BRIEF REPORT

Implanted System for Orthostatic Hypotension in Multiple-System Atrophy

Jordan W. Squair, Ph.D., Maxime Berney, M.D., Mayte Castro Jimenez, M.D., Nicolas Hankov, M.Sc., Robin Demesmaeker, Ph.D., Suje Amir, M.Sc., Aurelie Paley, M.Sc., Sergio Hernandez-Charpak, M.Sc., Gregory Dumont, Ph.D., Leonie Asboth, Ph.D., Gilles Allenbach, M.D., Fabio Becce, M.D., Patrick Schoettker, M.D., Gregoire Wuerzner, M.D., Julien F. Bally, M.D., Grégoire Courtine, Ph.D., and Jocelyne Bloch, M.D.

SUMMARY

Orthostatic hypotension is a cardinal feature of multiple-system atrophy. The upright posture provokes syncopal episodes that prevent patients from standing and walking for more than brief periods. We implanted a system to restore regulation of blood pressure and enable a patient with multiple-system atrophy to stand and walk after having lost these abilities because of orthostatic hypotension. This system involved epidural electrical stimulation delivered over the thoracic spinal cord with accelerometers that detected changes in body position. (Funded by the Defitech Foundation.)

Multiple-system atrophy is an adult-onset, sporadic, neurodegenerative disorder characterized by parkinsonian or cerebellar features[1,2] and autonomic failure that manifests as orthostatic hypotension or urodynamic dysregulation.[1] Orthostatic hypotension increases the risk of falls,[3] impedes upright positions and walking,[4] and is predictive of a decreased life expectancy.[5,6] This aspect of multiple-system atrophy is caused by degeneration of catecholaminergic neurons in the rostral ventrolateral medulla and partial degeneration of sympathetic preganglionic neurons in the thoracic spinal cord, with preservation of neurons in the sympathetic ganglia.[7-11] This pattern of neuronal degeneration disrupts the regulation of blood pressure and heart rate in response to an upright posture.

We recently developed an implantable neuroprosthesis that applied epidural electrical stimulation over the thoracic spinal cord to activate sympathetic preganglionic neurons in a patient with orthostatic hypotension due to cervical spinal cord injury.[12] Here, we report the use of this system to treat orthostatic hypotension by stimulating the dorsal-root entry zones of the thoracic spinal cord in a patient with multiple-system atrophy.

CASE REPORT

A 48-year-old woman had a 4-year history of limb rigidity, resting tremor in both hands, bradykinesia, and micrographia. These motor signs initially led to a diagnosis of idiopathic Parkinson's disease. Levodopa–benserazide partially reduced these signs. Several months after the initiation of treatment, limb spasticity, orthostatic hypotension, supine hypertension, postprandial vertigo, and incontinence began to develop; these signs were consistent with multiple-system atrophy of the parkinsonian type.

From the Center for Neuroprosthetics and the Brain Mind Institute, School of Life Sciences, Swiss Federal Institute of Technology (EPFL) (J.W.S., N.H., R.D., S.A., A.P., S.H.-C., G.D., L.A., G.C., J.B.), the Department of Clinical Neuroscience (J.W.S., N.H., R.D., S.A., A.P., S.H.-C., G.D., L.A., G.C., J.B.), the Service of Neurosurgery (J.W.S., G.C., J.B.), the Service of Nephrology and Hypertension (M.B., G.W.), the Service of Neurology (M.C.J., J.F.B.), the Department of Diagnostic and Interventional Radiology (F.B.), and the Service of Anesthesiology (P.S.), Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Defitech Center for Interventional Neurotherapies (NeuroRestore), EPFL–CHUV–UNIL (J.W.S., M.B., N.H., R.D., S.A., A.P., S.H.-C., G.D., L.A., G.C., J.B.), and the Department of Nuclear Medicine and Molecular Imaging, CHUV (G.A.) — all in Lausanne, Switzerland. Dr. Bloch can be contacted at jocelyne.bloch@chuv.ch or at the Department of Clinical Neuroscience, Service of Neurosurgery, BH08–633, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland. Dr. Courtine can be contacted at gregoire.courtine@epfl.ch or at the Brain Mind Institute, Swiss Federal Institute of Technology, Center for Neuroprosthetics (B3.3), 9, Chemin des Mines, CH-1202 Geneva, Switzerland.

Drs. Squair and Berney and Drs. Courtine and Bloch contributed equally to this article.

