Acta Biomed 2020; Vol. 91, Supplement 13: e2020020 DOI: 10.23750/abm.v91i13-S.10533 

Original article

# Genetic and physiological autonomic nervous system factors involved in failed back surgery syndrome: A review of the literature and report of nine cases treated with pulsed radiofrequency

*Manuela Baronio[1], Mirko Baglivo[2], Giuseppe Natalini[1], Paolo Notaro[3], Astrit Dautaj[4,5], Stefano Paolacci[6], Matteo Bertelli[2,5,6]*

[1] Department of Anaesthesia and Intensive Care, Fondazione Poliambulanza, Brescia, Italy; [2] MAGI EUREGIO, Bolzano, Italy; [3] Pain Service, Niguarda Hospital, Milan, Italy; [4] MAGI Balkans, Tirana, Albania; [5] EBTNA-LAB, Rovereto (TN), Italy; [6] MAGI'S LAB, Rovereto (TN), Italy

**Abstract.** *Background and aim*: failed back surgery syndrome is one of the most important causes of chronic low back pain that involve the physiology of autonomic nervous system factors. Some genetic and molecular factor can be determinant in the development of failed back surgery syndrome and novel therapy are needed. Pulsed radiofrequency treatment could be an innovative treatment option for this syndrome. *Methods:* 44 patients classified with failed back surgery syndrome from the Poliambulanza Foundation Hospital of Brescia patients were treated with standard therapy for six months; 9 of these patients who showed no improvement were candidates for pulsed radiofrequency therapy for three months. *Results and Conclusions:* reduction of lumbar and radicular pain, disability and number of drug classes prescribed improved significantly ($p < 0.001$) in patients treated with pulsed radiofrequency compared to whom that follow only the standard therapy. The role of the nervous system is important for understanding how pulsed radiofrequency can improve the health of patients with back pain. We suggest that some genetic and molecular studies are needed for better understand the role of this therapy in back pain. (www.actabiomedica.it)

**Key words:** Failed back surgery syndrome, sympathetic nervous system, pulsed radiofrequency, Numeric Rating Scale, Oswestry Disability Index, back pain, autonomic nervous system, genetic factors

## Introduction

*Failed back surgery syndrome*

Failed back surgery syndrome (FBSS) is one of the main causes of chronic low back pain. A diagnosis of FBSS is made when the final result of spinal surgery does not meet the patient's expectations, defined before the operation, of pain recovery and quality of life (1). Low back pain is a worldwide problem, with an estimated global incidence of 9.4%, creating more disability than any other condition in the world (2).

Failed back surgery syndrome describes a large and heterogeneous group of patients who have undergone different types of spinal surgery with unsatisfactory outcomes (3). Inaccurate diagnosis is a major factor leading to FBSS, with as much as 58% of FBSS resulting from undiagnosed lateral stenosis of the lumbar spine (4). Surprisingly, numerous reports have demonstrated that 90-95% of cases normally classified as FBSS do not depend on the operation (5-7). Prior epidemiological studies indicate that between 0 and 83% of the underlying causes of FBSS are nonsurgical but intrinsic or pre-existing, and that it is difficult to diagnose them with clinical imaging tools (8).

*Functional role of the sympathetic nervous system in chronic back pain*

The sympathetic nervous system (SNS) is an integral anatomical and functional component of the spinal cord. It plays a fundamental role in pain control along the spinal tract and in its physiological sustainability. Several studies have investigated the implications and SNS involvement in chronic pain (9,10).

It has been postulated that autonomic nervous system dysfunction could affect the function of the muscles that control lumbosacral stability. This suggests an indirect cause due to functional impairment of the sympathetic nerves (11). In fact, musculoskeletal disorders are associated with altered regulation of the autonomic nervous system, which is the main cause of perceived pain (12).

The literature indicates that sympathetic nervous system impairment may contribute to the intensity and chronicity of pain. This may also be true for FBSS patients (9,10). Many studies have shown that some genetic alterations associated with sympathetic nervous system dysfunction can affect predisposition for chronic pain. Various forms of sympathetic chain neurolysis (sympathectomy) have, at one time or another, promised to be effective treatment options for complex regional pain syndrome. Over the past decade, spinal cord stimulation has emerged as a popular treatment for a variety of chronic neuropathic pain states, including complex regional pain syndrome. More sophisticated technology and better patient selection criteria have helped to improve spinal cord stimulation treatment outcomes. A recent review of the literature reported spinal cord stimulation to be effective in the management of complex regional pain syndrome, with success rates between 60% and 91% (13).

