Attempted bladder reinnervation and creation of a scratch reflex for bladder emptying through a somatic-to-autonomic intradural anastomosis

Case report

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An intradural somatic-to-autonomic anastomosis, or Xiao procedure, has been described to create a “skin-CNS-bladder” reflex that improves bladder and bowel function in patients with neurogenic bladder and bowel dysfunction. The authors present their experience with a 10-year-old boy with chronic neurogenic bladder and bowel dysfunction related to spinal cord injury who underwent the Xiao procedure. After undergoing a left L-5 ventral root to left S2–3 intradural anastomosis, the patient reported that his bladder and bowel dysfunction improved between 6 and 12 months. Two years after the procedure, however, he reported that there was no change in his bladder or bowel dysfunction as compared with his condition prior to the procedure. Frequent, systematic multidisciplinary evaluations produced conflicting data.

Electrophysiological and histological evaluation of the previously performed anastomosis during surgical reexploration 3 years after the Xiao procedure revealed that the anastomosis was in anatomical continuity but neuroma formation had prevented reinnervation. Nerve action potentials were not demonstrable across the anastomosis, and stimulation of the nerve above and below the anastomosis created no bladder or perineal contractions.

This is the first clinical report on the outcome of the Xiao procedure in a child with spinal cord injury outside of China. It is impossible to draw broad conclusions about the efficacy of the procedure based on a single patient with no demonstrable benefit. However, future studies should carefully interpret transient improvements in bladder function, urodynamic findings, and the patient’s ability to void in response to scratching after the Xiao procedure. The authors’ experience with the featured patient, in whom reinnervation could not be demonstrated, suggests that such changes could be related to factors other than the establishment of a skin-CNS-bladder reflex as a result of a somatic-to-autonomic anastomosis. (http://thejns.org/doi/abs/10.3171/2013.4.PEDS12302)

Key Words • spinal cord injury • neurogenic bladder • reflex • neuroma • anastomosis • Xiao procedure

Neurogenic bladder dysfunction as the result of spinal cord injury greatly impacts patient quality of life and can lead to chronic urinary tract infections, renal dysfunction, and even death.6 Multiple medical and surgical adjuncts to CIC have been explored with some success.3 Until recently, such modalities have focused on pharmacological, electrical, or mechanical mechanisms to counteract the loss of a coordinated neurological control mechanism that resides in the normal spinal cord to allow for a normal bladder-emptying mechanism.6 None of these alternative management strategies, alone or in combination, offer continence or normal voiding function for patients with neurogenic bladder.

Xiao8 has studied a mechanism for reestablishing a neurourological reflex that is absent in spinal cord malformation or injury. He describes rerouting motor portions of somatic nerves usually involved in limb function to connect directly to autonomic nerves destined to control the bladder, creating a somatic-autonomic reflex pathway that allows patients to initiate urination by scratching themselves on the part of their body usually innervated

Abbreviations used in this paper: BAM = bladder active medication; CIC = chronic intermittent catheterization; DLPP = detrusor leak point pressure; DSD = detrusor sphincter dyssynergia; UDC = uninhibited detrusor contraction.
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by the sensory portion of the somatic nerve used in the rerouting procedure (Fig. 1).6,9 Typically, the L-5 ventral motor root is sectioned and anastomosed to the S-3 nerve root intradurally. Once this “skin-CNS-bladder” reflex is functional, patients who previously had no control of their bladder function are reportedly able to initiate normal voiding by scratching themselves in the L-5 nerve root sensory distribution.5 Xiao has indicated that patients who have undergone this procedure develop a voiding mechanism that has led to a decline in urinary tract infections, improved bladder capacity and control, continence, and independence from a CIC program.1

Xiao and colleagues first established this skin-CNS-bladder reflex in experimental studies in rats12 and cats.10 A separate Chinese group performed confirmatory experiments in a canine spinal cord injury model.13 Xiao et al.11 published the first human trial of this procedure in 2003, in which 10 (67%) of 15 adults with chronic neurogenic bladder dysfunction after spinal cord injury regained satisfactory bladder control within 18 months of L-5 ventral root to S2–3 intradural anastomosis. These results were replicated in a study performed in 2009 by a separate group of Chinese investigators:4 their study similarly showed that 9 (75%) of 12 spinal cord–injured patients regained satisfactory bladder control within 12 months of the skin-CNS-bladder procedure. Recently, Xiao9 reported that this procedure has been performed in 306 patients with spinal cord injury in China, although the results were not published given difficulties with the follow-up.