N Engl J Med 2022;386:1339-44.
DOI: 10.1056/NEJMoa2112809

A Quick Take is available at NEJM.org

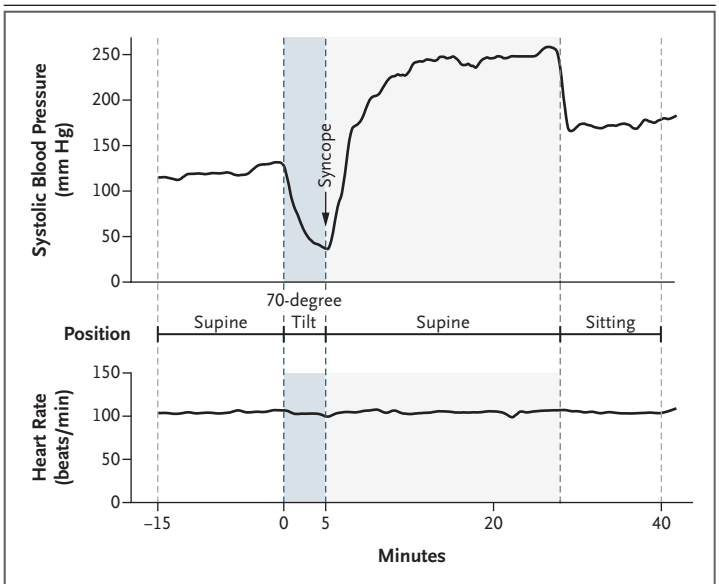

Figure 1. Preoperative Assessment of Orthostatic Hypotension.

Shown are changes in the patient's systolic blood pressure and heart rate during the tilt-table test before implantation of the spinal cord stimulation system. Beat-to-beat measurements of blood pressure and heart rate were obtained with the use of finger photoplethysmography (Finometer, Finapres Medical Systems).

The patient's motor and autonomic functions continued to deteriorate. Cardiac imaging showed preservation of sympathetic innervation (Fig. S1A in the Supplementary Appendix, available with the full text of this article at NEJM.org), a finding consistent with the sparing of postganglionic neurons that is characteristic of multiple-system atrophy. Less than 1 year later, the patient could no longer stand for more than a few minutes, she could not walk farther than short distances, and she was having one to three syncopal episodes per day.

In addition to levodopa–benserazide at a levodopa-equivalent dose of 300 mg (100 mg of levodopa and 25 mg of benserazide, both administered three times per day), the patient received fludrocortisone (0.1 mg per day), midodrine (2.5 mg three times per day), and domperidone (10 mg three times per day). Supine hypertension (blood pressure, >200/120 mm Hg) developed and was attributed in part to the use of fludrocortisone, which was then discontinued. Midodrine caused scalp pruritus. Her medication doses were changed to 2.5 mg of midodrine twice per day and 20 mg of domperidone three times per day, and the use of levodopa–benserazide was continued.

One month later, when the patient was in an upright position, her blood pressure dropped to less than 75/45 mm Hg, and she had presyncopal symptoms during attempts to stand, as well as three or four episodes of syncope per day. To reduce the patient's symptoms of parkinsonism, we increased the dose of levodopa–benserazide to a levodopa-equivalent dose of 400 mg (100 mg of levodopa and 25 mg of benserazide, both administered four times per day). However, because of increasing orthostatic hypotension, the levodopa-equivalent dose was later reduced to 300 mg (100 mg of levodopa and 25 mg of benserazide, both administered three times per day).

As a result of syncope that occurred within 60 seconds after standing, the patient became bedridden. The addition of conservative measures, including leg crossing and the use of compression stockings, was not sufficient to prevent these episodes.

METHODS

STUDY PATIENT AND ETHICAL STANDARDS

Because of the failure of pharmacologic treatments in this patient, we considered implantation of a system to apply electrical stimulation over the thoracic spinal cord in order to manage orthostatic hypotension.[12] We had previously used the same approach to treat a patient with orthostatic hypotension due to a spinal cord injury.[12] The current patient provided written informed consent to undergo the procedure, and this study conformed to the ethical standards of the institutional and national research committees as well as the Declaration of Helsinki of 1964 and its amendments.

PREOPERATIVE ASSESSMENTS

We measured the patient's arterial blood pressure and heart rate noninvasively with finger photoplethysmography during orthostatic challenges on a tilt table (Fig. S2A). The resting supine blood pressure and heart rate were recorded continuously for 15 minutes until a stable systolic blood pressure of at least 120 mm Hg was established.

