Intro and Welcome: Dr. Bonnemann

Steven Kolter MDA rep in NM clinic at CHOP

What does MDA do? MDA Camp, DME $$ help, DME loan closet, support group once a month (nurse Patti facilitates) w/ simultaneous kids group at Inglis Foundation, MDA.org chat groups.

Coming up:
Workshop w/ attorney about rights of kids with disabilities
"Muscle summit" this fall
Nov 1 Muscle Team Challenge fundraiser muscleteamchallenge.org

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Dr. Bonnemann Phenotype of col6 disorders

Umbrella of Congenital Muscular Dystrophy (CMD)—group of heterogeneous diseases, but treated as group b/c all start in early life, often infancy or at birth, in contrast to Duchenne's—babies unaffected and disease does not show up until later

It has taken time to get neuromuscular (NM) community to think differently about CMD than Duchenne's—different presentation, different needs/treatment plans/etc

Bethlem

- Described first in Holland by J. Bethlem 1976
- congenital: at birth or early onset muscular weakness and low muscle tone (hypotonia)
- joints may be hypermobile early on, followed by the development of contractures, in particular of Achilles tendons, elbows, fingers
- torticollis at birth often (50%?), but usually goes away, although some need surgical release
- contractures typically show up at end of first decade
- contractures tend to be more progressive than weakness
- very slowly progressive, loss of the ability to walk in 50% of patients beyond age 60 (according to early Bethlem study—Meredith's note: not sure what current statistics would be!)
- contractures can cause more of problem than weakness…contractures need TREATMENT
- no cardiac involvement known so far (except one patient in London study w/arrythmia that may or may not be related to Bethlem, so a Holter Monitor is recommended every 2-3 years)
- nighttime breathing problems can occur in adulthood due to combination of weakness of diaphragm (gets more affected than other muscles) and a stiff ribcage (ribcage contractures)

pics from Bushby article of fingers, elbows, ankles contractures, shoulders
(ullrich contractures similar and earlier)

- lots of patients early on have very non-specific symptoms, so they are not recognized as having Bethlem
- hard to tell unless you have a "feel" for the joints and skin of Bethlem…(Meredith's note: so probably other neuromuscular docs around the country are unlike to know Bethlem when they see it, unless they have experience with it!)
- orthopedic complications: pectus deformities, foot deformities at birth, keloids and cigarette paper scars

- w/in family, can vary A LOT—some have more weakness, some more contractures

Ullrich--other end of spectrum

- Otto Ullrich (geneticist) 1930 atonic-sclerotic muscular dystrophy (low tone and contractures)
- very accurate description in this 1930 article (if you can read it in the original German!)
- condition forgotten for a long time; not believed as separate entity until Bertini 2002 article! WOW
- patients not so rare as previously though…many, many misdiagnosed until somehow they find their way to UCMD (many at conference self-diagnosed via internet before getting in touch with Dr. B)
- more severe congenital hypotonia than BM
- joint hypermobility in the hands and feet and particular
- sometimes contractures or scoliosis, torticollis at birth
- joint hypermobility common feature among all patients
- later, contractures may increase, also more weakness. Contractures increase independent of weakness and become debilitating more than weakness (esp in terms of walking)
- quite variable severity (spectrum between Bethlem and Ullrich very very very variable)
- walking may be achieved, though often delayed (some don't walk at all)
- combination of weakness and orthopedic complications make walking impossible (contractures, scoliosis)
- some patients never walk, except on knees b/c of contractures—enough strength to walk on knees is noteworthy, but legs too tight from contractures to straighten legs to walk
- nocturnal hypoventilation may set in from 5 years to teenage, often preceded by declining pulmonary function tests—PROACTIVE w/ breathing important; nighttime breathing support very important
- after manifestation of breathing problems and intervention w/cpap/bipap/etc, breathing tends to be stable from there

Bertini patient with NO col6 in muscle—scoliosis, feet/hands very bendy
Holland patient, knees and elbow contractures, fingers and feet very lax—only see this in Ullrich**

Proximal muscles can have strength for mobility, so it's worth rehab of joint contractures to have ambulation
Ambulation with knee walking not typical in other NM disorders—only Ullrich**

French family:

- Mom has BM, Mom's sister has UCMD
- Kids have BM, UCMD, BM, (and one more…not sure if that child was unaffected or died….)
- All were found to have same genetic defect, but each presented with different phenotype (ie, different symptoms)