*Genetic factors involved in structural malformation of the spinal cord*

Several candidate genes have also been identified for familial inheritance of predisposition for adolescent idiopathic scoliosis. Some genome-wide association studies revealed that genes with Mendelian inheritance are associated with structural dysfunction of the spinal cord. For example, the gene most significantly associated with adolescent idiopathic scoliosis and scoliosis severity is *FBN1*, suggesting that rare variants may be useful predictors of curve progression (14). Marfan syndrome, a genetic connective tissue disorder caused by mutations in *FBN1*, is also related to painful scoliosis (15). Likewise *FBN2* has been studied in adolescent idiopathic scoliosis and also found to be associated with contractural arachnodactyly, a pathology characterized by chronic joint pain (14,16). *GPR126*, highly expressed in cartilage, was found to show variants in a large Japanese genome-wide association study (17). In another study, exome sequencing of three members with familial idiopathic scoliosis reveled *HSPG2* to be a potential contributor to the phenotype. Mendelian transmission of a rare missense variant in HSPG2, which encodes an extracellular matrix protein also known as perlecan, has been reported (18). Table 1 summarizes the genes involved in painful disorders of the spine.

*Pulsed radiofrequency treatment*

Pulsed radiofrequency treatment (PRF) consists in applying a pulsed electric field to nerve tissue with the aim of modulating transmission of the nerve impulse without the damaging heating effect. The field consists of 20 msec activation spikes at 500 kHz, alternating with 0.5 sec pauses (2 cycles/sec). With this method the temperature does not exceed 42°C. The treatment has characteristics that make it a better therapeutic option than conventional continuous radiofrequency. It is minimally invasive and does not cause discomfort to the patient (19).

Pulsed radiofrequency treatment could be a treatment option for FBSS because it is a non-neurolesive technique and does not cause any type of discomfort to the patient. It can be used in cases of neuropathic pain and repeated at short intervals. It is less subject to complications than other antalgic approaches to spinal pain.

## Materials and methods

A group of 44 FBSS patients from the Poliambulanza Foundation Hospital of Brescia were enrolled in

the present study. Clinical features (number and type of spinal operations, time between last surgery and onset of pain) were recorded. Information was collected on the diagnostic investigations performed. Detailed analgesic evaluation was made into pain characteristics and treatment (pharmacological and non-pharmacological), distinguishing antidepressant, anticonvulsant and non-steroidal anti-inflammatory drugs, opioids, physical and psychological rehabilitation, neurostimulation techniques, blockades and peridural infiltrations. Patients scored pain intensity according to a numerical rating scale (NRS) and level of disability by the Oswestry Disability Index (ODI).

All 44 patients followed 6-month standard therapy for FBSS. To monitor response to this treatment, lumbar and radicular pain (NRS), disability (ODI) and number of drug classes prescribed were recorded at zero time (T0), after two months (T2) and after six months (T6) of the standard therapy.

In our group of 44 patients with FBSS, those not responsive to standard pharmacological treatments (n=9) were proposed for and underwent peripheral pulsed radiofrequency treatment (PRF) applied at the paravertebral periganglion site. Inclusion criteria for PRF were: a diagnosis of FBSS; age >18 years; on drug treatment for at least six months; NRS>4; ODI>40%; intolerance of conventional therapies with side effects from drugs; no further indications for surgery or refusal of further surgical treatment; additional diagnostic/imaging results (traditional radiography, CT, MRI and EMG) in line with reported symptoms. All patients signed written informed consent to PRF.

The skin of the points identified for anesthesia was infiltrated with a 100 mm sterile disposable needle at an average depth of 6-8 cm, keeping the needle about 2.5-3 cm away from the spinal processes. Sensory stimulation was performed at 50 Hz for 1 msec and motor stimulation at 2 Hz for 2 msec to monitor pain perception. Then 1200 45-volt 20-msec pulses (500 kHz) were administered at each point with a Neurotherm pulse generator. The temperature never exceeded 42°C. At the end of the procedure the needle was removed, 2 cc naropine 0.2% was administered for local pain control and the patient was positioned supine.

The data is expressed as mean ± SD, median (1Q-3Q) or frequency (%). Pairwise comparison was performed by Student›s T, Wilcoxon, $\chi^2$ or Fisher's exact test as appropriate. Comparisons of data at 0, 2 and 6 months of treatment was performed with Friedman's test and post-hoc comparisons with Wilcoxon's test and Bonferroni correction.