We then tilted the patient to a 70-degree upright posture. Within 1 minute, her systolic blood pressure decreased from 120 mm Hg or higher

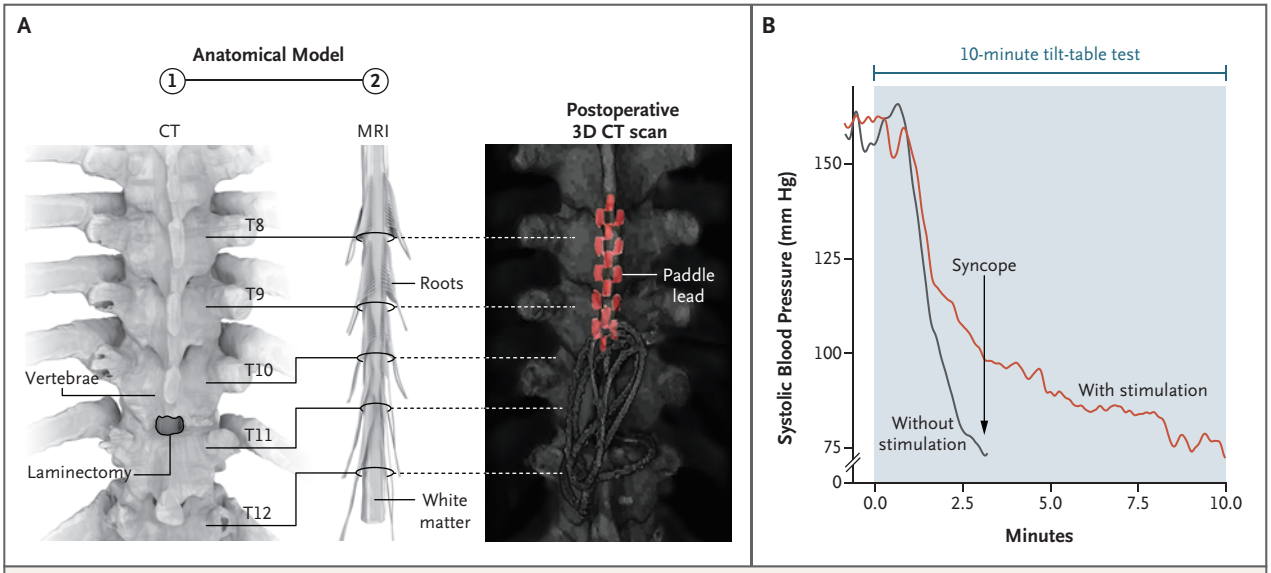

Figure 2. Implantation, Configuration, and Effects of the Spinal Cord Stimulation System.

Panel A shows a personalized anatomical model used for preoperative planning. A postoperative three-dimensional (3D) computed tomographic (CT) scan shows the final position of the paddle lead. MRI denotes magnetic resonance imaging. Panel B shows changes in the patient's systolic blood pressure over the course of a representative 10-minute tilt-table test with the system turned off (without stimulation) and with the system turned on (with stimulation). Beat-to-beat measurements of blood pressure and heart rate were obtained with the use of an implanted arterial catheter connected to a monitoring system. Similar results were obtained on subsequent tests.

to less than 50 mm Hg (Figs. 1, S2B, and S2C). The patient reported feeling presyncopal, and she was returned to the horizontal position, with resolution of the symptoms and an increase in systolic blood pressure to more than 250 mm Hg in less than 5 minutes. Throughout this challenge, her heart rate remained approximately 100 beats per minute (Fig. 1). The tilt-table test was repeated twice on 2 separate days, with similar results.

IMPLANTABLE SYSTEM

We used an implantable pulse generator that includes an embedded three-axis accelerometer (Intellis, Medtronic) to detect body position, as well as the Specify 5-6-5 paddle surgical lead (Medtronic). Together, the generator and paddle lead are typically used as a spinal cord stimulation system to treat chronic pain.[13] The system requires external wireless recharging.

We previously found that the most pronounced pressor responses to spinal cord stimulation occurred in a patient with a spinal cord injury when the region of the dorsal-root entry zones innervating the lower thoracic spinal segments was stimulated.[12] We developed a magnetic resonance imaging sequence that increases the contrast between the cerebrospinal fluid and neural structures[14]; this sequence enabled us to identify the target area containing the dorsal-root entry zone of the lower thoracic spinal segments in the current patient (Fig. 2A).