What contributes to the problems found in BM/UCMD:

- Two aspects:
    - Muscle weakness
    - Connective tissue disease
- Results in orthopedic problems
- Connective tissue skin features—roughness (keratosis), softness, abnormal scars—cigarette paper and keloid, stria
- CHOP is collaborating w/ Hammersmith for skin study to add info for skin phenotype description for BM/ UCMD

- Electron microscope study of skin from Ullrich patient looks like EDS
- Early scoliosis, hip dislocation—orthpedic issues
- Orthopedic survey today as well to help get connective tissue phenotype
- When contractures really take off—NEEDS treatment to maintain function

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Dr. Amelie Nadeau (from Hammersmith, been doing research at CHOP, now going to Montreal?)

- Work to better characterize presentation/issues col6 disorders
- Did a retrospective review of medical charts of patients at Hammersmith with BM/UCMD from 1976-2007
- reviewed patients w/ col6 problem and/or mutation
- collected clinical data on 38 ullrich 24 bethlem patients; mean age 14 UCMD 15 BM
- 2 UCMD patients died during study, ages 10 and 15—one refused night vent; other died from pneumonia just before night vent
- BM age when first presented in clinic 0-9 years/ mean 2 years
- ullrich 0-3 years/mean .7 years
    - bethlem neonatal presentation less noticeable/ presented later on
- all BM patients could walk, 40% could run at some point
- UCMD group most could walk at some point; 30% walk w/ support, none could run
    - BM group only one patient 11 years old wheelchair bound after leg fracture
    - UCMD group 5 years 12% full time wheel chair 10 years 35% 15 years 65%
- spine problems:
    - rigidity 63% UCMD 45% BM
    - scoliosis 63% UCMD 20% BM
    - more severe in UCMD group
    - mean age 6 years UCMD 10 years BM (for scoliosis)
    - 28% had scoliosis surgery in UCMD group
- respiratory—normal in BM group; UCMD group Forced Vital Capacity FVC not normal—decline in 1st decade; stabilizes after
    - bipap use UCMD group12% 10years 71% 15year 88% 20years
    - no BM bipap users
    - respiratory problems can happen before loss of ambulation in ullrich or much later—no relationship important to follow respiratory status closely from early on
- feeding
- 45% UCMD under weight 8% BM
    - chewing/swallowing problems 29% UCMD 4% BM
    - gtube 24% UCMD none BM—most UCMD failed to gain weight on it
    - gtube 13 years mean age UCMD
    - Chewing problems if contractures of jaw
    - Swallowing problems in some patients…but not usually bad enough to prevent eating
- skin data lacking in clinic notes

Bonnemann and Mutoni are doing studies, trying to define the cut off/overlap between Bethlem and Ullrich… there's a good sense of either end of the BM/ UCMD spectrum, but then what do you call patients in the middle? Collagen 6 myopathies?

Dr. A. Reghan Foley, CHOP NM Fellow

"CHOP CoPS"
Col 6 defect patient survey

Ullrich—genetically recessive OR dominant (Meredith's note: or new mutation and not inherited….)

Bethlem—genetically dominant (Meredith's note: or new mutation and not inherited….)

- Study is trying to find out if UCMD/BM are phenotypically distinct?
    - Is there a clinical spectrum or are the distinct?
    - Answering this helps develop criteria for clinical trials of meds/treatments
    - Clinical trial coming next summer phase 2 at CHOP for drug for BM/Ullrich

- There are 56 BM/UCMD patients identified in US, 1 in Canada (Meredith's note: hmm…think I know this Canadian!)
- 39 surveys sent out; only 16 returned so far. Sample size is too small to draw any conclusions yet… working on getting more surveys back from CHOP folks and seeking surveys from elsewhere in US, UK
56 in us, 1 CA patients identified, not all followed at CHOP (39 at CHOP)

- some findings so far….
    - a lot of fractures/easy fractures
    - patients are quite bright by parent/self report
- Question to ask down the line…is there a correlation between genetic tests and muscle/skin biopsy and the phenotype/clinical presentation?
- Dr. Kathy North in Australia…trying to add patients to the study, as well as from UK

