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Sacral Neuromodulation in Lower Urinary Tract Dysfunction

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Abstract

Vesico-urethral dysfunction is a major problem in daily medical practice due to its psychological disturbances, its social costs and its high impact on quality of life. Recently, sacral neuromodulation, namely the electrical stimulation of the sacral nerves, appears to have become an alternative for radical bladder surgery particularly in cases of idiopathic bladder overactivity. The mechanism of action is only partially understood but it seems to involve a modulation in the spinal cord due to stimulation of inhibitory interneurons.

Temporary sacral nerve stimulation is the first step. It comprises the temporary application of neuromodulation as a diagnostic test to determine the best location for the implant and to control the integrity of the sacral root. If test stimulation is successful, a permanent device is implanted. This procedure is safe in experienced hands.

So-called idiopathic bladder overactivity still the major indication for this technique. Patients not likely to benefit from the procedure were those with complete or almost complete spinal lesions, but incomplete spinal lesions seemed to be a potential indication. This technique is now also indicated in the case of idiopathic chronic retention and chronic pelvic pain syndrome.

When selection is performed, more than three-quarters of the patients showed a clinically significant response with 50% or more reduction in the frequency of incontinent episodes, but the results vary according to the author's mode of evaluation. From the economic point of view, the initial investment in the device is amortized in the mid-term by savings related to lower urinary tract dysfunction.

Finally, this technique requires an attentive follow-up and adjustments to the electric parameters so as to optimize the equilibrium between the neurological systems.

Keywords: Bladder neurogenic; electric stimulation therapy; voiding dysfunction; urinary urge incontinence; urinary retention.

Introduction

Vesico-urethral dysfunction is a major problem in daily medical practice due to its psychological disturbances, its social costs and its high impact on quality of life. A complex neuroanatomic network governs the relationships between the spinal, pons and supra-pons centers, and the vegetative and somatic systems. Despite this complexity, the consequence of these

relationships is always the same, i.e. retention and emptying of the bladder to ensure continence and micturition and to protect the upper urinary tract. To restore its function, surgical techniques intervening in the peripheral or central nervous systems have always played an important role. Recently, sacral neuromodulation, namely the electrical stimulation of the sacral nerves, appears to have become an alternative for radical bladder surgery particularly in cases of idiopathic bladder overactivity. The mechanism of action is only partially understood but it seems to involve a modulation in the spinal cord due to stimulation of inhibitory interneurons. This technique is also indicated in the case of idiopathic chronic retention and chronic pelvic pain syndrome.

Anatomy and Physiology of the Lower Urinary Tract

The lower urinary tract has two main functions: storage and periodic elimination of urine. These two functions are regulated by a complex neural control system involving a central pathway located in the spinal cord, pons and brain and as well as the peripheral autonomic and somatic neural pathways. This control system functions like a switching circuit to maintain a reciprocal relationship between the bladder and outlet components of the lower urinary tract. Because of these complex neural regulations, the central nervous system control of the lower urinary tract is susceptible to a variety of neurologic disorders which, among a wide range of non-invasive therapeutic modalities, may be improved by sacral neuromodulation.

The storage and periodic elimination of urine are dependent on the reciprocal activity of two functional units in the lower urinary tract: a reservoir, the bladder and an outlet represented by the bladder neck and the smooth and striated sphincter muscles of the urethra. During urine storage, the bladder outlet is closed and the bladder smooth muscle is quiescent, allowing intravesical pressure to remain low over a wide range of bladder volumes. During voluntary voiding, the initial event is a relaxation of the pelvic floor and striated urethral muscles, followed by a detrusor muscle contraction and opening of the bladder neck. This activity is mediated by three sets of peripheral nerves: parasympathetic (pelvic), sympathetic (hypogastric) and somatic (pudendal) nerves (Fig. 1). These nerves also contain afferent axons terminating in the lower urinary tract which are involved in initiating micturition.

Spinal Levels

Efferent Pathway

The parasympathetic efferent pathway is the main excitatory input to the bladder. Parasympathetic preganglionic axons originate in the intermedio-

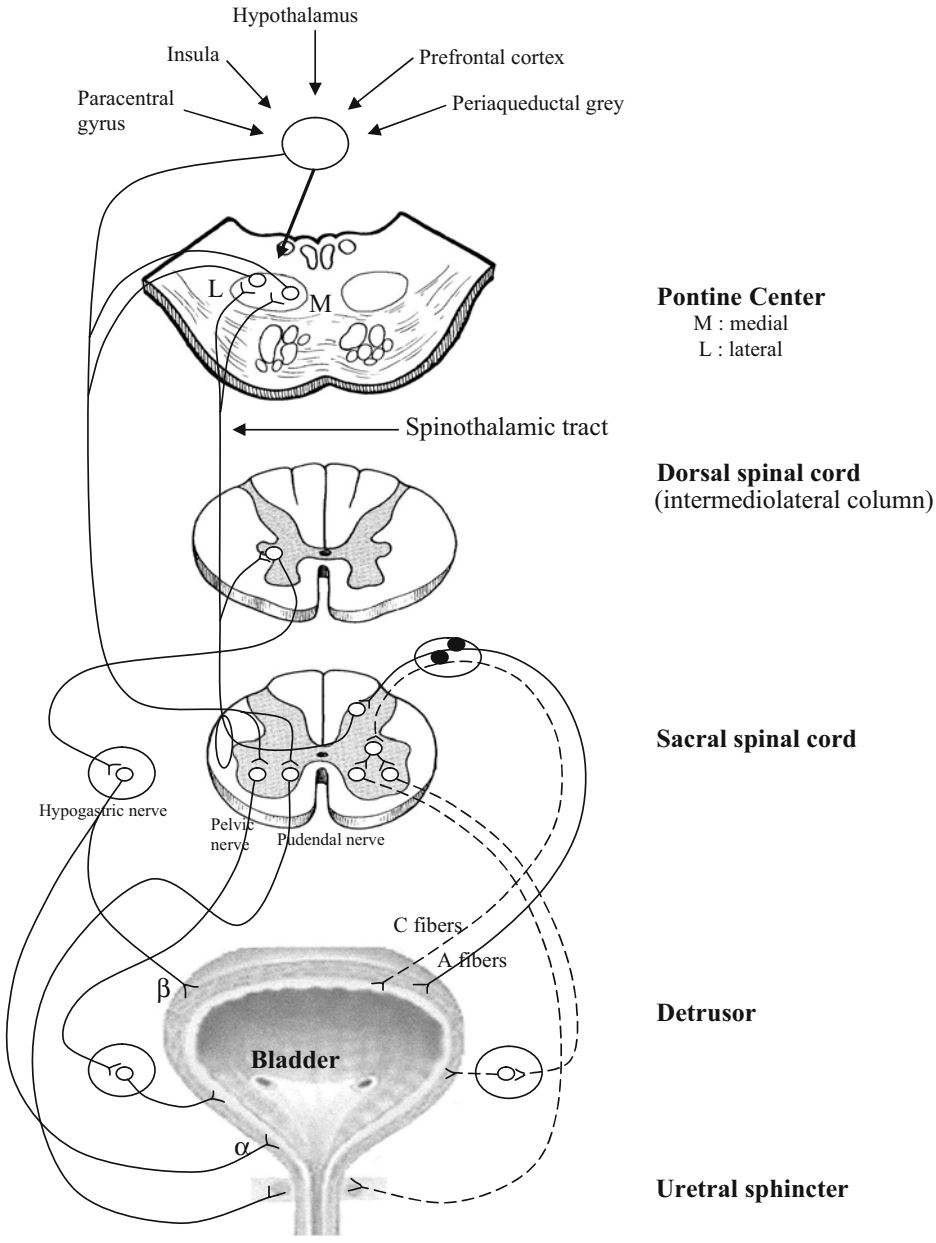

Fig. 1. Anatomy and physiology of the lower urinary tract

lateral column of the S2 to S4 spinal cord and terminate in the post-ganglionic neurons in the bladder wall and in the pelvic plexus [98]. The main neurotransmitter released by the parasympathetic postganglionic nerve terminals is acetylcholine. Acetylcholine can act on different subtypes

of detrusor muscarinic receptors, among which the M3 are most important for mediating evoked smooth-muscle contractions neurally in the bladder [40].

The sympathetic preganglionic neurons are located within the intermediolateral cell column of the T11 to L2 spinal cord. They make synaptic connections with postganglionic neurons in the inferior mesenteric ganglionic neurons in the paravertebral ganglia and pelvic ganglia. Sympathetic postganglionic terminals release norepinephrine which acts on alpha-1 vesical and urethral receptors and beta-2 adrenergic detrusor receptors. The effect of norepinephrine on the former is a contraction of the bladder base and urethral smooth muscle. Norepinephrine, via an action of the Beta 2 receptors, can also relax the bladder body.

Somatic afferent pathways that originate from the motoneurons in the Onuf nucleus of the anterior horn of the S2 to S4 spinal cord innervate the external striated urethral sphincter muscle and the pelvic floor musculature. Somatic nerve terminals release acetylcholine, which acts on nicotinic receptors to induce a muscle contraction. The striated urethral sphincter also receives noradrenergic input from the sympathetic nerves. The combined activation of the sympathetic and somatic pathways elevates bladder outlet resistance and contributes to urinary continence. The striated sphincter (via the pudendal nerve) is the unique element of voluntary continence and micturition.