To our knowledge, this report is the first published on the results of Xiao’s skin-CNS-bladder procedure performed in a child with neurogenic bladder dysfunction related to spinal cord injury outside of China.

Case Report

Background. Our aim was to replicate the Xiao procedure in spinal cord–injured patients.5,8,11 Two of the authors (G.F.T. and L.F.R.) traveled to China to learn Xiao’s patient selection method, surgical technique, and postoperative management strategy before designing a clinical trial at our institution. Based on their observations, we designed a study to offer Xiao’s somatic-to-autonomic intradural nerve anastomosis to children with neurogenic bowel and bladder dysfunction related to spinal cord injury. Institutional review board approval was obtained in February 2009.

After we obtained informed consent, the patient and his mother completed detailed questionnaires concerning bladder, bowel, erectile, motor, and sensory function. Physical therapists completed objective assessments of motor and sensory function. Urodynamic testing was performed under the supervision of one of the investigators. All evaluations were completed before and 6, 12, 18, and 24 months after surgery. All CIC and BAMs were stopped immediately after surgery, and the child remained off CIC and BAMs for the duration of the 2-year follow-up. The cessation of CIC and BAM was instituted as recommended by Xiao, as this was similar to his practice pattern with his patients in China.

A designated data and safety monitoring board closely tracked the patient’s progress for the duration of his follow-up. The patient described herein is the only patient enrolled in this protocol because of funding limitations. Clinical features described in the following sections are summarized in Table 1.

Patient History and Examination. This 10-year-old boy presented with neurogenic bowel and bladder dysfunction related to a T10–11 complete spinal cord injury that had been caused by a hemorrhagic spinal epidural neuroblastoma treated 9 years earlier. Renal failure developed as a result of the neurogenic bladder dysfunction combined with the patient’s reluctance to perform CIC. He had no motor or sensory function below T-10, and he had no control of his bowel or bladder function. Preoperative MRI showed a normal position of the conus at L1–2 and an anatomically intact spinal cord with signs of myelomalacia at T10–11 (Fig. 2).

Operation. The somatic-to-autonomic intradural anastomosis was performed under the direct supervision of C.

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Fig. 1. Diagram of the somatic-to-autonomic intradural anastomosis. Ventral motor root (S-1) anastomosed to the ventral sacral root (S-2) to create a skin-CNS-bladder reflex. Reproduced with permission from Lin et al: J Neurosurg Spine 10:452–457, 2009.
The patient's postoperative recovery was complicated by a superficial wound infection that resolved with antibiotics. He had no change in his motor or sensory function and no immediate change in his bladder or bowel function in the initial postoperative period. Over the ensuing 2 years, he remained off all CICs and BAMs without urinary tract infection or worsening of his preexistent hydronephrosis. His renal function remained poor, requiring him to continue the dialysis treatments he had received for several years prior to this surgery.

He underwent the same multidisciplinary evaluations at 6, 12, 18, and 24 months after surgery that he did before the operation. However, the neurosurgeons and urologist involved in the procedure were specifically eliminated from most of the evaluation process to minimize bias. Physical therapists participating in the study evaluated strength, sensation, and mobility. A research nurse (L.T.) administered multiple questionnaires concerning bladder, bowel, and sexual function; continence; and the presence or absence of a cutaneously triggered voiding reflex. Urodynamic testing was performed under direct supervision of the research nurse (L.T.) and often the principal investigator (G.F.T.) and/or a urologist (Y.L.H. or E.G.P.).

**Effect of Surgery on Voiding and Continence.** Prior to enrolling in this study, the patient was taking antimuscarinic medications and he intermittently catheterized his bladder. His lack of adherence to a CIC regimen contributed to his chronic renal failure. He was incontinent of urine, dribbled urine with intermittent dry episodes, had enuresis 2–3 times a week, and wore a diaper continuously.