We performed surgery to implant the system while the patient was under general anesthesia (with propofol) to minimize depression of sympathetic nervous system activity.[12] The patient's blood pressure and heart rate were monitored with the use of an implanted arterial catheter that was connected to a monitoring system (IntelliVue X3, Koninklijke Philips). While the patient was in a prone position, a bilateral inferior laminectomy was performed at the T10 level and a flavectomy was performed at the T10 and T11 levels. A three-column, 16-contact (5-6-5) paddle surgical lead (Specify SureScan, Medtronic) was implanted epidurally through the T10–T11 laminectomy and advanced over the dorsal-root entry zone of the lower thoracic spinal segments (Fig. 2A). The stimulator and accelerometer were implanted subcutaneously in the paraumbilical

region and were connected to the electrode paddle by subcutaneous wires. There were no postoperative complications.

To verify that the position of the paddle lead induced pressor responses, we delivered continuous stimulation at a frequency of 100 Hz for 0.5 msec, with a current of 0 to 25 milliamperes. This stimulation triggered pressor responses that increased linearly with the amplitude of stimulation, reaching a maximum increase in systolic blood pressure of 20 mm Hg (Fig. S3). Stimulation configurations that did not target the dorsal roots induced pressor responses of limited amplitudes. The final location of the paddle lead is shown in Figure 2A.

STIMULATION SETTINGS

Stimulation waveforms were configured with the use of the CT900 Clinician Tablet Programmer (Model A710 Intellis software application, Medtronic). The system was configured 1 day after surgery with the use of the indwelling arterial catheter that was placed during surgery to measure blood pressure. Minor adjustments in stimulation waveforms were made at later time points. These configuration sessions, which were conducted while the patient was in the supine, sitting, and upright postural positions, occurred over a period of 7 days, with an average duration of 2 hours for each session.

Increases in the patient's blood pressure occurred when the entire range of accessible dorsal-root entry zones in the thoracic spinal cord was targeted. We thus configured three combinations of anodes and cathodes that targeted all the dorsal-root entry zones, from both sides (Fig. S4A). The amplitude and frequency of stimulation were fine-tuned so that the patient could maintain an upright position for at least 5 minutes while avoiding discomfort from muscle contraction or paresthesia due to local stimulation. Stimulation protocols were then created by combining three waveforms targeting the lower thoracic dorsal-root entry zones, as described previously.[12]

Accelerometer and stimulator responses to the upright, sitting, and supine positions were selected with the use of an external programmer. Detection of these postural orientations led to automated adjustment of the stimulation amplitude according to a prespecified, position-dependent stimulation protocol that had been defined by the patient and clinician. This closed-loop adjustment of the amplitudes adapted the system to the orthostatic challenge (Fig. S5). In order to measure sympathetic activation with stimulation, sudomotor efferent activity was quantified with the Sudoscan device (Impeto Medical) on the basis of measurements of chloride conductance in the patient's feet and hands. The assessment of sudomotor efferent activity was conducted without stimulation and with stimulation.

RESULTS

EVALUATION AFTER IMPLANTATION

We performed 20 tilt-table tests over a period of 7 days after the surgical implantation of the spinal cord stimulation system (Fig. S6). With the system turned off, tilting the patient to an upright position induced a decrease in systolic blood pressure from 160 mm Hg to 75 mm Hg in less than 3 minutes, after which the test was terminated and the patient was returned to the horizontal position (Figs. 2B, S7A, and S7B). With the system turned on, tilting the patient led to a slower decline in systolic blood pressure from 160 mm Hg to 75 mm Hg over a period of 10 minutes. Thus, the patient was able to complete a 10-minute tilt-table test without presyncopal symptoms (Fig. 2B). Moreover, there was an increase in sudomotor function in the patient's feet (Fig. S8).

During the next 3 weeks, for 3 consecutive days every week, the patient underwent autonomic neurorehabilitation in the hospital (Fig. S9). Each session consisted of approximately 5 repeated tilt-table tests with the system turned on. Under these conditions, the patient's systolic blood pressure remained above 80 mm Hg, so that she was able to complete a 10-minute tilt-table test without presyncope. After each of these sessions, the system was turned off.

During these first 3 weeks of neurorehabilitation, the patient reported episodes of postvoiding syncope while at home with the system turned off. These episodes occurred once per week, after 3 days without stimulation. Subsequently, we provided the patient with the oppor-

tunity to use the system at home with the previously determined programming configuration. After 3 additional weeks of autonomic neurorehabilitation and continuous use of the system turned on at home during the day while the patient was standing, she no longer had syncopal episodes or presyncopal prodromal symptoms such as ringing or buzzing in the ears and dizziness while standing or urinating.