Afferent Pathway

Sensory information regarding bladder fullness is conveyed to the spinal cord via afferent axons in the pelvic and hypogastric nerves, which possess neuronal somata in the dorsal root ganglia at the S2 to S4 and T11 to L2 spinal segmental levels. Afferent fibers passing in the pelvic nerve carry impulses from tension receptors in the bladder wall to neurons in the dorsal horn of the spinal cord. These are mainly small myelinated (Aδ fibers) [49, 110] and unmyelinated (C fibers) axons [28]. In several mammalian species including the human, the normal micturition reflex is mainly mediated by Aδ fibers afferents that respond to bladder distension [91]. The C fibers, which have a high mechanical threshold, are usually unresponsive to bladder distension and are thus called silent C-fibers, but many of them do respond to chemical, noxious or cold stimuli [58, 74].

Spinal Centers

The sacral micturition center involves laminae VI, VII and X. The innterneurones participate in local control of elementary programs via para-

sympathetic and somatic pathways [73]. The C fibers project to the dorsal horn and via a polysynaptic reflex [48] with medullar interneurones [140] to form the «C reflex» of Bradley [28].

Pontine Centers

Among the sub-encephalic centers involved in micturitional control (Fig. 1), the most important are localized at the pontine level [10, 16]. This part of the tegmentum receives afferent pathways from collateral spinothalamic (from dorsal horn, laminae I and IV) to form the spino-pontospinal reflex or the «A reflex» of Bradley [28]. Two pontine centers have been characterized in mammalians [98]. The first is localized in the medial part of the dorsolateral pontine tegmentum, and is thus called the M-region or Pontine Micturitional Center (PMC) [121]. The PMC projects to the sacral intermediolateral cell column, in which are localized the parasympathetic center connected to the bladder motoneurons and to the sacral intermedioventral cell column. The PMC is involved in the voiding phase via both these projections. The excitatory PMC projection to bladder motoneurons is responsible for an increase in bladder pressure during micturition. The relaxation of the striated uretral sphincter during micturition is due to excitatory projection to inhibitory interneurones in the spinal dorsal gray commissure.

The second pontine center, located more ventrally and more laterally in the pontine tegmentum than the PMC, is involved in the storage of urine during continence. During the storage phase, this L-center or Pontine Storage Center (PSC) acts by direct excitatory projection to the urethral sphincter in the nucleus of Onuf [85].

Suprapontine Controls

Several other central structures located in the forebrain and the cerebral cortex have been thought to be involved in lower urinary tract control. At the mesencephalic level, the periaqueductal gray (PAG) is considered as the main center involved in micturitional control. The PAG is thought to act as a central sensorimotor integrative relay of the micturition reflex, via the reception of sensory information concerning bladder fullness and the direct projection to the PMC [15].

In the forebrain, the most documented structure is the pre-optic area of the hypothalamus, which is thought to play a role in the initiation of the voiding phase via direct projection to the PMC. In addition, the anterior cingulated gyrus, amygdala, bed nucleus of the stria terminalis and septal nuclei are susceptible, when excited, to elicit bladder contraction [16]. The

superomedial part of the precentral gyrus and the superolateral part of the precentral gyrus seem to be involved in voluntary control on the pelvic floors and in abdominal straining, respectively. Finally, the exact role of the cerebellum is not fully understood, but both afferent and efferent contributions to the micturitional reflex have been proposed [122].

Reflex Mechanisms Controlling Micturition

Storage Reflexes

The bladder functions as a low pressure reservoir during urine storage due to the combined effect of the visco-elasticity of the bladder wall and the quiescence of the parasympathetic pathway to the bladder. Continence during bladder filling is reinforced by the activation of a sacral-to-thoracolumbar intersegmental spinal reflex pathway, initiated by afferent fibers linked to a bladder tension receptor, which triggers firing in sympathetic pathways to the bladder, thus mediating an inhibition of bladder activity and a contraction of the bladder neck and proximal urethra. Simultaneously, the activation of pudendal motoneurons during bladder filling induces a contraction of the striated sphincter muscle, which in turn contributes to urinary continence.

In addition to these spinal continence reflexes, a supraspinal urine storage center located in the dorsolateral pons is involved in continence via descending inputs activating the pudendal motoneurons to increase urethral resistance (Fig. 1).

Voiding Reflexes

When bladder volumes reach the micturition threshold, intense afferent activity originating in the bladder mechanoceptors triggers the micturition reflex, which consists of spino-bulbo-spinal reflex pathways passing through the pontine micturition center. Activation of the pontine micturition center induces both a firing in the sacral parasympathetic pathways leading to bladder contraction and secondarily to inhibition of the sympathetic and somatic pathways relaxing urethral and bladder outflow. Before reaching the pontine micturition center, afferent inputs from the spinal cord pass through an integrative relay center in the periacqueductal gray. This center functions as an "on-off" switch activated by afferent activity derived from bladder mechanoceptors, and it also receives inhibitory and excitatory inputs from the brain regions (Fig. 1).

Voiding is also facilitated by an urethrovesical reflex initiated by the stimulation of urethral afferents triggered by urine flow in the urethra, thereby enhancing bladder contractions.

The suppression of the striated urethral sphincter activity during micturition is mainly due to a direct pontine micturition center projection to sacral inhibitory interneurons in the dorsal gray commissure, also known as the intermediomedial cell column. These inhibitory dorsal gray commissure interneurons in turn inhibit sphincter motoneurons in Onuf's nucleus during micturition.

Historical Evolution of Functional Surgery in Lower Urinary Tract Dysfunction

Spinal Cord Stimulation

It was Budge who in 1858 opened up the concept of "micturition reflex" by stimulating the nervous system. Thanks to technical improvements made by Oersted in 1820 and especially Faraday in 1821, he was able to activate bladder contractions using an electrical stimulation in the sacral part of the spinal cord [130]. Over a century later in 1972, Friedman [64] performed selective bladder stimulation in animal models by implanting bipolar electrodes in the spinal cord. The preganglionic parasympathetic fibers that innervate the detrusor muscle emerge from the ventro-intermedial column of the sacral spinal cord, while the somatic efferent fibers that innervate the urethral sphincter come from the Onuf nucleus (anterior horn of 3rd and 4th sacral segments). The different localization of these two groups of motor neurons allowed selective bladder stimulation. Encouraged by these results, Grimes [69] operated five spinal cord injured patients by implanting two bipolar electrodes 2.5 mm deep at the level of S2. Four patients were then able to urinate by stimulation. Then Grimes and Nashold [68] analyzed a group of 10 patients: the clinical result was dramatically different depending on the position of the electrodes. Furthermore, low selectivity of this stimulation remains a major problem of this technique, which does not systematically avoid simultaneous contraction of the striated sphincter of the bladder. Sedan [134] made similar observations. Some are now re-assessing this abandoned technique, because it makes it possible to stimulate electively the motor neurons of the detrusor muscle, thus inducing efficient micturition without the need to perform a posterior rhizotomy [67, 167].

Intravesical Stimulation

In 1878, Saxtorph introduced the concept of direct stimulation of the bladder wall (and its nerve terminals) to induce a detrusor contraction and to activate urination in patients suffering from urinary retention [130]. In

1954, however, McGuire noted that the results differ depending on the position or the volume of the electrodes, as well as on the characteristics of stimulation [130]. From 1959, Boyce and Lathem [25] continued these efforts, as did Bradley who designed an implant system used initially in dog and then in human [27]. However, this technique was abandoned due to lack of encouraging results. Recently, Jiang and Linstrom [93] showed that intravesical stimulation could be used to activate a neurogenic bladder, especially in spina bifida patients.

Pelvic Nerve Stimulation

In 1957, Ingersoll [88] performed unilateral stimulation of a pelvic nerve. This technique, known as the Burgele-Ichim-Demetrescu technique [96], is theoretically possible and a few patients gained benefit from these implants (electro-stimulated micturition). However, the complexity in approaching the pelvic nerves and their fragility make this technique difficult. For some authors, it does not solve the problem of the simultaneous contraction of the detrusor and the sphincter produced by recurrent circuits, unless the pudendal nerves have been cut [12]. Mention should also be made of the less productive efforts of Hald in 1967 who tried to stimulate the detrusor muscle selectively through the pelvic nerve fibers [130].

Stimulation of Pelvic Floor Muscles

In 1963 Caldwell [130] performed the first stimulator implantation in a pelvic sphincter to treat urinary incontinence. However, it was observed shortly afterward that transrectal stimulation and transvaginal stimulation in women gave the same results. At present, the mechanism of these stimulations is known: the stimulated pudendal afferents activate the sympathetic inhibitor neurons, which in turn inhibit the central parasympathetic neurons, thereby reducing bladder hyperactivity [108].

Stimulation of Sacral Nerve Roots

Since 1971, it has been demonstrated in monkey and then in human beings that direct stimulation of the anterior sacral roots allows bladder emptying. The electrodes can be placed in the extra- or intradural space. Strong electrical stimulations cause simultaneous contraction of the detrusor and the striated sphincter of the urethra. However, due to its smooth muscle, detrusor contraction lasts longer than striated sphincter contraction, which relaxes intermittently, letting urine flow and thus protecting the upper urinary tract. GB Brindley pioneered the technique of adding a posterior

rhizotomy, thereby improving bladder capacity and reducing bladder hyperreflexia. This is still the only technique for restoring bladder function, retention (continence) and emptying (micturition). It is especially useful for patients suffering from a complete spinal cord lesion who are not able to empty their bladder by conventional methods [30, 31, 32, 33, 158, 159].

Sacral Nerve Deafferentation

The goal of this process is to suppress the vesico-medullary reflex, which is responsible for bladder hyperreflexia (or overactivity), a condition closely related to incontinence. The principle of sacral deafferentation was introduced a century ago to reduce spasticity [46]. Some C fibers are responsible for maintaining this ''short'' reflex (vesico-medullary) [169]. Posterior rhizotomy can be performed at the level of the conus medullaris [126], intradurally in the lumbar region [158, 159], and in the radiculo-medullary junction (DREZotomy) [118, 145]. This type of destructive surgery must be utilized only in the case of complete sensitivo-motor function loss. Owing to the severe side effects of sacral alcoholization, this technique should not be recommended [115]. Sacral nerve thermocoagulation in the foramens, thus sectioning the thermosensitive C fibers but respecting the other sensitive and motor fibers, could be a less invasive alternative to treat bladder hyperreflexia, but it should be repetitive [102]. Recently, techniques involving denervation by intravesical instillation of some C fiber specific neurotoxins (capsaicin, resiniferatoxin) have been approved [52, 62].