Variations in pain score (NRS) and disability (ODI) and the number of drug classes were compared by analysis of variance for repeated measures. A p value less than 0.05 was considered significant. The mixed linear effects model was used to evaluate associations between number of treatments, NRS and ODI. Statistical analysis was performed with R 3.0.2 (http://www.R-project.org /).

## Results

Standard therapy did not bring about any improvement in terms of pain, disability and number of drug classes prescribed in nine FBSS patients. Table 1 shows their scores at T0, T2 and T6 after standard therapies (Table 2).

**Table 1**. Genes involved in painful disorders of the spine

| Gene (OMIM ID) | Disease (OMIM ID) | Inheritance | Manifestation |
|---|---|---|---|
| *FBN1* (*134797) | MFS (#154700) | AD | Painful scoliosis, kyphoscoliosis (14, 15) |
| *FBN2* (*612570) | CCA (#121050) | AD | Idiopathic spinal defect, kyphoscoliosis (14, 16) |
| *GPR126* (*612243) | LCCS9 (#616503) | AR | Adolescent idiopathic scoliosis (17) |
| *HSPG2* (*142461) | SJS1 (#255800) | AD | Adolescent idiopathic scoliosis (18) |

HGPPS = familial horizontal gaze palsy with progressive scoliosis; MFS = Marfan Syndrome; CCA = congenital contractural arachnodactyly; LCCS9 = lethal congenital contracture syndrome 9; SJS1 = Schwartz-Jampel Syndrome, type 1

**Table 2**. Pain, disability and number of drug classes in the first 6 months of standard therapy in nine non-responder FBSS patients

| | T0 | T2 | T6 | p |
|---|---|---|---|---|
| Lumbar Pain (NRS) | 5 (5-7) | 3 (2.75-4)* | 5 (4-6) | <0.001 |
| Radicular Pain (NRS) | 8 (7-9.25) | 5 (4-6)* | 8 (7-9) | <0.001 |
| Disability (ODI) | 62 (52-70.5) | 40 (32-54)* | 44 (35.5-56)* | <0.001 |
| no. drug classes | 2 (2-3) | 4 (4-5)* | 4 (4-5)* | <0.001 |

Values are medians *: p <0.01 with respect to T0.

**Table 3**. Comparison of NRS, ODI and number of drug classes in control and PRF group at T6 and T9. The p value compares the change occurring in the interval T6-T9 in the two groups

| | Control group (n=35) | | Pulsed radiofrequency (n=9) | | |
|---|---|---|---|---|---|
| | T6 | T9 | T6 | T9 | p |
| **Lumbar Pain (NRS)** | 4.5±1.8 | 4.4±1.9 | 5±1.6 | 1.3±1.1 | <0.001 |
| **Radicular Pain (NRS)** | 7.3±1.9 | 7.2±2.2 | 9±1.3 | 2.7±1.7 | <0.001 |
| **Disability (ODI)** | 44±11 | 49±11 | 53±23 | 29±14 | <0.001 |
| **Number of drug classes (*)** | 4.3±0.9 | 4.2±1.1 | 3.8±0.7 | 1.3±0.7 | <0.001 |

*: number of current therapies in the following classes: anticonvulsants, antidepressants, NSAIDs, opioids, blockades/infiltrations.

Pulsed radiofrequency treatment was begun at T6 for these nine FBSS patients. Lumbar and radicular NRS, ODI and number of drug classes improved significantly (p <0.001) in these patients between T6 and T9 (3 months of PRF). Time T6 was considered the basal time, since PRF is not contemplated in the first 6 months of care of FBSS patients (Table 3), when only standard treatment options are tried. In patients treated with PRF, 9 months (T9) coincides with three months of PRF.

## Discussion and conclusions

Failed back surgery syndrome is a major cause of chronic low back pain. It affects a large and heterogeneous group of patients who share a history of technically successful spinal surgery but with unsatisfactory results in terms of the patient's or surgeon's expectations. It often cannot be diagnosed by magnetic resonance imaging, and may therefore involve functional rather than strictly structural damage (8). Impaired SNS functions are well documented in FBSS patients and SNS dysfunction may contribute to the intensity and chronicity of pain (9,10).

Chronic back pain is not always recognized by diagnostic imaging. The identification of genetic factors can help understand predisposition for this disorder. In some spinal cord diseases, genetic studies have proved useful for understanding predisposition for chronic pain. Since there are few spinal surgery prognostic indicators, it would be useful to understand the influence of the genetic factors on response to spinal surgery.