Tim Estilow, CHOP OT

- Role of OT is to maximize independence with ADLs, etc
- Functional assessment
- Environmental context
    - Physical:
        - Accessibility and availability of items
    - Social:
        - Expectations/support system
    - Cultural:
        - Customs/beliefs/norms
- We (parents/caregivers/docs/therapists) need to set the bar high—set goals and push to meet them
- Ask: What are limits, goals, where are they now?
- Treatment plan:
    - Monitor w/ standard testing and child/parent feedback
- Work on function first, form later
- Use 3 methods:
    - Biomechanical—maintain joint integrity and position
    - Rehabilitative—activities and/or exercises to restore or improve performance

    - Adaptive—use of assistive devices and environmental modifications to improve independence
- (for insurance, phrase goals around function to get things paid. Insurance hates lack of "progress…")
- Assistive Technology (AT)
    - chop has an AT clinic—make appt, try out different devices, see if they might help before trying to get them from insurance, etc.
- types of AT
    - ECU—environmental control units (remote control devices for items in home)
    - switches
    - scanning software
- therapeutic activities:
    - community—sports, dance, horseback, etc—anything and everything child wants to do with adaptations
    - motomed—therapeutic ergometer (exercise in clinic)
    - aquatics
    - Wii
- Adapting activities
- Modifying tasks or objects used to support child's skills and abilities…ideas:
    - Tee ball: wiffle ball bat and plastic ball
    - Hockey: stick secured to wheelchair
    - Soccer: use beach ball instead of soccer ball
    - Basketball: height adjustable rims or nerf ball
    - Volleyball: use balloons/nerf ball
- Motomed in clinics; Tim once saw a Nintendo game cube adaptive device to make Motomed exercise fun
- Why is aquatics good for our kids?
    - Low impact on joints
    - Reduced gravity environment for ease of movement
    - Provides resistance work
    - Great for breath support, postural control, joint stability
    - Fun and different from other typical therapy interventions

**Variety club "direct care for kids" program helps with insurance denied equipment—not all Variety Clubs have this, Philly does

- Benefits of aquatics
    - Core strength
    - Water resistance and helps OT to move/position the child easily in the water
    - Endless positions for postural work
    - Proximal strength
    - Increase endurance
    - Improving strength for ADLs and leisure
    - Water is movement friendly w/ weakness
    - Good for passive stretching

**DVD of exercises in water—Tim can give a copy—email him estilow@email.chop.edu

- www.pfd-a.com adaptive pfd for swimming—worked great for Alex (a young man at the conference)
- Moving on land:
    - WREX device (Gillian video)
        - eating writing typing games etc

        - mobile arm support—attaches to arm and uses rubber bands and amazing engineering to give mechanical support to weak arms so patient can reach w/range of motion they cannot do without because of weakness
        - esp useful for self feeding if too weak to reach own mouth
- Wii
- Has its value…but kids should get out and play, too!
- Wii fit
    - Slalom skiing game stand or use arms great for balance
    - Tightrope walking game also balance
    - Prone skills—do Wii on arms, lift head
    - Elevate balance board with cushion if needed
    - Tennis game…arm movement/range of motion
    - Boxing—makes you sweat!

PT Allan Glanzman Contracture Management

- Daily stretching program—contracture management program
    - Gentle, sustained stretch
    - Put it with something that happens every day to remember to do it, get into routine
    - Stabilize proximal joint, move distal limb segment, hold for at least 30 seconds longer as tolerated, make it a daily habit
    - Have them relax, count with you, don't over stretch
- Serial casting another option
    - Only non surgical way to reliably regain motion
    - Best for ankle, possible at knee
    - One to two weeks per cast
    - Able to walk in the cast
    - Tendon stretch and muscle growth
    - Knees…hard to walk in long leg cast…bigger project
- Night time splinting is another approach
    - Goals
        - Provide time with the muscle in a lengthened positioned
    - KAFO
        - Good to maintain knee extension
        - Can get with ratchet lock at the knee
    - Resting/stretching splints
        - Dafos 9 softy
        - Dafo 2
        - Articulating or solid mafo
    - Ultraflex (very expensive!)
        - Custom knee ankle foot spring loaded for night casting
        - Constant stretch, some wake up sore, but dial down and it doesn't help
    - Dynasplint
        - Off the shelf, for elbow or knee, less expensive
    - Nada chair—use WITH knee immobilizers
- Goals—standing