Sacral Neuromodulation

In 1981, Tanagho and Schmidt in California attempted a procedure in paraplegic patients similar to Brindley's protocol, i.e. extradural stimulation of the sacral roots to induce a detrusor contraction, followed by posterior rhizotomy to eliminate bladder sphincter hyperactivity. Subsequently, they limited their work by using percutaneous puncture to stimulate the root of S3 without lesioning. In fact, they obtained an adverse effect, i.e. the inhibition of contraction [154]. This is how the term of sacral neuromodulation was coined: an electrical stimulation of the sacral roots was found to modify the pathologic behavior of a hyperactive bladder. The princeps articles reported an improvement in bladder hyperactivity in patients suffering from spinal cord lesions, but the method soon showed its efficacy in the treatment of idiopathic bladder hyperactivity, without any obvious neurological lesion. Thereafter, urologists widely used this technique instead of radical bladder surgery, thus allowing conservative treatment of some incontinent patients. Since 1997, the FDA has approved the

utilization of this technique in urge incontinence, and since 1999 in cases of chronic retention. Recently the technique has proved efficient in some types of pelvic pain and fecal incontinence.

Methods and Techniques for Sacral Nerve Stimulation

Sacral Anatomy [107, 111]

The sacrum is normally composed of five modified vertebrae which are fused together. It is a triangular bone mass extending from the inferior vertebral column and containing the sacral and coccygeal nerves.

Posterior Sacrum

The skin in the sacral region is usually thick, and the subcutaneous tissue varies in thickness according to the habitus of the individual. It tends to be thinner than that found in the adjacent gluteal and lumbar regions. Situated deep below the superficial fascia are two layers of fibrous connective tissue (the thoracolumbar fascia and the tendon of the erector spinae muscle group of the deep back muscles). Deeper still are to be found a few muscle fibers of the erector spinae muscle group and many fibers of the inferior portion of the multifidus muscle layer. The left- and right-sided muscle groups are situated in a depression, whose medial and lateral walls are formed by the median sacral crest (spinous process) and the lateral sacral crest, respectively. The thickness of the tendon-muscle mass is approximately two centimeters in the region of the second sacral foramen, one centimeter near the third foramen, and 5 centimeters near the fourth foramen. Deep below the muscle mass, there is the periosteum covering the posterior surface of the bone. Components of the sacroiliac, sacrotuberous and sacrospinous ligaments are situated superiorly and laterally.

The dorsal surface of the sacrum is convex and irregular, with ridges and grooves. In the mid-line, there is the median sacral crest, consisting of three or four tubercles (rudimentary spinous process). At the inferior pole, the sacral hiatus is due to the failure of the fusion of the laminae of the fifth sacral vertebra. Laterally, the sacral crest just lateral to the sacral grooves comprises a row of four small tubercles representing the fusion of the articular processes. It forms the medial aspect of the posterior foramina. The lateral foramina correspond to the fusion of the transverse processes and are the site of insertion of the gluteus maximus muscle. The dorsal sacral foramina transmit the small dorsal rami of the sacral spinal nerves from the sacral canal to the deep back muscle compartment. The foramina are closed by a thin membrane. Small bony projections may be formed on the medial aspects of the foramina and are associated with muscle attachment points.

Sacral Foramen

The posterior foraminae become smaller from top to bottom. They appear to be equidistant in the vertical plane from the midline. Within the sacral foramina, there is abundant adipose tissue, particularly at the level of the third and fourth posterior foramina enclosing the nerve roots. Each nerve root follows an oblique course from top to bottom and from internally to externally. Each nerve root contains afferent and efferent parts of the somatic and parasympathic branches. A thin branch of each sacral root joins the skin surface and provides the buttock with topographic sensitivity. A foraminal arterial branch is always present lateral to the ventral nerve root, close to the inferolateral edge of each posterior sacral foramen. A veinous plexus is generally observed near the midline. The second foramen is nearly half filled by its nerve root along with its ganglion, which partially plugs the foramen. The third and fourth nerve roots occupy a relatively smaller proportion of their respective foramina.

The sacral foramina can be considered as a cylindrical space into which the sacral neuromodulation electrode is introduced. The upper sacrum tends to more curved than its lower part, especially in males. Needles can be inserted into the foramina as far as the anterior part of the foramen in order to reach the sacral root, at a wide range of angles in both the vertical and horizontal planes. For the third sacral cylinder, the angle is approximately 60 to 70 degrees to the posterior surface of the sacrum.

Anterior Sacrum

The ventral surface is concave in the vertical plan. There are four transverse lines on the surface which represent the original division of the bone into five separate vertebral bodies. Immediately anterior to the bone of the sacrum in the midline, there is the periosteum and continuation of the anterior longitudinal ligament. The piriformis muscle is attached to the sloping surfaces of the anterior foramina. Then, a layer contains portions of the pelvic nerve, components of the hypogastric plexuses, and blood vessels before the posterior pelvic viscera (rectum and lower sigmoid colon).

Localization of Sacral Foramen

Anatomical Landmarks

There are few methods to locate the posterior foramen. Usually, this depends on the positions of the posterior superior iliac spine, coccygeal tip,

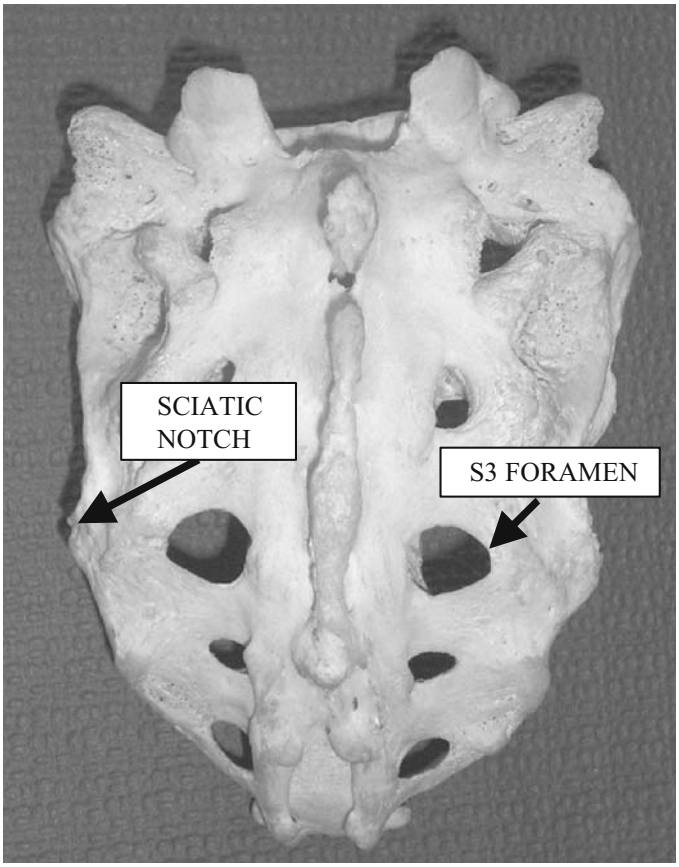

Fig. 2. Anatomical landmarks of S3 foramen

and midline. There are three sets of landmarks to confirm location of the S3 foramen, which is the elective foramen for neuromodulation.

– The S3 foramen is found by palpating the upper edge of the greater sciatic notch, 2 cm just lateral to the sacrum [thon, wju, 1991].

– Another technique [111] estimates the location of the S3 foramina approximately 2 cm from the midline, and 9 cm above the sacrococcygeal junction cephalad from the tip of the coccyx, identified by a knuckle-like protuberance at the apex of the sacrum (equidistant between apex of the sacrum and coccyx). However, this technique is sometimes difficult, especially in obese patients.

– The sacral crest, the region where the sacrum approaches the horizontal plane, corresponds to S4. From this point, the sacral spine curves downward to S3, which is located 2 cm above the S4 landmark.

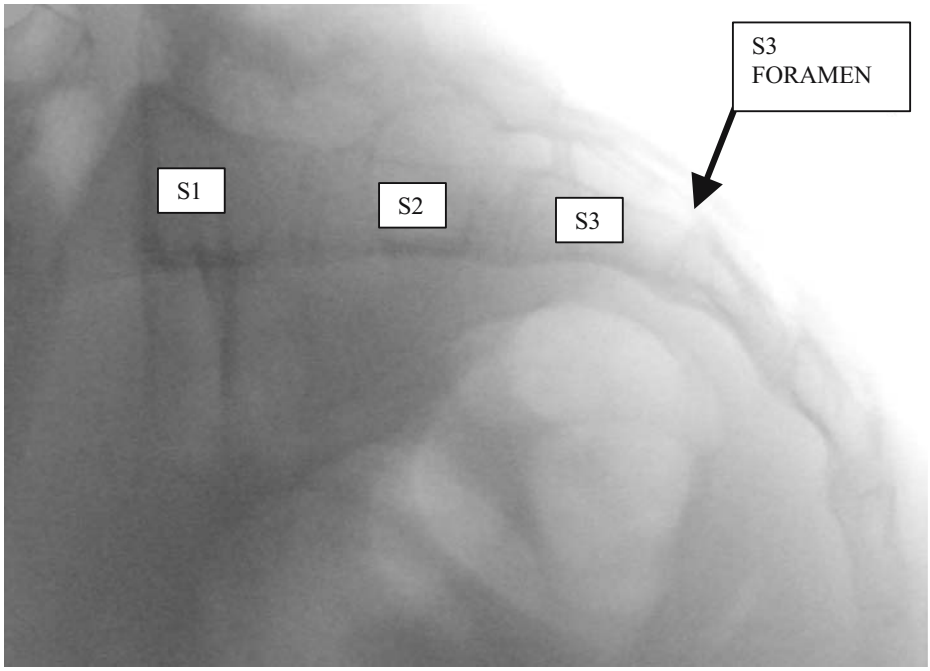

Fig. 3. Radiological landmarks of S3 foramen

Radiological Landmarks

The use of fluoroscopy is certainly the best approach for a quick and effective electrode placement, especially in overweight patients. Even though the sacral foramina may not be visualized fluoroscopically, interrelationships between fluoroscopically identifiable landmarks may be used to deduce their location. On anteroposterior radiographs of the pelvis, the interrupted line across the inferior aspect of the sacroiliac joint corresponds with the S3 foramen. On lateral views of the sacrum, the S3 foramen corresponds to the midpoint between the base of the sacrum and the tip of the coccyx.

