

Lumbar to Sacral Nerve Rerouting to Restore Voiding and Bowel Function in Spina Bifida

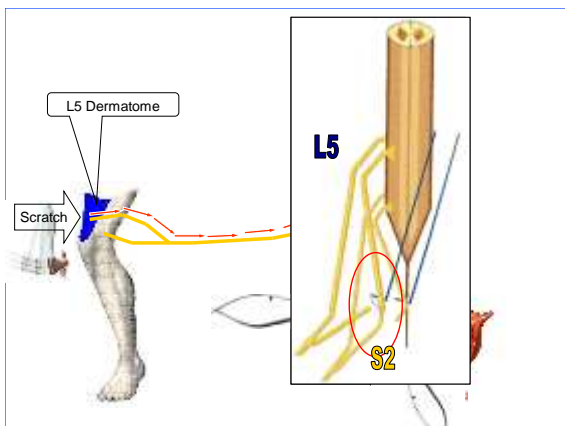
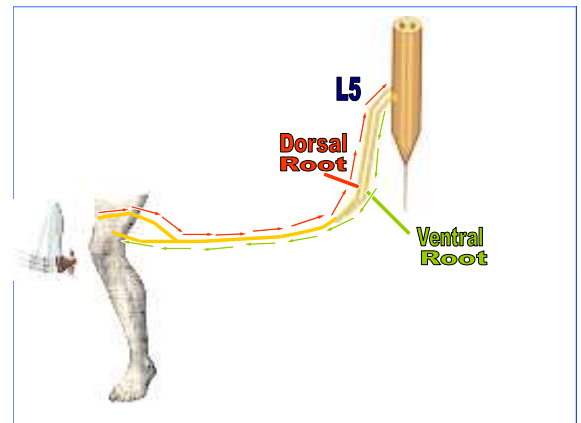
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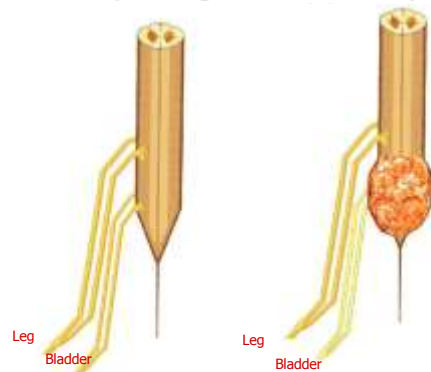
Disclosures

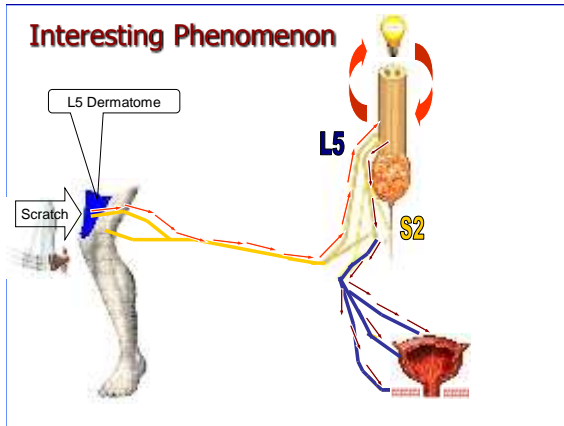
- No relevant financial disclosures

Background



Expanding the Xiao Concept to





History of Nerve Bridging

- The idea of replacing injured nerves with new nerves to improve organ function is not a new idea
 - Flourens, (*Ann des Sci Naturelles*, 3: 113, 1828) showed that the central end of one transected nerve could make functional union with the peripheral end of another nerve.
 - Many other studies (1880-1900) showed that the central end of any nerve supplying skeletal muscle or skin can make functional connections with the peripheral end of any other similar nerve.
- Cross union of different kinds of nerves (Langley and Anderson, *J. Physiology* 1904)
 - Cholinergic motor axons to striated muscle can make connections to autonomic ganglia innervating visceral organs.
 - Cholinergic preganglionic autonomic nerves can make connections to striated muscle.
 - Motor axons to striated muscle do not make functional connections with postganglionic autonomic nerves or smooth muscle.
 - Conclusion: peripheral nerves have an "attractive chemostatic influence" exerted by "nerve substances" on central outgrowing nerve fibers. These substances promote cross union between autonomic and somatic nerves.