    - Maintain flexibility, gi, bone health, etc
- Vertical/free standers
    - Theradapt better than rifton for support, accommodate knee contracture
    - Also Kaye stander
    - Fillauer standing frame for 1-3 year old
        - Good head control imp
        - Easier/quicker to get…coded as an orthotic is the reason
- Easy stand
    - Accommodates contractures well
- Gazelle stander by snug seat
    - Prone stander acc. Contractures
- Gait trainers/walkers—goal is support and allow success, practice standing, dynamic weight shift
    - Walker-kaye or nimbo stable, folds, heavy to pull, can provide protection from other kids
    - Lite gait-walkable in tx
    - Up n go
        - true partial weight bearing
        - limited trunk support
    - rifton gait trainer
        - can put weight in it
- power mobility
    - wheelchair/scooter/power assist
        - limit fatigue in school
        - community mobility
        - increased independence playground, day long fairs, vacation
        - participation in sports
- 4 major power chairs manufacturers
    - permobil
    - invacare
    - sunrise (eg, quickie rhythm)
    - pride medical
- think about:
    - electronics (built in ecus to control tv, computer)
    - growth in seating
    - power/range of battery
    - seat height from floor
    - seat functions
    - midwheel/rearwheel drive (midwheel gets stuck on things according to Margaret; Simon says it works really well)
    - seating
- midwheel drive can get stuck on divot in pavement, door jambs—the 4 outer wheels are adjustable to help w/ curb climbing
- midwheel turns in smaller circle than front/rearwheel
    - preschoolers—palyman/robo lets child get on floor
- portable power chair:
    - at'm invacare
        - friction drive

        - foldable power chair
        - 2 models one insurance coded one cash
        - potential mda funded
        - good back up
        - not comfortable long term
- Frank mobility
    - e-fix
    - direct drive
    - add on to manual frame
    - folds by removing wheels and battery
- manual assist
    - quickie extender
    - frank mobility emotion
        - funding more difficult for these
- scooters
    - transportable in a car
    - limited power and range
    - limited maneuverability
    - beware flipping over—4 wheels better
    - may not be bus transportable
    - potential mda funding
    - ok in-school option
- Columbia medical: versa and elite for getting in and out of tub

Allan has functional questionnaire—

Dr Mijail Serruya Penn neuro fellow and engineer

Did phd work w/ technologies for paralyzed folks

- Assist device engineering

- What's out there, what we could do, what do you want
    - Prevent contractures
    - Amplify remaining strength
    - Etc
- Neuroprosthetics for movement—rehab exoskeleton
- Dynamic lycra pressure garments
- Enable movement—wrex
- Powered orthotics (stroke rehab)
- FTM arm training program
- Assistive robotics for self feeding, robot arms
- Enable independent movement with neuroprosthetics….

- What would you most want a device to help you do?
- Would you want a device that you wear all the time?

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Nutritionist Maria Hanna

dxa machine

- have to be still for it…biggest issue, otherwise easy
- why dxa
  - non-invasive, rapid tool
  - spine/hip 30 sec; whole body 3 min
  - assesses presence of bone loss by measuring
- bmc—bone mineral content
- bmd—bone mineral density

  - safe, easily tolerated (1/100 of dental finlm radiation
  - can assess a couple of different sites
- Dual-energy Xray Absorptiometry=DXA
- why do on kids? (to look for bone density problems)
  - Inflammation: ibd, celiac, cf, jra
  - Short gut
  - Transplant
  - Epilepsy
  - CP
  - Neuromuscular
    - All above put kids at risk for bone density problems
- Life cycle changes in bone mass:
  - 1st 20 years—most of bone mass built up: peak bone mass age 20-30, then declines, esp menopause for women
  - inadequate environmental factors (food, activity), then won't reach full genetic potential of bone mass
- NIH osteoporosis conference: bone mineral accretion during childhood is a critical determinant of the risk of osteoporosis later in life
- Bone fragility influenced by bone mass, density, geometry (how thin/long bone is), mirco-repair
- Factors influencing development of osteo:
  - Body size
  - Nutrition
  - Dietary intake
  - Weight bearing physical activity
  - Smoking
  - Peak bone mass
  - Genetics, etc
- CHOP indications for DXA
  - Age 4 and up

