basic risk factors of CV disease, providing a unique opportunity to control all of the side-effect issues in one daily pill.

Will SERMs be systematically associated with ADT in a new-age maximal androgen blockade, optimized not for efficiency but for side effects? This is unclear. First, the increase in CV disease and the risk of fragility fracture remain low, albeit consistent, across studies. In the studies referenced in the AHA–AUA statement, the additional risk of experiencing a CV event is approximately 5%, and there is no consensus about whether it increases CV death [2]. In the toremifene trials, the risk of new vertebral fracture in the placebo group is 4.9% at 2 yr; in the denosumab trial, it is 3.9% at 3 yr [1,4]. Consequently, the risks and the benefits may be questioned. Objectively, toremifene reduces the risk of any fracture by 3.8% but increases the risk of VTE by 1.3%, a risk–benefit ratio of 3:1. Is it worth it to trade one toxicity for another?

Before embarking our patients on these treatments, we must stand strong against the hype and require more detailed analysis to select a population at higher risk of developing these side effects and therefore to improve the therapeutic index. Alibhai et al's epidemiologic survey confirms that the risk is not constant in all patients and that risk criteria exist, leaving room for better selective use of these agents.

Conflicts of interest: The author has nothing to disclose.

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Re: Outcomes of Lumbar to Sacral Nerve Rerouting for Spina Bifida

Peters KM, Girdler B, Turzewski C, et al

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Expert's summary:

Xiao reported an 87% success rate for regaining bladder control after lumbar to sacral nerve rerouting in spina bifida children in China [1]. The paper by Peters et al reports a US prospective study of nine cases that were operated with the aid of Xiao and thoroughly followed up over 1 yr. Although seven of nine patients were able to increase bladder pressure by cutaneous stimulation of the respective lumbar dermatome, only two patients were able to stop catheterization and no patient achieved complete urinary continence. Bowel function, however, was improved in the majority of patients. Eight of nine patients had initial weakness of lower-extremity muscles after lumbar ventral spinal root transection, and in one child, foot drop was persistent at 12 mo.

The authors conclude that despite the proof of principle that bladder contractions after lumbar to sacral nerve rerouting can be elicited and reproduced, the clinical validity for restoration of urinary continence and micturition was lower than previously published by Xiao [1]. Peters et al suggest that the procedure should be reserved only for research protocols with rigorous analysis of the risk–benefit ratio.

Expert's comments:

Surgical cross-innervation, an intriguing concept for bypassing damaged spinal cord segments, was applied by Xiao in 92 spinal cord injury patients, of whom 88% regained bladder control 1 yr postoperatively, and later on in 110 children with spina bifida, with an 87% success rate after 1 yr [1]. The concept of the surgery is to establish a new reflex arc of "skin–central nervous system–bladder" by transecting an intact lumbar ventral spinal root (usually L4 or L5) above the level of the spinal cord lesion and anastomosing it to a transected sacral ventral spinal root (usually S2 or S3) affected from or below the spinal cord lesion. The respective dorsal lumbar spinal root, where the ventral lumbar spinal root is transected, is left intact. After reinnervation, the patient is able to stimulate the reinnervated sacral nerve and elicit a bladder contraction by scratching the skin of the respective lumbar dermatome. This has been done in hyperreflexive neurogenic bladders ("decentralized" with an intact but out of control sacral reflex arc) with detrusor–sphincter dyssynergia (DSD) and in areflexive bladders in which a sacral lesion had compromised the sacral reflex arc.

The neuroanatomic foundation and the effects of this type of surgical cross-innervation raise several concerns.

Neuroanatomy

The lumbar ventral spinal roots, one of which is used in this procedure as donor, are mixed nerves with predominant somatic and some autonomic (sympathetic and parasympathetic) outflow. Transection thus affects the somatic end organs of L4/L5, so respective lower-extremity muscle weakness is to be expected.

The sacral ventral spinal roots, one of which is used in this procedure as recipient, are also mixed nerves with somatic and autonomic outflow. In humans, S2 has a

predominant somatic component (eg, innervating pelvic floor muscles) and S3 has a predominant autonomic component comprising the parasympathetic outflow to bladder and bowel, but it also has a somatic component. Bladder innervation arises from the sacral segments S2–S5 with predominance of S3 but a considerable individual amount of variation among the segments [2,3]. This variation is greater in spina bifida patients due to inherent neuroanatomic abnormalities compared with spinal cord injury patients.