Courtesy of Chet DeGroat, Ph.D.

History of Bladder Reinnervation

- Following the Langley and Andersson publication, Kilvington (1907) proposed that the neurogenic urinary bladder might be reinnervated by somatic nerves to improve function. Attempted in one patient but failed.
- During the past century, numerous studies have been conducted in animals and humans to evaluate the possible functional consequences of bladder reinnervation using somatic-autonomic nerve cross union (or nerve rerouting)
 - Trumble, Puusepp, Chiasserini, 1920-1930's
 - Sundin and coworkers (1960-1980's)
 - Vorstman and coworkers (1980's) (E. Virginia Med School)
 - Xiao and coworkers, USA and China, 1990-2010 (E. Virginia Med School)
 - Multiple groups (USA: Michigan, Pennsylvania, Florida, Louisiana; China, Germany, Philippines) have begun to evaluate the "Xiao technique" for bladder reinnervation in animal and clinical studies during the past three years.

Courtesy of Chet DeGroat, Ph.D.

Human Studies

- Kilvington (1907) one paraplegic patient
 - Attempted thoracic to dorsal root anastomosis, but surgery failed
- Frazier and Mills (1912) one paraplegic patient
 - Lumbar 1 to S3-S4 ventral root
 - Bladder function recovered but appeared too early to be due to reinnervation
- Puusepp (1923) one paraplegic patient
 - Thoracic 12 to multiple cauda equina nerves
 - Early recovery of bladder function – unlikely to be due to reinnervation
- Chiasserini (1935) four paraplegic patients
 - Intercostal nerves to multiple cauda equina nerves
 - Early recovery of bladder function – unlikely to be due to reinnervation
- Carlsson and Sundin (1967) spina bifida patient, 4 years old
 - Thoracic 10-11 ventral roots to S1-S2 ventral roots
 - Eight months recovery – reflex micturition and bladder sensation appeared
- Carlsson and Sundin (1980) paraplegic patients
 - Thoracic 12 ventral roots to S2-S3 ventral roots
 - Two of six patients – reflex between contractions occurred during CMGs but DSD interfered with voiding requiring external sphincterotomy
- Xiao et al. (2003) 15 paraplegic patients
 - Lumbar 5 ventral root to S2-S3 ventral roots
 - Prior to surgery patients exhibited NDO and DSD
 - 12-18 months post surgery 10 of 15 patients regained "satisfactory bladder control" including decreased residual volume (332 -> 31 ml), decreased infection, reduced DSD and NDO
 - Stimulation of the skin of the leg induced reflex, bladder contractions and voiding
- Xiao et al. (2005) 20 patients spina bifida; 14 had areflexic bladders; 6 had NDO and DSD
 - Lumbar ventral root to S3 ventral root
 - 17 of 20 patients gained satisfactory bladder control

Courtesy of Chet DeGroat, Ph.D.

Xiao Animal Studies

- Bench to Bedside
 - Rat Studies – Late 1980s
 - L4 to L6 Anastomosis
 - Bladder contraction with electrical stimulation
 - Neural Tracing (HRP)
 - Somatic motor axons regenerated successfully into the pelvic nerve
 - Bladder was reinnervated by the L4 motor neurons
 - New concept: the impulse delivered by the efferent neurons of a somatic reflex arc can be transferred to initiate responses of an autonomic effector

Courtesy of Chet DeGroat, Ph.D.

Xiao Animal Studies

- Bench to Bedside
 - Higher animal experiments:
 - Continued experiments focused on the underlying mechanism of the somatic-autonomic reflex pathway for micturition
 - Pharmacological studies:
 - New nerve pathway mediated by cholinergic transmission
 - Nicotinic and Muscarinic Receptors
 - Because the same neurotransmitter is released, somatic reflex activity can be transferred to the bladder smooth muscle and cause a detrusor contraction
 - Can induce reflex in intact animal and after acute spinal cord injury

Courtesy of Chet DeGroat, Ph.D.