    - Abnormal finding on plain xray
    - History of fractures
    - Use of meds like steroids, phenobarb
    - Malnutrition, stunted growth
    - Fat malabsorption
    - Other chronic disease (liver/renal)
- DXA at CHOP interpreted by ISCD certified ped nutrition specialist (int'l soc for clinical densitometry)
- Z score is the only one that should be used with children b/c only one age normed for children w/ standard deviation from mean
- T score is used for adults compares peak bone mass in 20s—not to be used in kids who are still building their bones! Otherwise, they may read as having osteoperosis b/c comparing to adults, not kids same age.
- What's a normal dxa?
    - Z score of –1 sd or greater
    - Meshwork of the bone is tightly woven and more resistant to force
- Osteopenia
    - Z score between –1 and –2.5 in adults meshwork of bone is beginning to thin
- What's osteoperosis
    - Z score less than –2.5

- Calcium by age in diet and supplements
    - (Age 9-18 1300mg or 4.33 glasses of milk) (Meredith's note: my kids' ages…check scan of the handout for full list)
    - Best sources dairy, nuts, greens
    - Don't take more than 500mg calcium supplements at a time
- Vitamin D
    - Few foods have it, so best source is sun and supplements
    - Assess and monitor vitamin d-25-oh level by blood test
    - We carry a precursor of vitamin d in skin, sun turns it into vitamin d
    - Sun lamp w/ UVB rays give vitamin d (usually opposite of what is sold for SAD)
- Fat soluable vitamin that is key to calcium absorption and balance
- Immune and muscle function implication
- Osteomalacia (vitamin D deficiency)—vague systems of muscle pain, fatigue, weakness
- Vit D deficiency assoc w/
    - Cancer, cardiovasc disease
    - Hypertension
    - Stroke
    - Diabetes
    - MS
    - RA
    - IBD
    - Periodontal disease
    - (On and on)
- What is the ideal vitamin d level?
    - >/= 15 to prevent rickets and osteomalacia
    - 20-30 at least for bone health benefits
- season, time of day, cloud cover, sunblock use, meds, age, obesity, skin color, covering of clothing, car window tint

- vitamin d3 cholecalciferol
    - amount needed varies with
        - body weight
        - body fat
        - skin color
        - season
        - latitude
        - sun/tanning habits
- recommendations for d3 supplements
    - periodic monitoring recommended treat levels less than 40; goal 40-65
    - recommended dose, including sun, 4,000 to 10,000 iu a day
- why d3?
    - Longer half life
    - Maintains d longer than d2
    - More potent (3-10s)—need lower dosage
- Concerns:
    - Finding reliable high dose d3 supplements
    - Cost? Otc—no insurance
    - Toxicity not really an issue:
        - 5000 to 10000 day for many months is excessive mostly very high blood levels 125-150
        - rare to have dose that high

- angle of sun doesn't give you vitamin d synthesis in skin 3 months of winter, even if you are in the sun
- goal is to get excess during other seasons and fat stores it for winter
- biphosphonates (eg fosomax)
    - anti resorptive: slows down bone removal
    - complex dosing regimen of oral form
    - gi irritation
    - not fda approved in kids
    - used infrequently in kids; usually setting of fractures; under guidance of experts like endocrine and metabolism
    - long term effects on kids and growing bone not yet known
- dxa at chop, follow up 6 months to 2 years, depending
    - if concerns on dxa, center for bone health at chop referral
    - biphosh currently used with post puberty; painful spine problems
- walking also improves bone density
- col6 disorders—affect of disease on bone density is hypothesized….

Lungs

Pulmo former CHOP fellow/ now at Dupont Dr. Robert A. Heinle

Did cough study last year…

Pulmonary overwiew: promoting function and preventing infections

- Respiratory system
  - Brain controllers
  - Pump—muscles, bones, connective tissue, airway, pleura, spinal cord
  - Peripheral nerves
  - Pleura is chest wall, diaphragm
  - Muscles
  - Bones
  - Airways
- Respiratory maneuvers
  - Sighs
    - Fully expands the lungs
    - Opens distant air sacs preventing collapse (balloon analogy—first breath is hard; next ones easier…lungs—if airways collapse, harder to get more air in)
  - Ambulation
    - Promotes deep breathing
    - Vibrations help mucociliary ladder clear secretions
    - Repositions areas of lungs that are prone to collection of secretion, collapse
  - Cough
    - Clears airway of secretion
    - Prevents pneumonia
- Impact of NM weakness
  - Diaphragm: usually very strong
  - Intercostals muscles in ribs may have difficulty maintaining chest wall, moving ribs
  - If muscles are not expanding lungs/giving lungs room in chest to expand
- Dysychrony (sp?) is when diaphragm and ribs don't expand together