Surgical Approach

Electrodes are generally placed in the third sacral foramen (S3). The electrode leads are subsequently attached to an implantable pulse generator. Patients undergoing sacral nerve stimulation must complete three phases of therapy.

Phase 1 or the ‘‘acute phase’’ involves a percutaneous test stimulation where a temporary electrode is placed in the S3 foramen and connected to an external pulse generator.

Phase 2 or the ''sub-chronic phase'' follows on from the acute phase. It involves monitoring and adjusting the external pulse generator to identify the optimal comfort level of stimulation and to evaluate therapy.

Phases 1 and 2 are dependent on an external generator and are considered as peripheral nerve evaluation (PNE).

During phase 3 or the ''chronic phase'', a permanent device is implanted.

Peripheral Nerve Evaluation

Temporary sacral nerve stimulation is the first step. It comprises the temporary application of neuromodulation as a diagnostic test to determine the best location for the implant and to control the integrity of the sacral root. This stage is important and may generate a number of technical difficulties [7]. Operators should always follow the manufacturer's instructions.

Preoperative Considerations:

The physician can verify electrode placement with anatomical or radiological landmarks (# chapter), and by analyzing motor or sensitive responses. There is considerable disagreement whether PNE can be performed outside of a hospital setting, with or without fluoroscopy, and with or without muscle responses [142]. However, neurologic patients may develop severe dysautonomia during electric sacral nerve stimulation [135, 136].

Material:

The testing hardware consists of a needle, test lead, test stimulator, interconnect cabling and a ground pad. A 20-gauge foramen needle with a beveled tip is used to gain access to the sacral nerve for placing the test stimulation lead. The stainless steel needle is depth-marked along its length (9 or 12 cm) and electrically isolated along its central part. The portion near the hub is exposed to allow connection to the test stimulator. By stimulating through the unisolated tip of the needle, the physician can determine the correct sacral nerve stimulation site for the test stimulation lead. For PNE, the test lead is a fluoro-polymer-coated, coiled, 11-stranded straight wire. An exposed metal tip at the distal end serves as an electrode. The lead contains its own stylet, which is removed once the correct position has been found. The external test stimulator is used both for patient screening and for intraoperative usage in determining lead placement thresholds. This provides output characteristics that are similar to

those of the implantable neurostimulator and can be operated in either monopolar or bipolar modes. Amplitude control is accessible to the patient when it is being used as a screening device. The physician can set amplitude limits to ensure patient safety and the validity of the test. Finally, the ground pad (stuck to the patient's skin) provides the positive polarity in the electrical circuit during the test stimulation and the evaluation.

Surgery:

Anatomical orientation is much easier in a prone position. The patient must be comfortable, and a local anesthesia is administered to infiltrate the skin and subcutaneous tissues (particularly the periosteum).

Once the needle is in place, it is possible to determine nerve responses. Variations in neural anatomy may induce S3 motor responses whereas stimulation is given at S2 or S4. Consequently, the levels must be defined functionally as well as anatomically. In general, two levels of sacral nerve sites are tested to locate the optimum response. In most patients, stimulation of the S3 sacral nerve yields optimal results.

Typical S3 responses include the following: contraction of the levator ani muscles, causing a "bellows" contraction of the perineum (deepening and flattening of the buttock groove); plantar flexion of the big toe (and sometimes other toes) due to sciatic nerve stimulation and paresthesia in the rectum, perineum, scrotum or vagina.

Stimulation of S2 causes the following: rotation of the leg or hip, plantar flexion of the entire foot, contraction of the calf, contraction of the superficial pelvic floor, and a pulling sensation in the genital area and in the leg.

Stimulation of S4 causes activation of the posterior levator ani muscles, no motor response in the lower extremities, and pulling sensations in the rectum only.

The lead is then threaded through the needle cannula, and the foramen needle and lead stylet are removed. When the electrode is in place, the appropriate response is reconfirmed and the lead is coiled under the skin. Anterior/posterior and cross-table lateral X-rays of the sacral region provide documentation of the lead's position. This X-ray can serve as a reference for positioning during the implantation phase.

Duration of the "Sub-Chronic Phase":

As in the standard test stimulation procedure, the equipment is set up for 3 to 7 days of evaluation. At the end of the evaluation, the percutaneous lead extension is removed. If test stimulation is successful, a permanent device is implanted.

Implantation of Neurostimulator

The original technique for implanting a long-term sacral neuromodulator was described by Schmidt *et al.* [132]. The manufacturer's recommendations should be followed.

Implant Equipment:

Initially, neurostimulators were used for pain control (Itrel II®, MEDTRONIC). Then a specific neurostimulator (InterStim®, MEDTRONIC) was developed with the same technology. The chronic lead has four electrodes and a larger stimulation zone than the temporary test stimulation lead. Control equipment are used to adjust stimulation parameters (generally amplitude at 0.1 volts, rate at 10 to 14 pulses per second (Hz), and pulse width at 210 microseconds).

''Classic Surgery'':

The patient is given a general anesthetic without long-acting muscle relaxants, which could block the motor responses needed to verify the effects of stimulation. During the implant procedure, the sacral region, buttocks and feet should also be visible to allow observation of motor responses. The patient is positioned facedown with slight hip flexion. Prior to incising, some surgeons provide a local anesthetic to prevent postoperative pain.

To implant and anchor the lead, the sacral foramen must first be located and fluoroscopy is recommended at the beginning of the procedure to help lead placement. Then a 5 cm midline or paramedial incision over the selected foramen is made. The skin and adipose tissue are dissected down to the glistening, white, fibrous lumbodorsal fascia. The fascia is then divided approximately 1.5 cm lateral from the midline, parallel to the spine over the appropriate foramen. The distal end of the lead is inserted into the foramen. Beginning at the distal tip of the lead, the four electrodes are numbered from zero to three; the numbered connector contacts correspond to these electrodes. Each of the four metal contacts should be tested and the lead repositioned to obtain the desired response. The optimal nerve responses are identified, the distal end of the lead is anchored to the lumbodorsal fascia and the lead is connected to the extension. The neurostimulator is placed in a subcutaneous pocket in the upper buttock. The neurostimulator may also be placed in a pocket in the abdomen (particularly in very thin patients). Postoperatively, the lead and neurostimulator placements are usually documented with X-rays.

Minimally Invasive Surgery:

Recently, Spinelli [148] reported a new technique of sacral nerve stimulation, characterized by a percutaneous approach to the sacral nerves resulting in minimal invasiveness of the procedure and the ability to have the patient awake during electrode placement. Under local anesthesia, it is possible to place a definitive quadripolar lead during the percutaneous test, which could reduce the risk of an inconclusive stimulation response. If test stimulation is successful, the pulse generator can be implanted under local anesthesia. Nevertheless, long-term evaluation of this technique is mandatory.

Unilateral or Bilateral Stimulation?

Since the original technique described by Tanagho and Schmidt, the unilateral sacral foramen electrode has been the gold standard for sacral neuromodulation [165]. Indeed, bilateral is not superior to unilateral sacral neuromodulation [127]. In rare cases, bilateral chronic sacral neuromodulation may prove necessary [84] particularly when unilateral percutaneous nerve evaluation fails [127].

It seems that bilateral stimulation does not increase the excitatory response but increases bladder inhibition at a lower stimulation intensity. Some authors have reported success with bilateral stimulation but the risk of complications is increased [84] and life of the device is significantly shorter.

Clinical Application of Sacral Neuromodulation

Indications

Neuromodulation of the sacral nerves is a therapeutic option for voiding dysfunction in patients who do not respond to the common non-invasive therapies and in whom disturbance in reflex coordination between the bladder, sphincter and pelvic floor is suspected. The rationale for using electrical stimulation techniques for the treatment of such voiding dysfunction is that this stimulation turns the neurological control mechanism back towards a more functional status. The main indications are urge incontinence, OAB syndrome, urinary retention and chronic pelvic pain.

OAB syndrome, which is also called urge syndrome or urgency-frequency syndrome, is characterized by urgency, with or without urge incontinence, usually with increased daytime frequency and nocturia, in the absence of local or metabolic factors explaining these symptoms [4]. In patients suffering from an OAB, sacral neuromodulation is an appealing

therapeutic modality for symptoms refractory to conventional pharmacotherapy, and is relevant for both neurologic and non-neurologic causes.

In patients suffering from chronic urinary retention, sacral neuromodulation should be reserved for functional urinary retention without evidence of mechanical obstruction. Various indications such as Fowler's syndrome, spastic pelvic floor syndrome and bladder hypo/acontractility have been proposed.