Xiao Human Studies – Spinal Cord Injury

- Spinal Cord Injury – J Urology 2003
 - 15 Males – Hyperreflexic Bladder and DESD
 - 67% success
 - Synergistic Voiding

Xiao Human Studies – Spina Bifida

- Spina Bifida – J Urology 2005
 - 20 Children – 14 Areflexic, 6 Hyperreflexic NGB
 - 85% success
- Update – European Urology 2006
 - 92 Spinal Cord Injury, 88% success
 - 110 Spina Bifida, 87% success

Beaumont Initial Pilot Trial

- 2006- Traveled to China to visit Dr. Xiao
 - Met patients who underwent this surgery
 - Operated with Dr. Xiao doing nerve rerouting
- Believed it was important to study this procedure in a rigorous way in U.S.
- Developed a pilot study protocol funded through philanthropy
- In the first 5 months performed 11 NRR procedures (2 SCI and 9 Spina Bifida)
- Waited 1 year to do further surgery

The Beaumont Experience



Key Pilot Inclusion Criteria

- SB patients with stable neurological condition and on CIC for bladder management
- Ambulatory
- Normal Renal Function
- Stable neurogenic bladder for 1 year or more

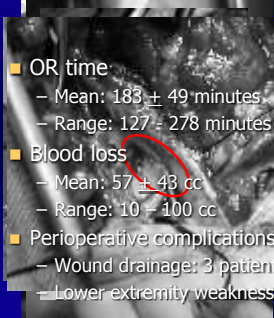
Key Pilot Exclusion Criteria

- h/o augment, radiation, bladder CA
- \geq grade 2 reflux
- AUS, SP tube, Sling, Mitrofanoff
- SB patients that underwent intrauterine closure *
- SB patients that require a walker or crutches to ambulate*

*Added after experience of first 9 patients

Beaumont Experience: Operation

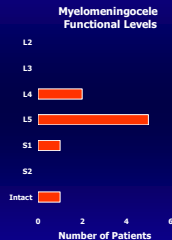
- 9 spina bifida patients treated
- Prone position
- Limited laminectomy
- Open dura
- Expose cauda equina
- Donor and recipient root identification
- End-to-end sutured anastomosis



- OR time
 - Mean: 183 ± 49 minutes
 - Range: 127 - 278 minutes
- Blood loss
 - Mean: 57 ± 48 cc
 - Range: 10 - 100 cc
- Perioperative complications
 - Wound drainage: 3 patients
 - Lower extremity weakness

Patient Characteristics

- 9 Patients
 - 3 males
 - 6 females
- Spina Bifida
- Age
 - Median: 8 years
 - Range: 6 to 37 years
- Ambulatory Status
 - AFOs: 5 patients
 - Forearm crutches: 2 patients
 - No assistance: 4 patients
- 5/9 on antimuscarinics at baseline
- 4/9 cord detethering
- 5/9 VP shunt



Published 1-year Outcomes

Outcomes of Lumbar to Sacral Nerve Rerouting For Spina Bifida

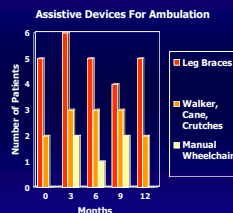
Journal of Urology, vol. 184, 702-708, August 2010

Early Outcomes

- SCI patients (n=2) no complications or improvement in symptoms over time
- Spina Bifida (n=9)
 - 1 patient with new onset foot-drop
 - 8 of 9 patients with worsening lower extremity weakness
 - Surgery much more difficult in subjects with intrauterine closure with worse weakness
 - No other significant perioperative concerns