- Other impact of NM
  - Sigh decreased
  - Decreased ambulation—less deep breathing, moving mucociliary ladder
  - Ineffective cough
- Cough mechanics
  - Inspiratory phase
    - Expands lungs to 60=90% capacity
  - Compressive phase voice box closes chest wall muscles increase pressue chest/lungs
  - Expulsive phase airway opens high flow pushed by increased pressue and moves secretions from airways
- NM weakness
  - Good news: tremendous redundancy in lungs
  - First sings of borderline respiratory status occur
    - During illness
    - Recurrent pneumonias
    - Prolonged frequent colds (longer than 3-4 days to a week)
    - Difficult tolerating illnesses/clearing cold on own (end up in ER/antibiotics)
    - While sleeping
    - Persistent nighttime cough
    - Restless sleep, awakenings (brain wakes you when levels get low)
    - Morning headaches (gone in 45 min…awake, gasses normalize)

        - Behavioral changes/fatigue
- Evalution of lung function
    - PFT—Pulmonary Function Tests
        - Forced exhalation
        - Lung volumes
    - Respiratory muscle strength
    - **Peak cough flow—expanding into pediatrics; used in adults
        - Mda recommends measuring Peak Cough Flow annually, but what to do with numbers w/out age norms?
    - Sleep study
    - Occasionally blood work
- Interventions
    - All therapies impact lifestyle
        - Time effort expense etc
        - It's a personal decision to determine best care plan
    - Immunizations (flu, aap schedule)
    - Pt—maintain flexibility of chest wall, spine
- Mucus mobilization
    - Manual chest percussion with postural drainage
    - Vest
    - Intrapulmonary percussive ventilation IPV pulses of high frequency air and shears mucus off airways so it can move out
    - Positive airway pressure (cpap, plpap, ventilator)—easier to clear secretions through a larger airway
- Decrease mucus viscosity w/meds—not proven to help w/ muscle weakness
    - Pulmozyme DNAse used in cp it's inhaled medication will help if secretions have white cells in sputum only
    - Hypertonic saline--breathe in salt (saline) in nebulizer; water goes where salt is in lungs and clears secretions…so saline nebs might be good?
- Sigh and cough assistance
    - Inspiratory
        - Simulate sighs and augment cough
        - Breathstacking
        - Glossopharyngeal breathing
        - Manual inflation (mask/ventilator)
    - Expiratory
        - Manually assisted cough—pressure on chest w/patient's cough
        - Exsufflation (negative pressure assistance)
    - Both—Cough Assist
- Respiratory asst
    - Cpap beneficial when obstructive sleep apnea
        - Increase airway diameter and mobilizing secretions
    - Bipap
        - Rests respiratory muscles
        - Improves nighttime breathing effectiveness
        - Increase airway diameter and mobilizing secretions
    - Machines are getting smaller and quieter and less invasive every year; better masks

- 24 hour respiratory assistance
    - mpv—mouthpiece ventilation
    - non-invasive intermittent daytime support
    - sip ventilator
        - in conjunction with nighttime bipap
- trach and full ventilation
    - vents smaller and more portable every year…size of large tax book
- finding a pulmo advice
- when?
    - Establish PFT baseline age 4-6 years
    - Using a wheelchair or airway clearance device
    - Decreased pfts (<80%)
    - Before surgery (weeks to months before)
- Symptoms indicating you should see a pulmo
    - Recurrent pneumonia
    - Prolonged, frequents, colds
    - Difficult tolerating illnesses
    - Persistent nighttime cough
    - Restless sleep, awakenings
    - Morning headaches
    - Behavioral changes/fatigue
- Info out there best on Duchenne's patients
- Age to start when they can cooperate with pfts
- Anesthesia complications and surgical stuff – want pulmo status to be good before surgery
    - See pulmo before surgery with time to intervene before surgery
    - Otherwise, only point would be to say "go or no go" for surgery
- Which pulmo?
    - Someone you trust
    - Experience caring for patients with nm disease
    - Resources to support and counsel patients with various levels of resp assistance (cpap, vent, etc)
    - Large multispecialty tertiary care facility may be a starting point, but not always best match…
    - Mda.org
    - ALSA.org—has lots of pulmo info
- Cough study update
    - Getting ready to publish…
    - Goal: Objective measure when someone is most at risk for frequent chest infections
    - Result: People in study were too healthy!