Pelvic pain syndrome is the occurrence of persistent or recurrent episodic pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynecological dysfunction, without any infection or other obvious pathology [4]. Chronic pelvic pain is defined as pain of a minimum of 6 months duration that is not related to any identifiable cause or etiology [125]. In patients suffering from chronic pelvic pain, sacral neuromodulation could be indicated when the symptoms are refractory to conventional pharmacotherapy after exclusion of obvious local pathological conditions.

Evaluation

Before the implantation of a neuromodulatory device, each patient should undergo a minimal investigation performed to confirm the pertinence of the indication, exclude any contraindications and to have baseline values.

The work-up for treatment by sacral neuromodulation must include careful assessment of past history with special emphasis on drugs influencing bladder function. A physical examination may be given to assess neurologic status, togther with a perineal examination with urodynamic investigation to assess bladder and sphincter function. To rule out any other lower urinary tract pathological conditions, urine culture can be performed to exclude urinary tract infection. Cytology and cystoscopy are helpful in ruling out carcinoma cystitis, and when indicated, imaging of the upper tract may be performed. It is recommended to perform MRI of the entire spinal cord to screen for neurologic diseases such as multiple sclerosis, a neoplasm, syringomyela, lipoma, etc.

For treatment of incontinence, the primary outcome measure should include a voiding diary recording the number of episodes of incontinence and micturition during a specified time. Recording the mean number of pads used per 24 hours may be helpful. For some authors, the quantification of the amount of urine lost during the pad test is also recommended [14]. Patient assessment of the severity of the symptoms can be recorded by a validated urinary incontinence outcome score, such as the Urogital Distress Inventory, the Bristol Female Lower Urinary Tract Symptoms or the Incontinence Impact Questionnaire [89, 90, 141, 168]. Many scores, such as the Short-form-36 (SF-36) and Beck Depression Inventory (BDI), may

be used to evaluate the repercussion of the incontinence on quality of life [163]. Even if there is no systematic correlation between severity of clinical OAB symptoms and urodynamic parameters of detrusor overactivity, most authors recommended the use of cystometrograms to evaluate the responsiveness to sacral neuromodulation. The maximum cystometric capacity (volume at which the patient feels he/she can no longer delay micturition), the reflex volume (volume at which the first uninhibited contraction of the detrusor occurs), the sensation of bladder filling and the degree of bladder compliance (relationship between change in bladder volume and change in detrusor pressure) may reflect the extent of bladder activity.

In the treatment of urinary retention, the primary outcome measure should be the post-void residual urine [14]. Most authors recommended evaluating the mean voided volume and the mean number of intermittent catheterizations per 24 hours. Urodynamically, it seems reasonable to evaluate the urine flow with pressure flow studies (measuring the relationship between pressure in the bladder and urine during bladder emptying) or, at least by recording flow rate and voiding time, to assess bladder contractility during cystometry.

For painful bladder syndromes, the primary outcome measure should ideally be based on a validated pain assessment instrument. In addition, patients considered candidates for implantation may have benefited from psychological screening [14].

Pediatric Setting

There are some specific etiologies of urinary dysfunction in children, such as neurogenic bladder (myelomeningocele, occult spinal dysraphism, sacral agenesis, tethered cord syndrome, cord lipoma, cerebral palsy), non-neurogenic bladder (anatomic bladder exstrophy), functional bladder (enuresis, urinary infection), and non-neurogenic neurogenic bladder (Hinman syndrome). Various electric stimulation modalities are possible in children.

Intravesical electrical stimulation (IVES) is used to treat underactive detrusor, idiopathic or neurogenic in children. IVES is given by a catheter electrode in the bladder (cathode) with the anode attached to the suprapubic abdominal skin or the thoracic region. Continuous stimulation from 20 to 100 Hz is delivered (pulses = 0.2 to 10 ms, intensity from 0.1 to 64 mA). Sessions are 60 to 90 min daily over a period of 3 weeks to 3 months. For Gladh *et al.* [65], the frequency of urinary tract infections and incontinence decreased significantly and long-term normalization of voiding was obtained for 83% children with idiopathic problems and 40% with neurogenic problems. Another study [18] showed an absence of improvement in

patients with myelomeningocele. This kind of stimulation is proposed as an alternative to clean intermittent catheterization.

Transcutaneous stimulation may be attempted to treat urinary urgency and incontinence in children. Current is delivered via skin electrodes for a short duration daily on a home treatment basis. Surface electrodes are placed at the level of the sacral root S3. Stimulation of 2 Hz is applied from 1 to 2 hours every day. For non-neurological bladder dysfunction, dryness improved in 73.3% of children, with a significant increase in mean voided volume [82]. 68% responded after 1 month of trial therapy with an increase in bladder capacity, decrease in urgency, and decrease in incontinence and/or better sensitivity. In the series of Hoebeke *et al.*, 56% of children were cured after 1 year. In a randomized controlled trial, no difference was found between the active spina bifida group and the placebo group [112].

Sacral neuromodulation was applied in children at the beginning of the nineties [153]. Contrary to adults, there has been no large randomized prospective study. Recently, a prospective randomized study [75] reported results of sacral neuromodulation in 42 patients (spina bifida in 38 cases) from 5 to 19 years old (mean age 11.9 years). Patients were compared (clinical examination, voiding diary, urodynamic evaluation) every three months for a minimal period of 12 months. Despite the improvement noted in implanted patients, the difference was not significant between the two groups. A multicenter study now seems to be necessary to increase the number of patients. The integrity of the nerves (even incomplete) is also a predictive factor of success.

The Overactive Bladder

Definition

Until the most recent definition of the International Continence Society (ICS), the term of bladder overactivity referred to urodynamic status. The bladder was considered as overactive when objectively shown to contract, spontaneously or on stimulation, during the filling phase of a cystometrogram while the patient is attempting to inhibit micturition [2]. Furthermore, in the first standardization report, the threshold of 15cmH20 was necessary to conclude that an uninhibited bladder was related to detrusor overactivity [11]. The definition currently endorsed by the ICS is that of a symptom syndrome suggestive of lower urinary tract dysfunction characterized by urgency, with or without urge incontinence, usually with increased daytime frequency and nocturia, in the absence of local or metabolic factors explaining these symptoms [2]. This overactive bladder syndrome can also be described as urge syndrome or urgency-frequency syndrome.

Diagnosis of Overactive Bladder

Clinical Parameters

The major role of cystometry in the diagnosis of overactive bladder (OAB) has recently been dissipated since overactive bladder is now taken to be a medical condition referring to the symptoms of frequency and urgency, with or without urge incontinence [2]. Thus the diagnosis of the OAB symptom complex is based upon the subjective perception of lower urinary tract dysfunction. However, as emphasized above, the OAB is a complex of symptoms that can be diagnosed as such only when there is no proven urinary tract infection or other obvious pathology.

Urgency is the complaint of a sudden compelling desire to pass urine that is difficult to defer [2]. Increased daytime frequency, or pollakiuria, is the complaint of voiding too often during the day [2]. Nocturia is having to get up one or more times at night to void [2]. Urge incontinence is characterized by a strong desire to void coupled with an involuntary loss of urine [2]. Since asking patients to record micturition and symptoms for a period of days provides invaluable information, measurement of lower urinary tract symptoms is based on a bladder diary. The bladder diary records the times of micturition and voided volumes, episodes of incontinence, pad usage and other information such as fluid intake, the degree of urgency and the degree of incontinence [2]. Validated questionnaires may also be useful for recording symptoms, their frequency, severity and bother, and the impact on quality of life [89, 168, 141].

Urodynamic Parameters [60]

Even if urodynamic testing is not yet required to define an OAB syndrome, it is often suggestive of urodynamically demonstrable detrusor overactivity. Detrusor overactivity is the urodynamic observation of involuntary detrusor contractions, whatever their amplitude, during the filling phase, which may be spontaneous or induced (Fig. 4).

The main interest of cystometry in patients suffering from OAB syndrome is to improve the diagnostic evaluation both by defining the underlying pathophysiology and by indicating treatment. However, there are controversial data concerning the correlation between OAB symptoms and urodynamic findings. Indeed, most authors do not recommend a filling and voiding study in the first-line treatment of OAB, but only in previously failed and complicated cases of OAB and prior invasive therapy.

Classification of Overactive Bladder

In some cases, detrusor overactivity may be further classified according to cause. Three main distinguishable types of detrusor overactivity are

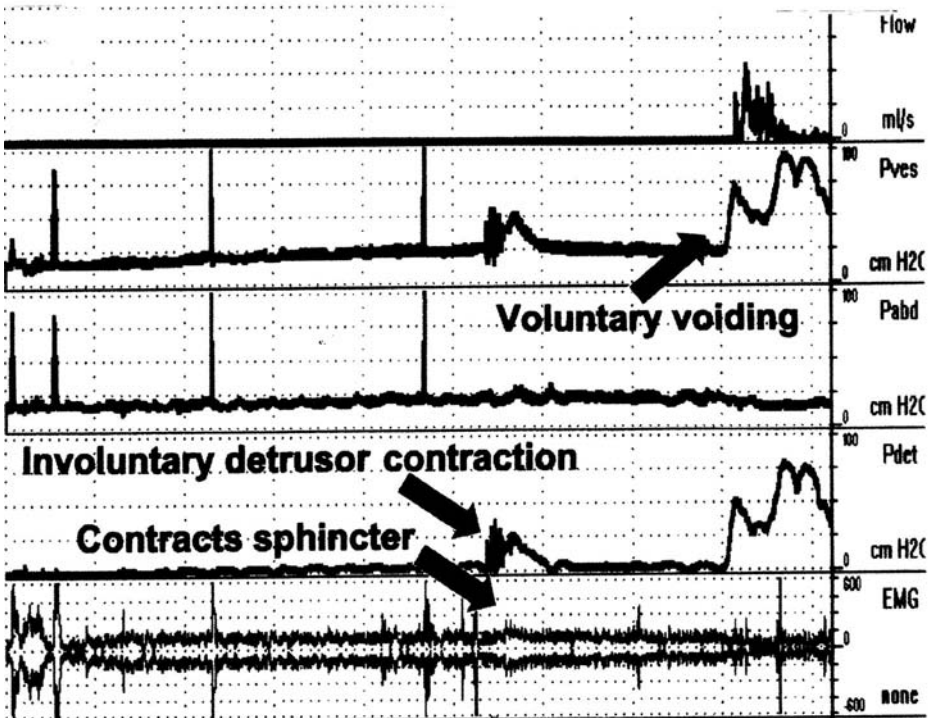

Fig. 4. Urodynamical characteristics of detrusor overactivity

usually considered [119]. The first is neurogenic detrusor overactivity (formerly detrusor hyperreflexia) in which there is a relevant neurological condition. Secondly, there is idiopathic detrusor overactivity (formerly detrusor instability) in which there is no defined cause. Finally, detrusor instability is related to bladder outlet obstruction or other conditions irrelevant for defining neurological causes.