By 6 months after surgery, he and his mother noted significant improvement in his bladder function: he could elicit a “scratch reflex” whereby he would scratch his left leg and a small amount of urine would be expelled. He believed there was a marked improvement in his ability to empty his bladder without catheters and in his overall quality of life. His dry episodes before surgery ranged from 4 to 5 hours, whereas 6 months after surgery they ranged from 2 to 7 hours. However, he was only able to void a small amount in response to scratching, and the effect was not easily reproducible when tested in the presence of study personnel (that is, sometimes he could void when he scratched and other times he could not). He was still wearing a diaper continuously, his enuresis had increased to every night, and he still considered himself incontinent.

The patient’s and his mother’s optimism at 6 months gradually waned over the ensuing 18 months. By 1 year after surgery, he was no longer able to initiate any voiding by scratching himself on either leg; he remained incontinent of urine, requiring a continuous diaper; he had frequent enuresis; and he classified his improvement in bladder function after surgery as only slight. By 2 years after surgery, he and his mother believed that he had had no improvement in bladder function since the surgery and no improvement in his quality of life as a result of the surgery; he was incontinent, in a diaper and wetting the bed every night, and he no longer had an urge to void when he

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**TABLE 1: Clinical features before and after an L-5 to S2–3 intradural anastomosis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Surgery</th>
<th>6 Mos</th>
<th>12 Mos</th>
<th>18 Mos</th>
<th>24 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>urinary incontinence</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>no. of hrs dry each day</td>
<td>4–5</td>
<td>2–7</td>
<td>0</td>
<td>1–2</td>
<td>0</td>
</tr>
<tr>
<td>urge to urinate w/o scratching</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>urge to urinate when scratching leg</td>
<td>unknown</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>wears a pull-up or diaper</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>continence of stool</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>erectile hardness scale</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>overall change in ability to empty bladder w/o catheters since surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall change in ability to control bowels since surgery</td>
<td>no change</td>
<td>moderate improvement</td>
<td>moderate improvement</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>overall change in quality of life since surgery</td>
<td>moderate improvement</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
</tr>
</tbody>
</table>
scratched his leg. He and his mother asked to terminate their involvement in the study, to return to BAMs, and to consider other options for treating his neurogenic bladder dysfunction.

Effect of Surgery on Bowel and Erectile Function. Prior to surgery, the patient had no control of his bowel function, requiring stool softeners but no fecal disimpaction. As with bladder function, the patient and his mother believed that there was some improvement in his ability to control his bowel movements by 9 months, even though he required continuous diaper use. This perceived improvement in bowel control lagged behind the effect he perceived in bladder function by a few months. However, by 24 months after surgery, he noted no change in his ability to control his bowels when compared with his preoperative state.

The patient had some ability to achieve an erection before surgery, with a maximum erectile hardness rated as 2 on a scale of 0–4.1 He noted no change in erectile function as a result of the surgery at any point during the follow-up.

Urodynamic Evaluation and Scratch Reflex. Urodynamic testing was done prior to surgery, with the patient still taking antimuscarinic medications. He had typical findings of neurogenic bladder, including a total bladder capacity of 151 ml, DSD, UDCs, and a DLPP of 37 cm H2O. Total bladder capacity gradually increased from 151 to 202 ml over the course of the study, DLPP increased from 37 to 70 cm H2O, and DSD and UDCs persisted.

Bladder contractions and voiding, with and without a urodynamic bladder catheter in place, were tested in response to deep scratching at the T-10 through S-1 dermatomes bilaterally. For each dermatomal level, the research nurse scratched the skin continuously for 1 minute with the urodynamic catheter in and out, looking for voiding and/or bladder contractions. The patient was unable to void even a few milliliters of urine, with or without the catheter in place, in response to scratching in the left L-5 sensory dermatome or at any other dermatome from T-10 to S-1 at any time in the first 2 years after the operation.
Bladder contractions were measured in response to scratching as well (Fig. 4). At the 6-month interval, when the patient believed he might be able to urinate in response to scratching the left L-5 dermatome, he was found to have bladder contractions > 15 cm H2O in response to scratching in the right L-5 dermatomal distribution but not on the left (surgical) side. By 12 months after surgery, he had contractions > 15 cm H2O in response to scratching in the left L-5 dermatome (surgical side) but not in the contralateral L-5 distribution. By 18 and 24 months after surgery, his bladder contracted enough to raise pressure > 15 cm H2O when scratching on the control side (right L-5 dermatome) but not on the surgical side (left L-5).