Outcomes: Lower Extremity

- Early
 - 8/9 weak
- 1 Year
 - 8/9 at or near baseline
 - 1/9 with foot-drop

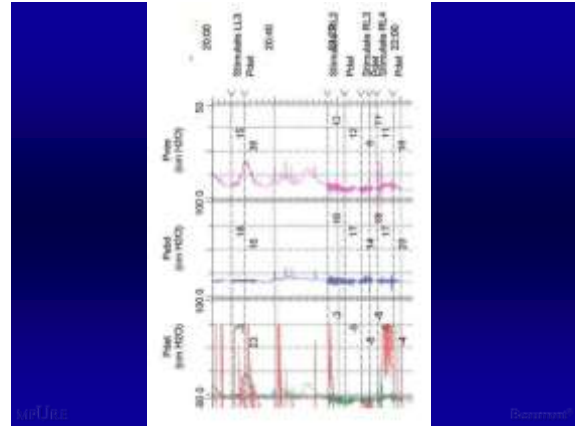
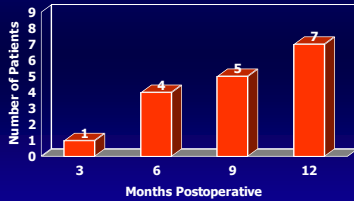


Early Outcomes

- Interesting Stories...
 - Bowel/Bladder Neurological Changes
 - Sudden Worsening of Urinary and/or Fecal Incontinence
 - Improved Continence
 - Ability to Initiate Voiding

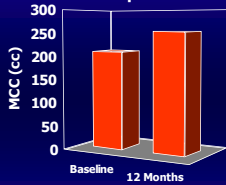
Outcomes: Bladder

Presence of Novel Reflex Arc with Stimulation



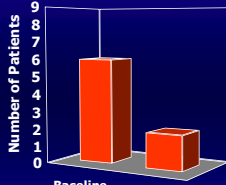
1-Year Outcomes: Bladder

Bladder Capacity (MCC) Comparison



P = 0.18

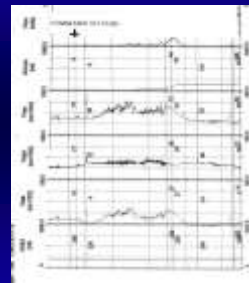
Involuntary Detrusor Contractions



P = 0.13

- Bladder Compliance improved from 16.1 to 21.8 ml/cmH20
- 2/3 subjects with bladder compliance < 10 ml/cmH20 normalized
- All subjects were able to safely stop their antimuscarinics

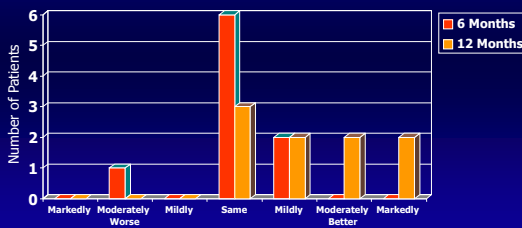
Pressure Flow Study- 12 months



- No void at baseline
- At 12 months, voiding off catheter
- Voided volume=185 cc
- PVR=15 cc
- + detrusor contraction

1- Year Outcomes: Bowel

- Baseline 1 subject continent of stool
- 12 months 4 subjects continent of stool
- Baseline 5 subjects required laxative use
- 12 months 2 subjects required laxative use



36-Month Update

- Recently finished 3 year follow-up
- 7 of 9 returned for follow-up
- 1 (37 yo male) no change in symptoms
- 2 subjects not returning considered non-responders
- Bowels improved 5/7 on GRA
- Bladder improved 4/7 on GRA
- Incontinence still problem in most
- 6/7 would undergo surgery again
- Success? Not Sure

36-Month Catheterization

- Baseline all subjects were on clean intermittent catheterization
- 36-months: 4 (5) of 7 off catheterization
 - One subject's mother had her restart ISC prior to 36-month visit due to a single UTI
 - Patient is sexually active teen with a PVR<50cc
 - Now off ISC
- 1 subject catheterizes only 1 x/day
- 1 subject (37 year old male) had no change in bladder from surgery and on ISC

Voiding

Void Diary

- Baseline 2/9 voided some
 - Mean voided volume 27cc
- 36-month 6/7 voided (without scratching)
 - Mean voided volume 156cc

Uroflow-36 Month n=6 (37 yo male could not void)

- Mean voided volume: 248 cc (without scratching)
- Mean PVR: 93 cc
- Voiding efficiency: 73%