Etiology

The different forms of overactivity may result from neurogenic or myogenic causes, or a combination of the two. These neurogenic and myogenic defects could be due to a wide variety of pathogenic conditions, which may be classified in 6 principal subtypes [119, 149].

1) Neurologic illness or injury, most commonly traumatic or medical spinal cord injury, demyelinating disease including multiple sclerosis, supraspinal disease such as stroke, Parkinson disease, tumor, degenerative disease or dementia. The neurogenic mechanism of OAB may be related to various changes in both peripheral and central neural pathways, such as

a decreased peripheral or central inhibitory control, an enhancement of excitatory transmission in the micturition reflex pathway, an increased primary afferent input from the lower urinary tract, the emergence of bladder reflexes that are resistant to central inhibition, or some combination of these factors [50].

2) Bladder outlet obstruction, which alters sensory and motor aspects of micturitional reflexes and points to an abnormal activity pattern of the detrusor cells characterized by a spontaneous mechanical activity, a hypersensitivity to acetylcholine with depressed responses to intrinsic nerve stimulation and increased sensitivity to direct electrical stimulation [Brading 1997].

3) A hypersensitivity-induced overactivity due to the emergence of a aberrant voiding reflex mediated by unmyelinated capsaicin-sensitive C-afferents, which may be caused by neurogenic disease or factors not yet fully understood [109, 50].

4) Urethral weakness due to smooth sphincter deficiency and pelvic relaxation in middle-aged and elderly women [56].

5) Detrusor hyperactivity and impaired contractility in elderly patients [123].

6) So-called idiopathic bladder overactivity, which has no defined cause but may be due to an unknown combination of some of the above-mentioned factors [57, 124].

Results of Sacral Neuromodulation

To date, effectiveness has been assessed by objective and subjective measures. In evaluating the effectiveness of sacral nerve stimulation, results are frequently discussed according to urge incontinence chronic urinary retention, and chronic pelvic pain.

However, subjective measures are difficult to implement because the definition tends to vary from what actual improvement occurs in patients.

Urge Incontinence

In a multicenter randomized controlled trial, Schmidt *et al.* [131] observed at six months after sacral nerve stimulator implantation in 34 patients followed up. Approximately three-quarters of the patients showed a clinically significant response with 50% reduction in the frequency of incontinent episodes. There was an improvement from the baseline average of 9.7 mean leaks per day to 2.6 per day after 6 months of treatment. Efficacy was defined as a clinical effect greater than 50% reduction in symptomes. At 18 months, 84% were clinically successful in eliminating heavy leaking episodes, 76% were successful in eliminating or reducing (by 50%) the

number of pads and 47% were completely dry. In contrast, patients in the control group experienced either no improvement or worsening symptoms. Similar results were reported in a randomized controlled trial [164] with a significant decline in leakage episodes (improvement by 88%) and pad use (improvement by 90%) compared with baseline. Finally, 56% of patients were completely dry. Another prospective randomized multicentric study [79] showed a significant reduction in the number of daily voids from 16.9 to 9.3 at 6 months follow-up, and 56% of patients demonstrated a reduction of 50% or more in the number of voids.

Some case series studies report the change in the average number of incontinence episodes post-implantation compared to baseline and at 30 months the daily frequency of leaking episodes had significantly reduced from 10.9 to 4.2 [22]. Results from the Italian national register [147] show a decrease in mean incontinence episodes from 5.4 to 1.1 at 12 months follow up. Similar results were obtained with a reduction in leaking episodes from 6.4 to 2.0 per day at 24 months in a case series of 44 patients [1].

The reduction in pad consumption (mean reduction from 4.8 to 2.2 pads) was found to be statistically significant in some studies [19, 23, 165]. In a multicenter investigation [92], the number of pads used daily dropped significantly from 7.1 to 3.8 per day ($p < 0.0001$): 33% of patients were dry and 28% experienced a greater than 50% improvement in pad use. At least 61% of patients have excellent or good results.

Generally speaking, on urodynamic assessment, bladder capacity is found to increase statistically from baseline measures [84, 165]. Voided volume has also been found to increase [71, 84].

In the case of urge incontinence, the objective measures reported in the literature are not usually adapted to assessing the number of episodes of micturition, whereas pollakiuria is a major symptom impacting on quality of life.

Chronic Urinary Retention

In a multicenter randomized controlled trial, Grunewald *et al.* [72] observed that 69% of patients with chronic idiopathic urinary retention achieved complete micturition without catheterization (versus 9% without electric stimulation). The number of catheterizations decreased > 50% in 83% patients (versus 9% without electric stimulation). Another prospective, randomized multicenter study [94] investigated the efficacy of sacral neuromodulation in patients with chronic non obstructive urinary retention. Compared to the control group, implanted patients had statistically and clinically significant reductions in catheter volume per catheterization. 69% of patients eliminated catheterization at 6 months and 14% of

patients had a 50% or greater reduction in catheter volume per catheterization. 83% of patients achieved sucessful results at 6 and 18 months compared to 9% of the control group.

In a case study, Elabbady *et al.* [56] reported a significant percentage increase in voided volume from 15% to 71% among seven patients. Grunewald *et al.* [71] and Hohenfellner *et al.* [84] reported significant increases in voided volume (respectively 490 and 334 ml). Decreases in mean residual volumes of 455 and 334 ml respectively were noted by the same authors. For Spinelli *et al.* [147] stimulation can decrease average residual volume from 227 to 108 ml; in their series, 50% of patients stopped catheterization and 13% needed it only once daily. In other studies, bladder capacity was not found to change significantly from baseline to post-implantation [56, 84, 139]. Reported success rates vary from 52% [156] to 82% [71] but there is no consensus regarding the definition of success.

Pain

Although frequent, chronic pelvic pain syndrome probably receives little attention from clinicians. It is a diagnostic and therapeutic challenge and is often related to psychological and psychosomatic disorders. Theoretically, neurogenic inflammation is responsible for neurogenic pain, as in a complex regional pain syndrome [13]. Trauma may also induce pain (fracture, nerve damage). Compared to dorsal column or peripheral nerve stimulations, some authors propose sacral nerve stimulation for the treatment of chronic pelvic pain syndrome. To date, few results have been reported for this technique but it is feasible. Aboseif *et al.* [1] analyzed a group of 41 patients with chronic pelvic pain associated with other voiding symptoms: stimulation decreased the severity of pain from 5.8 to 3.7 on their scale.

Long-Term Effectiveness

The results seem stable over time. Some authors [22] report a reduction in the benefit at 5 years. However, long-term studies are lacking and until now, there have not been any studies with control groups. In a multicentrer, prospective study, Siegel *el al.* [143] demonstrate that after three years, 56% of 41 urge incontinent patients showed greater than 50% reduction in leaking episodes per day with 32% of patients being completely dry. After two years, 34% of urgency-frequency patients showed greater than 50% reduction in voids per day, including 21% of patients who attained a normal range of voiding frequency. After 1.5 years, 70% of 42 patients with urinary retention showed greater than 50% reduction in catheter volume per catheterization, including 58% of patients who eliminated use of catheterization.

Impact on Quality of Life

When the SF-36 and BDI scales are administered, no significant improvement in quality of life is demonstrated but these scales are not powerful in the setting of urinary handicap. However, patients seemed satisfied by their device in one study, probably due to the decrease in the number of incontinence episodes [36]. Approximately two-thirds were satisfied by their implant. Elsewhere, quality of life results were superior for implanted patients on some components [131].

Results for Neurogenic Bladder

The first publications showed an improvement in bladder hyperactivity among spinal cord lesion patients [63, 154]. Bosch and Groen [20] showed that treatment of refractory urge incontinence by chronic S3 nerve stimulation was feasible in selected multiple sclerosis patients. The fact that no irreversible changes to the bladder or nerves occur is an advantage of this treatment option over destructive alternatives. However, the unpredictable evolution of the disease and particularly cognitive alterations are contreindicated in case of rapid evolution. In a case series, Chartier-Kastler *et al.* [41] reported 9 women with spinal diseases (including vascular myelitis, multiple sclerosis and traumatic spinal cord injury) undergoing neuromodulation. All patients reported an improvement of 75% in their visual analog scale at last follow-up (mean follow-up 43 months). In another case series, Hohenfellner *et al.* [83] evaluated patients with neurogenic bladder (complete or incomplete spinal cord lesions, inflammatory neuronal reaction, borreliosis, lumbar herniated disk). Patients not likely to benefit from the procedure were those with complete or almost complete spinal lesions, but incomplete spinal lesions seemed to be a potential indication [23, 83].