Findings at Surgical Reexploration: Anatomy, Electrophysiology, and Histology. By 3 years after the surgery, the urologist and nephrologist caring for the child believed that he would benefit from a renal transplant and that the somatic-to-autonomic nerve transfer procedure did not adequately improve bladder volumes or pressures to allow the child to undergo a renal transplant. He then underwent urodynamic testing before and during induction of a caudal anesthetic to simulate the effects of sacral rhizotomy. These tests showed that bladder capacity increased (220 to 367 ml) and that DSD and UDCs resolved with the induction of caudal anesthesia. After considering various options, such as bladder augmentation with Mitrofanoff stoma, the child and his mother elected sacral rhizotomy as a possible measure to improve bladder volume. This procedure had proven effective for other patients and has been described by one of the authors (B.B.S.)2,7

At the time of selective sacral rhizotomy, the previously performed left L-5 to left S2–3 anastomosis was identified and found to be in anatomical continuity with expected scar tissue surrounding the nerve. Electrical stimulation of the nerve above and below the anastomosis produced no contractions of the bladder as measured by a bladder wall electrode placed through a suprapubic incision. Nerve action potentials were similarly not measurable across the anastomosis (Fig. 3 lower). Because the patient had had no clinical benefit from the anastomosis, because no electrical conduction could be demonstrated across the anastomosis, and because there were no measurable contractions of the bladder when electrically stimulating above and below the anastomosis, the nerve was sectioned above and below the anastomosis. Microscopy using standard H & E staining combined with neurofilament and S100 staining revealed neuroma formation at the anastomotic site, with very few axons (fewer than 1%) crossing the anastomotic site (Fig. 5).

At 2 months after sacral rhizotomy, the child’s bladder capacity was approximately 200 ml—not significantly different from his capacity prior to sacral rhizotomy. However, his DLPP was significantly decreased (23 vs 37 cm H2O), and DSD and UDCs were markedly reduced compared with his state prior to sacral rhizotomy.

Discussion

This report describes the outcome of the Xiao procedure in only 1 patient. We believe this is the first peer-reviewed published report concerning the use of this procedure in a spinal cord–injured child outside of China. In addition, we believe this is the first description of intraoperative electrophysiological testing and histological analysis performed after the procedure in a human.

The spinal cord–injured patient described here had no subjective or objective improvement in bowel or bladder function when assessed 2 years after the Xiao procedure. In addition, intraoperative electrophysiological testing and histological examination of the anastomosis 3 years after the experimental surgery confirmed that there was no electrophysiological reinnervation and negligible growth of axons across the anastomosis.

Failure of the procedure in this patient could simply be related to chance considering that previous reports have documented significant improvement in approximately 70% of 27 Chinese patients with spinal cord injury in whom the procedure was performed; their results have been reported in peer-reviewed publications.5,11 Technical variations do not explain the difference because we went to great lengths to replicate Dr. Xiao’s technique precisely—not only by observing his performance of the procedure in China, but also by having him present in the operating room at All Children’s Hospital, carefully
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instructing us every step of the way so that we performed the operation to his specifications. Our choice of a ventral L-5 root as the donor root and S2–3 as the recipients was also supervised by Dr. Xiao, as described in his previous publication. Lin et al. chose an S-1 to S-2 anastomosis instead. Note that Xiao and other authors have not closely defined patient selection criteria, so there may be some question about the appropriateness of our choice to enroll a patient with a complete spinal cord injury with myelomalacia a few segments above the conus.

Despite the ultimate failure of the procedure, the patient and the physicians caring for him saw some encouraging results early in his follow-up. He was able to stay off all CIC and BAMs throughout the study period without a detrimental effect on his hydronephrosis. Whether this would have been possible without the procedure is not known because he had been on sporadic CIC and BAMs continuously for many years prior to the Xiao procedure.