Voiding Pattern at 36 Months

- 6/7 leak urine, all with stress incontinence
- 2/7 occasionally start stream by thinking
- 1/7 no valsalva to void, 4 /7 valsalva void greater than 1/2 time and 1/7 valsalva void always
- Urine stream described as: Strong-2, Weak-3 and dribble in 2
- Daytime continence: 1-dry, 3 occasional leak and 3 frequent leak
- Sensation of bladder fullness: Yes-7, No-0
- Improvement in bladder sensation: Yes-4, No-3

3-year Compliance Data (n=7)

- Median compliance 15.2 ml/cmH2O baseline vs 28.4 ml/cmH2O at 36 months
- 3 children had compliance less than 10 at baseline:
 - All normalized at 36 months
 - 7.0 → 34.3
 - 9.4 → 21.2
 - 8.3 → 28.4

3- year Bladder MCC and NDO (n=7)

- Baseline MCC: Mean=210 cc; Median=200 cc
- 36-month MCC: Mean=293 cc; Median=316 cc
 - *Children are 3-years older
- Baseline: 4/7 had NDO on UDT
- 36-month: 1/7 had NDO on UDT*
 - All patients off Antimuscarinics except 1*

*persistent DO-37 year old male

Bowel Continence

N=7	Daytime		Nighttime	
	Baseline	36-month	Baseline	36-month
Perfect	0	1	3	5
Leak Gas	1	3	2	1
Occ. Liquid Leak	2	2	0	0
Freq Liquid Leak	0	0	2	1
Occ. Solid Leak	3	1	0	0
Freq. Solid Leak	1	0	0	0

Bowel Data

N=7

	Baseline	36-months
Considers BM Normal	3/7	6/7
Time for BM < 30 Minutes	4/7	6/7
Laxative Use	4/7	2/7
Enema Use	3/7	2/7

Reflex

- By 12 months 7/9 had cutaneous to bladder reflex defined as at least a 10 cm/H2O pressure rise with stimulating dermatome on side of surgery (range 11-30 cm/H2O)
- At 36 months only ONE had reflex remaining and much weaker than earlier
- ? Suppression of reflex by CNS

Adverse Events

- No new long-term adverse events
- Stable renal function
- Stable renal ultrasounds

UPDATE

- 2009 added Holly Gilmer, MD a pediatric neurosurgeon as part of our team
- Dr. Xiao returned to Beaumont and proctored Dr. Gilmer on the rerouting procedure on 4 children with SB
- Transient weakness, no foot drop
- 2 subjects had dural leak
- At 1 year, 2/4 off catheter and meds

Conclusions

- Neurogenic bladder and bowel remains a significant clinical challenge
- Developed countries with adequate resources can often manage the patient with CIC and medications thus preventing significant infections, renal failure and death
- The concept of nerve rerouting to restore bladder and bowel function was popularized by CG Xiao from China

Conclusions

- Successful reinnervation of the bladder and bowel may not only improve QOL but also be life-saving in countries where catheterization and/or antimuscarinics are not readily available or affordable
- In the spina bifida population, our pilot trial demonstrated 6/9 (66%) had clinical improvement at 36 months
- A risk of lower extremity weakness is evident in that 1/9 subjects had a permanent foot-drop
- No other long-term adverse events were identified

Conclusions

- Defining clinical success is a difficult challenge in a disease state that impacts many aspects of bladder and bowel function
- In this study, stress incontinence remained a problem, although NDO and antimuscarinic use were reduced
- We feel strongly that multicenter clinical trials are needed to determine the utility of nerve rerouting in the neurogenic patient
- We should better define the ideal patient population, refine the surgical procedure, improve the evaluation of the urinary and bowel sphincters and assess quality of life



Special Thanks to:



- CG Xiao, MD - Nerve Rerouting Pioneer
- Benjamin Girdler, MD-Resident
- Kevin Feber, MD and Evan Kass, MD-Pediatric Urology
- Holly Gimer, MD
- William Nantau- Clinical Neurophysiology
- Gary Trock MD-Neurology
- Cindy Turzewski – Study Coordinator
- Our Patients



Questions?