Dr. David Spiegel, orthopod CHOP

How do we make informed decisions about orthopedic issues?

- Extrapolate using knowledge of natural history of disease and treatment results in similar (and dissimilar) conditions
- Definition of contracture

    - Contractures are the chronic loss of joint motion due to structural changes in non-bony tissue. These non-bony tissues include muscles, ligaments, and tendons.
- Why do they occur?
    - Muscle imbalance
    - Spasticity
    - Immobilization or disuse
    - Traumatic damage to a joint
- Etiology of contracture:
    - Inside joint
        - Fracture
        - arthrogryposis
    - Outside joint
        - No underlying disease process
        - Trauma, burns
        - Example, Splints too tight—muscle dies
    - Associated with other conditions
        - Flaccid weakness or paralysis (polio, sma, md)
        - Spasticity (CP)
        - Other (myelodysplasia, arthrogryposis)
- Natural history of the disease process:
    - Static or progressive? Will they get worse?
    - Functional status:
        - Ambulatory vs. nonambulary?
- Goals of treatment:
    - Ambulatory
        - Maximize efficiency of gait
    - Non ambulatory
        - Comfortable sitting
        - Straight spine over a level pelvis
    - Challenges: Achieve and maintain range of motion
- Non-surgical: stretching, serial casting, etc
- Surgical:
    - Soft tissue:
        - Muscle lengthening IF reason is muscle is short—but take care if muscle is functional to lengthen, not release
        - Release if muscle is non-functional
    - Bony—realign bone
    - Flaccid
        - Sma
        - Polio
        - NM
    - Spastic
        - Cp
        - Traumatic brain injury
    - Other
        - Post traumatic burns
        - Arthrogryposis

    - Ullrich lies somewhere between "flaccid and other"—still figuring out best way to deal with contractures b/c they are different than these other conditions/categories
- Contractures in ullrich/bethlem summary:
    - Proximal, typically (Meredith's note: what about fingers? Heel cords?)
    - Focus on functional consequences
    - Individualized treatment
- Nonoperative vs. operative
    - Example: Simon's elbows
        - 60/70 degree contractures
        - getting a few degrees worse each year
        - doesn't impact what Simon can do
        - (Meredith's note: so no reason to release them and it may take away function!)
- hip dysplasia, subluxation or dislocation
    - sublux—not all the way out
    - dislocated—all the way out
- what to do matters depending on disease process
- look at consequences, function
    - ambulators:
        - instability—hip piston is off
        - weakness
        - leg length discrepancy
    - non-ambulators
        - pelvic not level, relationship with scoliosis
    - symptoms…PAIN
- surgical treatment of hip
    - goal
        - restore normal anatomy
        - improve motion
    - reconstructive (keep hip in)
        - soft tissue release
        - open reduction
        - osteotomy
    - salvage (painful dislocated hip)
        - resection
        - osteotomy
    - Pain from hip tends to be from CP only
- indications for surgical relocation
    - developmental dysplasia
        - unilateral < 7-8years
        - bilateral < 5-6years
            - will do surgery up to the ages above
    - flaccid diseases sma dmd polio
        - no—treat only if symptomatic because hip tends to come out again anyway
        - if you don't have functional, active muscles around hip, hip won't stay in
    - myelodysplasia (spina bifida)
        - if one side and are walkers—surgery indicated
    - spastic (cp)

- more aggressive with surgery with CP

Dr. Carsten Bonnemann
(Meredith's note: sorry…got back from snack late and missed the first few minutes!)