Interestingly, between approximately 6 and 12 months after surgery, the patient and his mother believed that he was able to initiate voiding by scratching. Physicians and nurses involved in his care were unable to replicate this response during their evaluations and after 18 months the patient was no longer able to void after scratching. Urodynamic investigations produced contradictory results as well. Six months after surgery, contractions of 15 cm H2O were produced with scratching in the right L-5 dermatomes (control side), by 12 months bladder contractions only occurred with stimulation on the surgical side (left L-5), and by 18 and 24 months contractions were only produced when scratching the L-5 dermatome contralateral to the surgical side. Unfortunately, we did not test for contractions in response to scratching before the surgical procedure was performed, based on the assumptions of the urologists that scratching someone’s leg would not normally produce a bladder contraction of 15 cm H2O. To our knowledge, no data are available about the contractility of the bladder in response to extremity scratching in the presence or absence of spinal cord injury.

Without the unique electrophysiological and histological analysis of the tissue from the patient, one could attribute the transient improvements the patient and his caregivers witnessed during the 6- to 12-month intervals to reinnervation followed by decline. However, we have demonstrated that neuroma formed at the anastomosis and that only minimal axonal sprouting occurred. With this knowledge, we believe the transient effects can be explained by either the effect of sacral nerve sectioning and/or the placebo effect for the patient, his family, and the team caring for him. Some have hypothesized that rein-

Fig. 5. Histological analysis of anastomosis 3 years after the Xiao procedure. A: Oblique anastomotic site with a central area of caliber narrowing. H & E, original magnification ×2.5. B: Anastomotic site with marked irregular interstitial fibrosis and disorganized nerve fascicles. H & E, original magnification ×5. C: Neurofilament immunostaining showing few traversing axons across the anastomotic site. Original magnification ×10. D: Axonal disorganization at the anastomotic site is highlighted by Schwann cell staining with S100 protein. Original magnification ×10.
nervation might have occurred in the 1st year but then regressed after neuroma formation. To our knowledge, the scenario of reinnervation followed by neuroma formation and innervation reversal has not been described, making this possibility unlikely in our opinion.

It is not prudent for us to draw broad conclusions about the effectiveness of the Xiao procedure based on our experience with this single patient with spinal cord injury. Further studies are ongoing around the world, and clinical results should be forthcoming in the next several years. However, our experience with this patient, in whom there was histological and electrophysiological confirmation that reinnervation did not occur, provides context for the interpretation of future results. Based on our findings, it is clear that the patient’s subjective improvement in bladder and bowel control, the demonstration of a bladder scratch reflex by urodynamics, and his ability to remain off CIC and BAMS was not related to reinnervation through a somatic-to-autonomic reflex. Whether these changes were related to the placebo effect, from patient maturation, or a result of sectioning nerve roots of the cauda equina are issues that should be considered and addressed in future studies related to this procedure.

Conclusions

The Xiao procedure performed in a 10-year-old boy with chronic neurogenic bladder and bowel dysfunction did not result in enduring, meaningful improvements in bladder and bowel function, and the child was unable to consistently initiate voiding through a skin-CNS-bladder reflex. Reexploration of the anastomosed nerves 3 years after the Xiao procedure showed neuroma formation. The child did have transient clinical and urodynamic changes, which may be attributable to factors other than reinnervation.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Tuite, Homsy, Reilly, Rodriguez, Perlman. Acquisition of data: Tuite, Storrs, Homsy, Gaskill, Polsky, Reilly, Gonzalez-Gomez, Winesett, Carey, Perlman, Tetreault. Analysis and interpretation of data: Tuite, Storrs, Homsy, Polsky, Reilly, Gonzalez-Gomez, Winesett. Drafting the article: Tuite. Critically revising the article: Tuite, Storrs, Homsy, Gaskill, Polsky, Reilly, Gonzalez-Gomez, Winesett, Carey, Perlman, Tetreault. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Tuite. Study supervision: Tuite. Principal investigator on IRB: Tuite.

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References