BoNT-A were at no greater risk of moderate/serious AEs compared with a sham control procedure. There was no increased risk of moderate/serious AEs between one and two episodes of BoNT-A.
Clinical ethics is a field of study that promotes the use of rational thought and clinical judgment based on scientific knowledge to reach conclusions regarding complex clinical problems. Common subjects in clinical ethics include informed consent, surrogate decision-making, refusal of care, medical futility, end-of-life care, and quality of life. Spinal fusion in patients with cerebral palsy who have global involvement, defined as Gross Motor Function Classification System (GMFCS) level V, poses an ethical dilemma. A child with GMFCS level-V function has severely limited self-mobility, voluntary muscle control, and ability to keep the head and trunk upright. A so-called four-topic model has been developed and validated to assist the clinician in the analysis of ethical dilemmas in patient care. This model includes an evaluation of the indications, patient preferences, quality of life, and contextual features that underpin medical decisions. Indications include the problem, history, diagnosis, prognosis, acuity, how the patient may benefit, how harm may be avoided, goals of treatment, likelihood of success, and contingency plan in the event of failure. Patient preferences encompass the stated wishes of the patient or patient-centered decision-making by surrogates. Quality of life emphasizes the goals of restoring, maintaining, or improving the patient’s life. Contextual features are concerned with other factors that influence decisions such as religion, culture, the law, confidentiality, research, teaching, economics, and impact on the patient’s family and medical team. Stable balanced posture, improved health and function, increased comfort of the patient, and easing of burden to caregivers have been posited as indications for spinal fusion. There are neither randomized controlled trials nor prospective longitudinal studies comparing fusion of the spine with the natural history of the disease. Outcomes measured are mostly observational and based on evaluation by secondary parties rather than within the affected person. It is difficult to determine whether favorable rates of satisfaction are the result of improvement in appearance or whether they represent improvements in comfort and function. Several published studies have used the four-topic model to assist in complex clinical decision-making, such as chronic dialysis and craniectomy for traumatic brain injury. The four-topic model provides an organized framework for evaluation of ethical dilemmas in a logical, simplified manner and serves as the structure for the ethical evaluation of spinal fusion in a child with GMFCS level-V function.
AIM: Scoliosis is a common comorbidity in Rett syndrome and spinal fusion may be recommended if severe. We investigated the impact of spinal fusion on survival and risk of severe lower respiratory tract infection in Rett syndrome.

METHOD: Data were ascertained from hospital medical records, the Australian Rett Syndrome Database, a longitudinal and population-based registry, and from the Australian Institute of Health and Welfare National Death Index database. Cox regression and generalized estimating equation models were used to estimate the effects of spinal surgery on survival and severe respiratory infection respectively in 140 females who developed severe scoliosis (Cobb angle ≥45°) before adulthood.

RESULTS: After adjusting for mutation type and age of scoliosis onset, the rate of death was lower in the surgery group (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.12–0.74; p=0.009) compared to those without surgery. Rate of death was particularly reduced for those with early onset scoliosis (HR 0.17, 95% CI 0.06–0.52; p=0.002). There was some evidence to suggest that spinal fusion was associated with a reduction in risk of severe respiratory infection among those with early onset scoliosis (risk ratio 0.41, 95% CI 0.16–1.03; p=0.06).

INTERPRETATION: With appropriate cautions, spinal fusion confers an advantage to life expectancy in Rett syndrome.
The Changing Face of Survival in Rett Syndrome and MECP2-Related Disorders

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Introduction

Abstract

PURPOSE: Survival in Rett syndrome remains unclear. Although early estimates were grim, more recent data suggest that survival into adulthood is typical. We aimed to define survival in Rett syndrome more clearly and identify risk factors for early death.

METHODS: Participants with clinical Rett Syndrome or methyl-CpG-binding protein 2 mutations without clinical RTT were recruited through the Rett Syndrome Natural History study from 2006 to 2015. Clinical details were collected, and survival was determined using the Kaplan-Meier estimator. Risk factors were assessed using Cox proportional hazards models.

RESULTS: Among 1189 valid participants, 51 died (range 3.9-66.6 years) during the 9-year follow-up period. Those who died included 36 (3.9%) classic Rett syndrome females, 5 (5.9%) atypical severe Rett syndrome females, 1 (2.4%) non-Rett syndrome female, the single atypical severe male, 6 (30%) non-Rett syndrome males, and 2 (7.1%) methyl-CpG-binding protein 2 duplication syndrome males. All atypical mild Rett syndrome females, methyl-CpG-binding protein 2 duplication syndrome females, and the single classic Rett syndrome male remain alive. Most deaths were due to cardiorespiratory issues. Only one died from severe malnutrition, scoliosis, and extreme frailty. Survival for classic and atypical Rett syndrome was greater than 70% at 45 years. Overall severity and several modifiable risk factors, including ambulation, weight, and seizures, were associated with mortality in classic Rett syndrome.

CONCLUSIONS: Survival into the fifth decade is typical in Rett syndrome, and death due to extreme frailty has become rare. Although the leading cause of death remains cardiorespiratory compromise, many risk factors for early death are modifiable. Intense therapeutic interventions could further improve the prognosis for individuals with Rett syndrome.
The High Direct Medical Costs of Prader-Willi Syndrome.
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The Journal of Pediatrics, 2016:175:137-143 DOI:10.1016/j.jpeds.2016.05.018

Abstract

OBJECTIVE:
To assess medical resource utilization associated with Prader-Willi syndrome (PWS) in the US, hypothesized to be greater relative to a matched control group without PWS.

STUDY DESIGN:
We used a retrospective case-matched control design and longitudinal US administrative claims data (MarketScan) during a 5-year enrollment period (2009-2014). Patients with PWS were identified by Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 759.81. Controls were matched on age, sex, and payer type. Outcomes included total, outpatient, inpatient and prescription costs.

RESULTS:
After matching and application of inclusion/exclusion criteria, we identified 2030 patients with PWS (1161 commercial, 38 Medicare supplemental, and 831 Medicaid). Commercially insured patients with PWS (median age 10 years) had 8.8-times greater total annual direct medical costs than their counterparts without PWS (median age 10 years: median costs $14 907 vs $819; P < .0001; mean costs: $28 712 vs $3246). Outpatient care comprised the largest portion of medical resource utilization for enrollees with and without PWS (median $5605 vs $675; P < .0001; mean $11 032 vs $1804), followed by mean annual inpatient and medication costs, which were $10 879 vs $1015 (P < .001) and $6801 vs $428 (P < .001), respectively. Total annual direct medical costs were ~42% greater for Medicaid-insured patients with PWS than their commercially insured counterparts, an increase partly explained by claims for Medicaid Waiver day and residential habilitation.

CONCLUSION:
Direct medical resource utilization was considerably greater among patients with PWS than members without the condition. This study provides a first step toward quantifying the financial burden of PWS posed to individuals, families, and society.