Predictive Factors for Sacral Neuromodulation

Percutaneous nerve evaluation gives an accurate identification of suitable candidates [8]. Generally, authors consider an improvement of more than 50% in voiding parameters for definitive implantation and PNE is positive in 40% of patients with neurogenic and idiopathic etiologies [128]. On the other hand, a negative PNE did not reliably predict the therapeutic efficacy of the implanted system in a recent study and 25% of patients needed more than one PNE [164]. In fact, the higher the patient's age, the greater the number of test failures; moreover, longer lasting complaints result in a higher risk of a negative test [128]. Patients with neurogenic bladder dysfunction had a four-fold higher probability of negative test results compared with patients having no obvious neurologic problems. Patients with

urinary retention have a higher probability of having a negative test result compared with patients with urge incontinence. Urodynamic studies during test stimulation do not have any predictive influence.

Complications of Sacral Neuromodulation

Complications of Peripheral Nerve Evaluation (PNE)

Siegel *et al.* [143] noted 18.2% of adverse effects in 914 test stimulation procedures. The most common adverse events are lead migration from 11.8% [143] to 18.6% [143], technical problems (2.6%) and pain (2.1%). One surgical intervention (0.1%) was required to remove a test lead electrode that became dislodged during lead removal. Local infection and subcutaneous hematoma are rare [143].

Complications of Sacral Nerve Neuromodulation

For chronic sacral neuromodulation, complication rates range from 22 to 43% [19, 53, 138, 156] and re-operation rates from 6 to 50% [56, 99, 138, 156]. However, many studies do not discuss the complications arising from stimulation implants [21, 71, 156].

A prospective study was performed by the manufacturer Medtronic (Minneapolis, MN, USA) including 14 North American and 9 European centers [95]. Of the 633 patients enrolled in this study, 250 had been implanted with the sacral nerve stimulator system by the end of the reporting period, representing 6506 months of device experience. Of the 250 implanted patients, 157 (62.8%) experienced a total of 368 adverse events associated with the device for use of stimulation therapy. Of the reported 368 events, 56 (15.2%) required no intervention, 151 (41%) required non-surgical intervention and 161 (43.8%) required surgical intervention. Overall, 89.4% (329) events were fully resolved. In the 250 implanted patients, post-implant adverse events associated with the devices or use of stimulation were pain at the internal pulse generator site (14.2%), new pain (10.8%), suspected lead migration (9.1%), infection (7%), pain at lead site (5.5%), transient electric shock (5.6%), suspected device problem (2.2%), adverse change in bowel function (3%), technical problems (3.9%), persistent skin irritation (0.8%), change in menstrual cycle (0.9%), suspected nerve injury (0.4%), device rejection (0.4%) and others (14.1%).

Pain

Pain is a frequent adverse event occurring in 4% [22] to 29% [164] of patients. Little is known about the severity and treatment of pain related

to device implantation. Frequently, no distinction is made between post-operative pain, pain associated with the device, referred pain, pain related to stimulation, neuropathic pain and psychological pain. In one study, placement in the upper buttock reduced the rate of revision surgery but not pain [95]. The symptoms of pain should always be thoroughly analyzed in order to treat it.

Infection

Any infection should always be detected and treated early. Removing the device either temporarily or definitively may prove necessary. Despite being a common complication of all implantable devices, few studies refer to this adverse event. No information is available in the literature concerning the etiology, severity or timing of infection. Mention has been made of skin irritation requiring device explantation [131]. Compared to the Brindley technique (sacral anterior root stimulation with posterior rhizotomy) which has a maximum 2.4 infection % rate [158], the mean of 6.1% related to sacral neuromodulation [143] appears to be too high. Progress in prevention and device modification is required.

Problem of Nerve Injury

To date, there have been no reports of permanent injury or nerve damage [131]. Sometimes nerve injury is suspected [143] and there is a potential risk.

The configuration of the electrode itself (incorrect fit to the nerve), surgical trauma, pressure caused by post-surgical edema, excessive scar formation and tension on the electrode cables are all potential contributors to neural damage [120]. The peripheral nerve may be affected adversely by chronic constriction and compression [103]. However, these risks are less important in the case of epineural electrodes than in intraneural ones [105]. In animal studies, excessive or prolonged stimulation may cause early axonal degeneration [114]. The risk of injury is also affected by the duration of continuous stimulation [5]. It is well known that needle insertion into the sacral foramen can result in damage to nerve root and vessels [107]. Because these structures are more likely to be found on the medial aspect of the foramen, injury can be minimized by using a more lateral foramen entry. Increasing the angle of needle entry in the vertical plan can increase the risk of injury to the vessels (venous plexus), and therefore that of hematoma and fibrosis [77]. The S2 foramen is nearly half filled by its nerve root and ganglion, which increases the likelihood of penetration during needle placement. On the other hand, the S3 and S4 foramina are

filled mostly with fat and their nerve occupies a relatively smaller portion of the foramen [107]. It has been observed that the therapeutic efficacy of the implant sometimes becomes limited over time, and the potential formation of fibrosis between the electrode and target nerve has been suggested [83].

Technical Problems and Device-Related Complications

Bosch *et al.* [22] described difficulties in maintaining proper electrode positioning, breakage of the lead, fracture of the extension cable, electrode dislocation or malpositioning, early failure of pulse generator, contact lead point dysfunction and seroma around the generator site. However, device-related complications appear to be the most frequent. The following complications have been reported in patients undergoing sacral nerve stimulation for urinary urge incontinence:

– Device complications such as pain at the implant site [22], device rejection [143], early pulse generator failure [147], stimulation-dependent pain in leg or buttock [22] and current-related problems.

– Lead complications such as disturbed toe flexion, lead migration [22, 147], adverse changes in elimination function e.g. bowel (diarrhea) and urinary system [143], suspected nerve injury [143], lead site pain [143], transient electric shock [143] and fracture of the extension cable [22] or lead [147].

– Wound complications such as partial wound dehiscence of the sacral incision [22], hematoma [147], infection [147] or skin irritation [143].

Surgical Revision

More than one third of patients go to surgical revision [143], mostly for repositioning of the lead or the extension. Tempory removal with subsequent reimplantation is normally the result of infection or chronic pelvic pain. Repositioning of the internal pulse generator is performed to relieve pain at the site, or because the battery is dead. Permanent removal is to the result of infection, chronic intractable pain, or because the device has not proved satisfactory. Surgical revision does not appear to affect the overall degree of patient satisfaction [143], and it seems to decline with time [131].

Conclusion

Although relatively frequent, complications have until now received insufficient attention. Many patients require re-intervention to reposition or

remove the device due to displacement, breakage or migration. However, the procedure is safe in experienced hands.

Therapeutic Alternatives and Developping Treatments in Refractory Urge Incontinence and Idiopathic Bladder Overactivity

Medical Therapeutics

Conservative therapies such as pelvic floor exercises, bladder retraining, electrical stimulation of the pelvic floor and pharmacotherapy involving anticholinergics, antispasmodics and tricyclic antidepressants are primary discussed. The use of pelvic floor muscle training with or without biofeedback for overactive bladder is suggested to inhibit detrusor muscle contraction by voluntary contraction of the pelvic floor at the same time, and to prevent sudden falls in urethral pressure by change in pelvic floor muscle morphology, position and neuromuscular function [17]. Some promising results have been reported, and these treatments are widely used, but there is still a need for high quality randomized trials on the effect of pelvic floor exercises on the inhibition of detrusor contraction. Detrusor overactivity current pharmacological treatment involve use of muscarinic receptor antagonists, but their therapeutic activity is limited by side effects resulting in the non continuance of treatment in a significant number of patients. More selective muscarinic antagonists (M3 receptor subtype) as dariferacin and vancamine or percutaneous treatment (oxybutinin patches) may reduce side effects of these treatments. The development of new drugs can proceed by targeting alternative pathways affecting detrusor overactivity [100]. Intravesical agents appear to be attractive alternatives to oral medication [62]. *Vanilloids drugs* as Capsaicin and resiniferatoxin have showed some promising results. Capsaicin-sensitive bladder afferents do contribute to hyperactivity of the bladder in neurogenic and non-neurogenic detrusor overactivity [43, 152]. Capsaicin is a specific neurotoxin that desensitizes C-fibres afferent neurons which may be responsible for the signals that trigger detrusor overactivity. Resiniferatoxin is a less pugent agent which desensitizes as capsaicin afferent C-fibres but fail to depolarize nerves and may show less local side effects such as pain associated with capsaicin. The role of alcoholic vehicle in acute pain and irritation associated with capsaicin has to be clarified [166], as the duration of effects which have been reported to be shorter after resiniferatoxin intravesical application [45, 104]. Efficacy of vanilloids has been shown not only in patients with detrusor hyperreflexia due to spinal cord disease [52], but also patients with bladder hypersensitivity and idiopathic detrusor instability [45, 51, 97, 144]. Botulinum toxin interacts with components of the presynaptic membrane of cholinergic nerves and inhibits the vesicular

release of acetylcholine producing long lasting neuronal blockade. The effects of toxin lasts for up to 9 months and further injections may be required.