- On muscle biopsy in childhood, muscle fibers shrink (Meredith's note: meaning you see muscle fibers of different sizes from normal to small)…later if you do muscle biopsy on older (adult?) muscle fibers look like a dystrophy
- BM/UCMD something not quite right w/extra cellular matrix b/c of col6 problem
- Making dx of BM/UCMD
  - clinical picture most important—then do appropriate testing
  - can go to genetic testing now that test is avail in Utah
  - skin and muscle biopsy, (esp to confirm if genetic testing is negative, unavailable)
- To make col6, you need three genes to make the three parts of the col6 molecule
  - collagen genes on gene 2 and 21
- recessive mutations will knock out protein in affected gene
  - so no col6 is made by the body, severe situation
- dominant mutations—mutation causes problems with assembly with col6
  - the col 6 is made, but abnormal
  - "dominant negative mechanism"
- how could we treat BM/UCMD
  - 1) replace muscle cells—stem cell therapy
    - replace collagen VI in the recessive case—gene replacement tx only if no col6 to start with
  - 2) get rid of bad/mutant protein in the dominant negative case
    - leaves the normal copy and it's ok
  - 3) protect muscles cells from death and atrophy
  - stem cells very far from clinical practice
    - works in dish, but how do you make it good enough to work on muscles of body?
  - Replace col6 gene therapy uses virus that knows which cell to go to (cells in extracellular matrix)
    - How do we get rid of mutant protein? In lab—in dish—design molecular prob that only recognizes only the mutant col6, so the mutant col6 is degraded, leaving the normal col6 behind
    - Treat cells w/mutant protein in the dish w/ probe siRNA—normal col 6 reappears…in dish.
  - Muscle cells that do not have normal col6 around them may undergo premature cell death, apoptosis (programmed cell death)
    - If cell isn't in right place or behaving properly, cell programmed to die or it becomes cancerous
    - Apoptosis programmed by mitochondria—if cell death pathway is "turned on" by chemicals in cell, mitochondria leaks stuff that tells cell to die
    - Can you tell mitochondria to stay shut even though survival factors are not present in the cell?
- Cyclosporin A given to a few BM/UCMD patients
  - muscle biopsies before and after 4 weeks of tx
  - showed increase in muscle from tx
  - Study published in 2008
- Two versions of cyclosporin that can be used that are less toxic:

    - Debio 0027 (Debiopharm—drug co.)
    - Omigapil (Santhera—drug co.)
- Works well in animal model
- Santhera developing Omigapil into clinical trials
    - Novartis owns drug, tested in other disease (parkinson's?) without effect on disease, gave up
    - Study hasn't applied to FDA yet…
    - Only helps if people get stronger on it…study will look at FVC and muscle myometry to measure effect

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Dr. Ann Rutkowski from CA

Dr and mom of cmd kid, Maya age 10
Vp of Cure CMD

- Advocacy
    - Md care act reauthorized—includes cmd
    - Stipuates that NIH has to fund MD research
    - Cmd representation at MDCC—annual meeting re: MD research
    - Incorporate Cure CMD goal to focus attention, research
    - Collaboration with Parent Project MD and Myotonic Dystrophy Foundation
    - Meeting in LA in sept—signs and symptoms for CDC poster for ped offices!!!!
- 2009 goals
    - cmd patient registery
    - host int'l cmd therapeutic target conference
    - plan an all inclusive cmd family conference
    - establish a scientific advisory board, peer review process
    - raise funds for research grants
- partners mda, nih, dr. bonnemann, Indiana university
- sign up for registry on cure cmd website once its set up
- PTC therapeutics in NJ trailing drug for CF and DMD w/mutation with stop codon/nonsense (?) mutation
- P Bernardi: cyclosporine open pilot trial in 6 people with UCMD, doubling of muscle bulk on muscle biopsy-2008 study

- What is worst thing that has happened to you?
    - Diagnostic odyssey
    - Variability in medical care and knowledge
    - Lack of treatments to slow your disease progression
    - Dealing with child's disability
    - Dealing with insurance/state for resources
- After sma, cmds are most common NM in early childhood

Process of becoming an adult

Simon and Alan Tuttle, MSW (with some added input from Margaret as well!)

Simon

- Applied to two colleges—Penn State and Villanova
    - met w/ disability advisors--Penn State too far and not very accessible
- Villanova
    - disabled asian great for affirmative action! Oh, and smart, too!
    - gave scholarship for "underrepresented student"—paid for tuition
- Lived on campus in dorm
- Simon's advice: Don't let it hold you back—it's a part of you, not all of you
- Aide freshman year
    - Soph to senior years--brother helped him
- State agency aide jevs, liberty resources
- OVR helped with aide (office of vocational rehab)
    - Margaret
        - CA has in-home support services helps pay for personal care services
        - CA Dept of rehab helps w/ equipment to go to school
- A lot of universities have pca's – other students.
- Simon—now an environmental compliance engineer
- Transition resources in handouts
- Susan—Alex's mom—attended transition conference PATTAN at Penn State
    - PA Youth Leadership Network great booklet
        - "Toolkit for transition" starts in middle school!
    - "Transition Health Care checklist" from PA Dept of Healthcare
- sharedwork.org should have conference info