Since autonomic innervation of the pelvic organs, specifically the bladder, is bilateral, all unilateral interventions are less effective than bilateral ones. This has been clearly established by electrical stimulation procedures, such as the technique of neuromodulation [4].

Expected effects of surgical cross-innervation

Transection of the lumbar ventral spinal root donor

Lumbar ventral spinal roots have predominant somatic outflow. When transected, the somatic motor innervation of this specific spinal root to its effector muscles remains interrupted. If other spinal segments are less involved or are not involved in innervation of a specific muscle and thus cannot take over function to some degree, muscle paralysis will be permanent, as in the one reported case with persistent foot drop.

Transection of the sacral ventral spinal root recipient

In cases of a hyperreflexive detrusor, transection of the sacral ventral spinal root recipient with its autonomic motor outflow to the bladder and rectum will cause by itself some improvement of hyperreflexia due to (partial) motor denervation [5]. However, this effect is limited due to unilateral transection of one sacral ventral spinal root only (S2 or S3) and variable due to the selection of one root or another and a variable abundance of the unilateral sacral autonomic outflow in one of these ventral roots.

Because somatic fibers to pelvic floor muscles and external sphincters are transected, some improvement of pelvic floor spasticity and DSD is to be expected due to paralysis of the respective motor units. However, this effect is limited for the same reasons discussed above.

Effects of reinnervation of a sacral nerve

Successful reinnervation of one sacral nerve has been shown to allow voluntary eliciting of a detrusor contraction; however, its efficacy is expected to be limited by several facts. First, only one sacral nerve is reinnervated, but the sacral autonomic outflow derives from S2–S5 on both sides. Second, sacral nerves are mixed nerves carrying the autonomic outflow to the pelvic organs as well as the somatic outflow to the pelvic floor muscles and sphincters. Thus, in theory, some DSD is to be expected during stimulation after successful reinnervation.

Central nervous modulation of new reflex arc

Because the newly established reflex arc of skin–central nervous system–bladder is by no means a simple spinal reflex arc but travels by its long afferent fibers through thalamus into the sensory cortex and back, central nervous modulating effects are to be expected. These may act in both directions and either dampen (inhibit) or exaggerate (stimulate) the desired lumbar to sacral detrusor activation.

Secondary bladder changes

Bladder compliance and detrusor contractility is affected after neurologic injury or inborn neurologic lesions. Secondary changes such as muscle hypertrophy and detrusor muscle fibrosis are related to the duration of the neurologic deficit and may be reversible when early rehabilitation starts after spinal shock in spinal cord injury patients. However, with an inborn neurologic deficit, some of the secondary changes in the effector organ might be irreversible in spina bifida patients.

Conclusions

The important message of the paper by Peters et al is that the functional results of lumbar to sacral nerve rerouting in spina bifida, in their experience, are less favorable in terms of achieving voluntary micturition and urinary continence in children with spina bifida compared with the excellent reports of Xiao [1]. Actually, Peters et al's published urodynamic tracings (Figs. 2 and 3 of the reviewed paper) show better detrusor contractions of up to 30 cm H_2O compared with the published urodynamic tracings of Xiao (Figs. 3 and 4 [1]), where voiding is predominantly achieved by abdominal straining with concomitant pelvic floor activity and by only weak detrusor contraction with indiscernible DSD because of the simultaneous abdominal straining.

Nevertheless, the clinical results of Peters et al are expected based on the theoretical considerations noted. Even if reinnervation of one sacral nerve is completely successful, this means that only one of eight sacral nerves innervating the bladder with at best 20–30% of the total sacral parasympathetic outflow to the urinary bladder is activated on stimulation for initiation of micturition. Urinary incontinence in spina bifida patients might be related to detrusor hyperreflexia, to sphincter areflexia, or to both conditions. In addition, continence may be compromised by low bladder compliance due to detrusor hypertonicity or fibrosis. How all of these functional and possibly morphologic abnormalities should be controlled by reinnervation of a single sacral ventral spinal root remains unclear. Motor deficits as a result of transection of the lumbar ventral spinal donor root are permanent for the affected motor units. In terms of loss of function, this might be compensated when innervation of a specific muscle arises from several spinal segments, where other segment innervation can compensate for the lost function of the transected segment.

The authors' plea is noteworthy, to continue scientific evaluation of the risks and the benefits of this procedure before it may be taken enthusiastically into clinical practice on a broad base.

Conflicts of interest: The author has nothing to disclose.

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