Before surgery, the prodromal symptoms occurred so rapidly that the patient was unable to walk farther than 5 m before returning to a supine position. When the system was turned on during at-home use, she regained the ability to walk up to 50 m using only a four-wheeled walker for stability (Fig. 3A and Video 1). She also regained the ability to stand independently and return to bed without assistance (Fig. S10 and Video 1).

A video showing neuroprosthetic management of orthostatic hypotension is available at NEJM.org

EVALUATIONS AT 3 MONTHS AND LATER

Three months after implantation of the spinal cord stimulation system, the patient's systolic blood pressure remained above 75 mm Hg, a level that was sufficient to enable her to complete the entire 10-minute tilt-table test when the system was turned on. After this 3-month period, when the system was turned on, the patient reported almost no syncope when she was in an upright position at home (Fig. 3B). Continuous monitoring of her blood pressure over a period of 2 consecutive days confirmed that the system mediated an increase in the resting systolic blood pressure from 112 mm Hg to 125 mm Hg and reduced the variability of blood pressure by 18% (Fig. S11). At 3 months, when the system was turned on, she could walk more than 250 m using a walker at home (Fig. 3C). The patient also reported a general improvement in well-being (Video 1). During a follow-up session 8 months after implantation of the system, the patient reported that she was still using stimulation all day and that she no longer had syncope.

DISCUSSION

We report on a patient who had debilitating orthostatic hypotension due to multiple-system