Surgical Alternatives

The other treatments available are more invasive and often irreversible surgical procedures. Surgical therapy should only be considered when all conservative methods have failed. Endoscopic approaches have been used in urgency incontinence [162]. *Overdistension of the bladder* is thought to reduce bladder distension by causing degeneration of unmyelinated C afferent small sensory fibers. This technique requires anaesthesia and have some complications including hematuria, urinary retention and bladder perforation in 5% to 10% [146]. Although effective in short term management, this procedure is usually temporary in symptomatic control. *Bladder myectomy* (autoaugmentation) has beeen proposed as an alternative to enterocystoplasty. Detrusor myectomy involves incising and removing the bladder muscle to allow bladder mucosa to form a pseudodiverticulum. Detrusor myectomy for treatment of refractory urge incontinence due to detrusor overactivity in both sexes has been reported to be successful in a small number of patients [106, 151]. These data need to be confirmed in larger group and on a long term experience. *Enterocystoplasty* results are similar, good results vary from 58% to 88%, with an average of 77% [80]. The goal of enterocystoplasty is to create a low-pressure, large capacity reservoir with low-filling pressure, which protects the upper tract from pressure related reflux and infection, as well as providing urinary continence. The most frequently used bowel segment is ileum followed by sigmoid colon. It is generally agreed that it is best to de-tubularize the intestine into a sphere to reduce disrupt peristaltic contractions and increase capacity of the bladder [29, 77, 106, 113]. A minimum of 10% of patients requires intermittent catheterization for bladder emptying. This procedure has a significant complication rate and should be evaluated carefully when applying. Urinary tract infection and mucus production which can cause either catheter or voiding obstruction are significant long term problems. Electrolyte abnormalities such as hyperchloremic acidosis are reported. Perforation has been reported in 2–6% of patients in the long term and surgical revision rates range from 15 to 36% [61, 80]. *Urinary diversion* is rarely needed but may be useful in patients with intractable detrusor instability with a very small reservoir. It may be use to treat pelvic pain that may be associated. However, it represents a last step intervention in the surgical management of incontinence resultant from detrusor overactivity.

The best surgical procedure for detrusor overactivity is still to be elu-

cidated. Furthermore, the future of surgical treatment will depend on new developments in non-surgical therapy.

Perspectives in Electric Stimulation

Nonimplanted stimulators have been used for bladder inhibition. There is good evidence that the use of vaginal electrical stimulators can reduce the occurrence of symptoms of overactive bladder in about half of the patients treated [34]. Unfortunately, precise treatment protocols and patients selection remain unresolved as many different protocols and stimulators were used. *Pudendal nerve stimulation* positively impacts cystometric parameters in a significant number of patients with refractory detrusor instability. It may provide efficacious treatment for patients suffering from the symptoms of urgency-frequency and urge incontinence associated with overactive bladder syndrome [160]. Implantable microstimulator weighting less than 1 gram is now available. Electronics, rechargeable battery and stimulating electrode are integrated into a single implantable device. Implantation at Alcock's canal is performed using minimally-invasive procedure with local anaesthesia and an approach similar to the well-established transperineal pudendal block [35]. Patient sit on a custom cushion for approximately 20 minutes a day to recharge the microstimulator through radio waves. Treating clinician use bidirectional telemetry to program the neurostimulator and to retrieve information about the patient's use of the device. Patient use the remote control to stimulate or to turn the microstimulator on and off. Long term efficacy of this device need to be confirmed in larger group clinical trials.

Posterior tibial nerve electrical stimulation to inhibit detrusor activity have been used with success by Mc Guire *et al.* [116]. More recently, intermittent *posterior tibial nerve stimulation* was re-introduced as a treatment of patients presenting bladder overactivity [9]. A needle is inserted to allow 12 weekly outpatient treatment sessions, each lasting for 30 minutes. In this study a positive response was seen at 12 weeks follow-up in 60% of patients with a significant decrease in leakage episodes, number of pads used, voiding frequency and nocturia. Tolerance was excellent. Posterior tibial nerve stimulation may be technically less demanding and probably more cost-effective for management of lower urinary tract dysfunction. Percutaneous tibial nerve stimulation showed short term clinical efficacy in leakages, quality of life and significant cystometric data improvements in neurologic and non-neurologic patients suffering with detrusor overactivity [6, 157]. Further studies are needed to show if posterior tibial nerve stimulation may be use as a minimally invasive test to select candidates for definitive S3 neuromodulation or may constitute for some patients a long term therapeutic issue.

Cost of Sacral Neuromodulation

General Issues in Urge Incontinence Costs

Urinary incontinence and urinary retention are a costly illness that affect personal resources, medical treatment and quality of life. The overall prevalence of overactive bladder is similar between men (16.0%) and women (16.9%), but sex specific prevalence differed substantially by severity of symptomes [150]. Anatomic differences increase the frequency of urge incontinence linked to bladder overactivity among women compared with men. In women, prevalence of urge incontinence increase with age from 2.0% to 8.9%, and in men from 0.3% to 19%. Moreover, symptome occurrence is later in age in men. United States most recent estimates of the annual direct costs of incontinence in all ages are approximately $16 billion: $11 billion in community and $5 billion in nursing home (1994 dollars) [59]. These costs estimate increased by 250% over 10 years [86], greater than can be accounted by medical inflation. Data from the National Overactive Bladder Evaluation (NOBLE) survey in the United States had shown that the estimated total economic cost of overactive bladder was $12.02 billion in 2000, with $9.17 and $2.85 billion incurred in the community and institutions, respectively. NOBLE program in the US surveyed approximately 5,000 adults. The average cost per community-dwelling person with overactive bladder was $267 per year [87]. A prospective population study in US suggested that total urinary incontinence expense is as high as $16.3 billion, with 78% of cost issued from women and 22% from men. Overall surgical cost of incontinence (all techniques) represent 4 years of pads and care. Similar findings were shown in several non USA studies issued from European and Autralian studies [86]. Apart from the cost to the health system there is also the burden to the patient and his/her family [76]. Urinary incontinence may also affect individual's lost work time or interfere with job performance and productivity. Embarrassment, shame, need to change clothing altered social interactions, loss of self esteem, depression are frequent. Given the large number of patients (mainly younger women) and the relatively high prevalence of incontinence, future efforts to objectively quantify such impact is needed.

Expected Cost per Patient of Sacral Nerve Stimulator Implant Treatment

The initial expense of the therapy, especially measured over the 7–10 year life of any neurostimulator should be considered in relation to the potential savings to the healthcare system and to the effect on the patient's quality of life. Abrams *et al.* [3] examine the benefit-risk profile of neuromodulation in treating refractory urge incontinence and other voiding disorders. They feel that both efficacy and safety have improved beyond

the earlier studies as the development of new percutaneous technology and the minimally invasive placement of leads have improved the technique.

No studies of the cost-effectiveness of sacral nerve stimulator implant treatment were found in the literature, but some economic data looking at direct costs up to 12th month post implantation are available. Cost of equipment (percutaneous nerve evaluation and sacral nerve stimulator) is approximately of 9000€ per patient. It may be higher if bilateral stimulation is chosen. Surgery and re-surgery costs have been evaluated nearly to 8000€ in Australian review [117]. Oral anticholinergic treatment cost is much lower (200€ per year) but neuromodulation is usually used in refractory cases to these therapies. Reduction of pads and laundry for urge incontinence and catheterization for urinary retention is the main factor of cost reduction [131]. Unfortunately, studies have showed significant consummation variability of these equipments and some may have overestimated this data [86]. Over six months, sacral nerve stimulator implant treatment has an estimated cost per patient initiated to treatment with percutaneous sacral nerve evaluation of approximately 18 700€. These costs include medical treatment and re-operations arising from complications, for both indications (incontinence, urinary retention) [117].

Capellano *et al.* [37] reported economical and social impact of sacral nerve modulation therapy in 62 patients with lower urinary tract dysfunction. These patients were enrolled in the economic session of the Italian Sacral Nerve Modulation Registry from February 2000 to September 2002. 41 were incontinent patients (61% female) and 21 were affected by chronic urinary retention (71% female). A quarterly based analysis comparing the baseline data to the last follow-up (12th month) was performed. Visits to the general practitioner decreased from 1.1 to 0.05 ($p < 0.01$), visits to the urologist did not change significantly from baseline (1.5 to 1.2). Diagnostic tests decreased from 2 to 0.8 ($p < 0.01$). In the use of pads a major change was observed from a daily use of 2.1 (three months expenses per patient of €120.96) to 0.5 (three months expenses per patient of €28.8) ($p = 0.08$); and for urinary retention the use of catheters decreased from 1.1 baseline (three months expenses per patient of €178.2) to 0.1 at 12 months (three months expenses per patient of €16.2) ($p = 0.09$). Costs of drug consumption decreased significantly ($p < 0.05$) from €47.24 to €10.53. This study suggests that sacral nerve modulation therapy is efficient to improve the economic management of patients with lower urinary tract dysfunction. Furthermore, the reduction in the use of pads and catheters has also a positive effect on quality of life and patients' social interaction [36].

It has been suggested that the implant may last for up to five years. Over the long term the total cost saving in incontinence products is likely to increase if the device continues to be effective, but further revision sur-

gery may also be required. Optimal treatment can be define at the end of a fine tuning process which could take several months, during which specialist visits decrease progressively, allowing some cost reduction. A longer follow-up is therefore requested in order to evaluate long term costs after implant therapy is stabilized.

Conclusion

The technique of sacral neuromodulation is available in neuro-urologic situations in which there is an imbalance between the neurological systems which regulate retention and micturition. It is generally used to treat vesical overactivity with pollakiuria, which disturbs patients' quality of life. The need to urinate can even trigger urinary or fecal leakage. When the pharmacological arsenal has been tried to no avail, sacral neuromodulation remains an alternative to urologic interventions of the bladder. Neurogenic and idiopathic overactive bladder must be differentiated, and it is essential to considerer psychological factors affecting the patient. Urologic etiologies are a contra-indication for sacral neuromodulation. The major indication is bladder overactivity, followed by idiopathic chronic retention and chronic pelvic pains. Sacral neuromodulation is a mini-invasive technique but requires methodological rigor and a preliminary percutaneous test. When selection is performed, more than three-quarters of the patients showed a clinically significant response, but the results vary according to the author's mode of evaluation. From the economic point of view, the initial investment in the device is amortized in the mid-term by savings related to lower urinary tract dysfunction. Finally, this technique requires an attentive follow-up and adjustments to the electric parameters so as to optimize the equilibrium between the neurological systems.

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