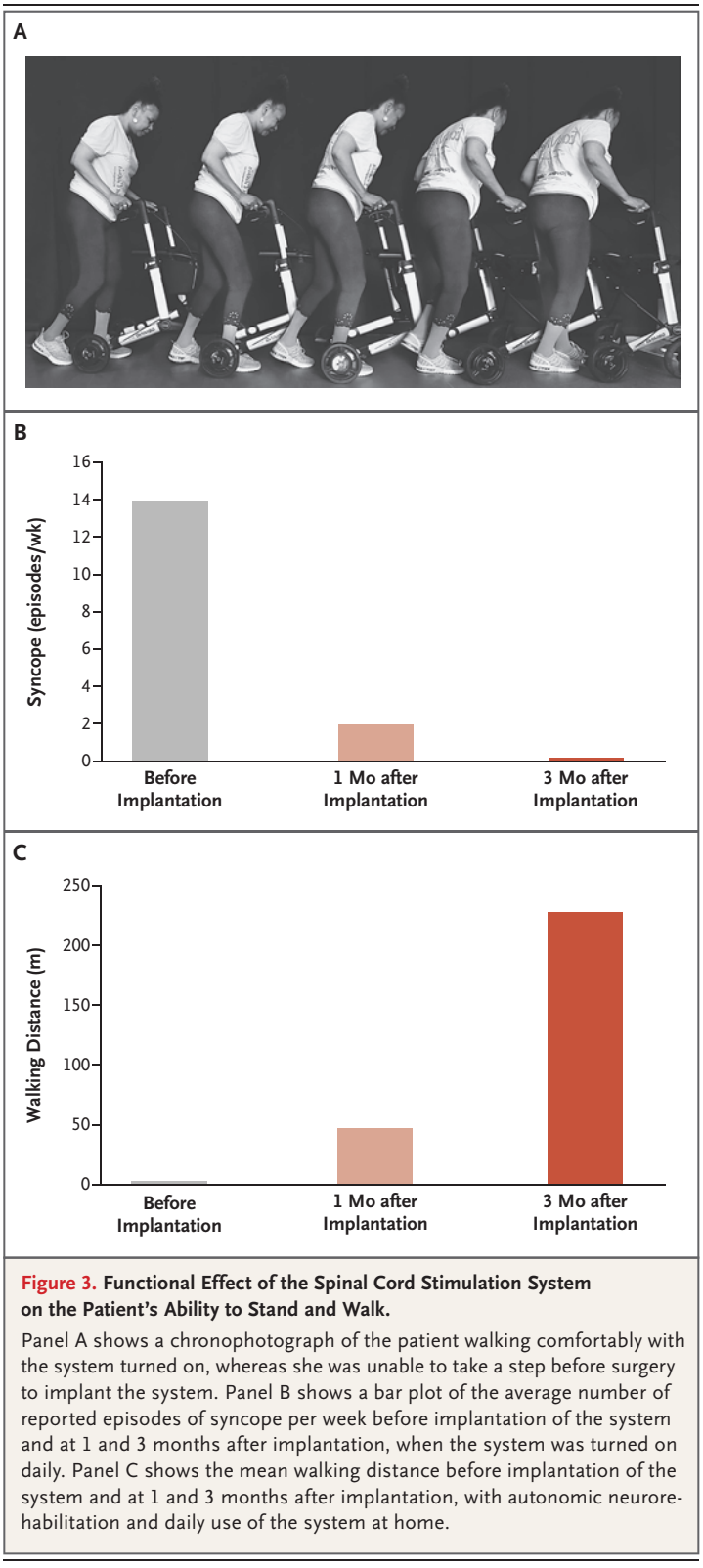

Figure 3. Functional Effect of the Spinal Cord Stimulation System on the Patient's Ability to Stand and Walk.

Panel A shows a chronophotograph of the patient walking comfortably with the system turned on, whereas she was unable to take a step before surgery to implant the system. Panel B shows a bar plot of the average number of reported episodes of syncope per week before implantation of the system and at 1 and 3 months after implantation, when the system was turned on daily. Panel C shows the mean walking distance before implantation of the system and at 1 and 3 months after implantation, with autonomic neurorehabilitation and daily use of the system at home.

atrophy of the parkinsonian type. For an 18-month period, she had been able to walk only 5 m or less without syncopal or presyncopal symptoms. We implanted a spinal cord stimulation system that ameliorated a drop in blood pressure when she assumed an upright posture, and at 3 months she was able to walk more than 250 m. The system slowed and delayed the development of hypotension after the patient stood, possibly allowing cerebral autoregulation to accommodate the reduced blood pressure.

Although the patient had undergone extensive rehabilitation before the surgical intervention, it remains possible that the combination of repeated tilt-table tests and walking attempts was partially responsible for the observed improvements. However, the stimulation had to be turned on in order for her to walk long distances, which suggests an essential role for the system in mediating clinical improvement.

Since the risks associated with this neurosurgical intervention appear to be limited and are similar to those associated with the use of the system for pain management, this approach may be considered for the support of hemodynamic stability in persons with multiple-system atrophy. In the current patient, the system mainly slowed the decline in blood pressure during orthostatic challenges, and the results were restricted to 8 months of follow-up. As of this writing, the patient has undergone 10 months of follow-up. In spite of the improvements in quality of life reported by this patient, the risks of implantation of the system should be balanced with the longer-term effectiveness of the treatment in patients with a progressive neurodegenerative disease.

Supported by the Defitech Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patient and her husband for their willingness to allow their experience to be shared.

REFERENCES

1. Stefanova N, Bücke P, Duerr S, Wenning GK. Multiple system atrophy: an update. Lancet Neurol 2009;8:1172-8.
2. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372:249-63.
3. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol 2018;18:125.
4. Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002;125:1070-83.
5. Figueroa JJ, Singer W, Parsaik A, et al. Multiple system atrophy: prognostic indicators of survival. Mov Disord 2014;29:1151-7.
6. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain 2008;131:1362-72.
7. Kato S, Oda M, Hayashi H, et al. Decrease of medullary catecholaminergic neurons in multiple system atrophy and Parkinson's disease and their preservation in amyotrophic lateral sclerosis. J Neurol Sci 1995;132:216-21.
8. Benarroch EE, Smithson IL, Low PA, Parisi JE. Depletion of catecholaminergic neurons of the rostral ventrolateral medulla in multiple systems atrophy with autonomic failure. Ann Neurol 1998;43:156-63.
9. Gray F, Vincent D, Hauw JJ. Quantitative study of lateral horn cells in 15 cases of multiple system atrophy. Acta Neuropathol 1988;75:513-8.
10. Oppenheimer DR. Lateral horn cells in progressive autonomic failure. J Neurol Sci 1980;46:393-404.
11. Nishie M, Mori F, Fujiwara H, et al. Accumulation of phosphorylated α-synuclein in the brain and peripheral ganglia of patients with multiple system atrophy. Acta Neuropathol 2004;107:292-8.
12. Squair JW, Gautier M, Mahe L, et al. Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury. Nature 2021;590:308-14.
13. Schultz DM, Webster L, Kosek P, Dar U, Tan Y, Sun M. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. Pain Physician 2012;15:1-12.
14. Rowald A, Komi S, Demesmaeker R, et al. Recovery of trunk and leg motor functions within one day after chronic complete paralysis. Nat Med (in press).