In this context, we selected a group of FBSS patients, who were unresponsive to conventional pharmacological treatments, to undergo PRF. They were selected according to very precise inclusion and exclusion criteria. We monitored pain (NRS), disability (ODI) and the number of drug classes during 3 months of PRF in the PRF group and compared the data with that of patients treated with traditional methods.

Although the treatment period was only 3 months, and the number of patients was small, we found a significant improvement in NRS (radicular and lumbar),

ODI and number of drug classes used, in the PRF group. Attenuation of pain was already detectable at the end of the first month of PRF (T7) and continued to the end of the third month with a further reduction for root pain. At T9 a significant reduction in the number of drug classes used was observed. Disability progressively improved from a severe to moderate. During the three months of PRF, no patient showed PRF-related complications and no patient underwent additional PRF treatments at the end of the 3-month period.

*Future of Pulsed Radiofrequency in the treatment of back pain*

Some authors report that the type of surgical approach, such as pulsed electromagnetic field therapy, may influence the response rate of FBSS in favor of microsurgery (20). Other studies indicate that involvement of the autonomic nervous system at systemic and local levels is an important element in the pathogenesis of chronic musculoskeletal pain. It is postulated that chronic musculoskeletal disorders can benefit from improved autonomic nervous system balance (12). Pulsed radiofrequency treatment seems to be just as effective as sympathetic block in the treatment of lower limb complex regional pain syndrome type 1 (21).

The role of the nervous system is important for understanding how PRF can improve the health of patients with back pain. Pulsed radiofrequency treatment exposes a target neural structure to high-frequency electromagnetic oscillations (300–500 kHz) for very brief intervals (20 ms) followed by a silent period (480 ms) for heat dissipation. The temperature of the electrode tip does not exceed 42°C. This mode of radiofrequency may induce changes in the activity of neural circuits that mediate pain states (21).

Unconventional techniques, like PRF and chiropractic, target the lumbar spine and modulate pain. Certain studies have highlighted that application of PRF to the impaired rat SNS reduced chronic-constriction-injury-induced neuropathic pain by up-regulating expression of glial-cell-line-derived neurotrophic factor in nerve tissue (22,23). The mechanism of action of PRF remains unclear, although laboratory reports suggest that it enlists a neurobiological phenomenon that alters pain signaling, which some have described as neuromodulatory (21). A previous study suggested that some pathophysiological mechanisms underlying complex regional pain syndrome involved inflammatory and neurological pathways. More studies are needed to understand the molecular aspects of pain syndromes like FBSS (24).

In conclusion, more insights into the role of genetics in the structural and functional dysfunction of backache could be useful. Some people are predisposed to developing structural malformations involving the spinal cord. Many genetic predictors could help us understand who could benefit from PRF. Genetic predisposition for scoliosis and joint or cartilage dysfunction could offer prognostic markers for FBSS patients undergoing PRF. It could therefore be interesting to gain more insights into the role of genetics in predisposition for FBSS.

## Acknowledgments

We would like to thank Helen Ampt for English language editing. This work was supported by funding from the Provincia Autonoma di Trento, LP 6/99 (dgp 1045/2017).

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

## References

1. Waguespack A, Schofferman J, Slosar P, Reynolds J. Etiology of long-term failures of lumbar spine surgery. Pain Med 2002; 3: 18-22.
2. Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014; 73: 968–74.
3. Rabb CH. Failed back syndrome and epidural fibrosis. Spine J 2010; 10: 454-5.
4. Baber Z, Erdek MA. Failed back surgery syndrome: current perspectives. J Pain Res 2016; 9: 979-87.
5. Nachemson L. The lumbar spine: an orthopaedic challenge. Spine 1976; 1: 59-71.
6. Timothy MS, Carey WS, Garrett J, Jackman A. The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors and orthopedic surgeons. N Engl J Med 1995; 333: 913-7.
7. Bueff HU, Van Der Reis W. Low back pain. Prim Care 1996; 23: 345-64.

8. Slipman CW, Shin CH, Patel RK, et al. Etiologies of failed back surgery syndrome. Pain Med 2002; 3: 200-14.
9. Sahin N, Müslümanoğlu L, Karataş O, Cakmak A, Ozcan E, Berker E. Evaluation of sympathetic response in cases with failed back surgery syndrome. Agri 2009; 21: 10-5.
10. El-Badawy MA, El Mikkawy DME. Sympathetic dysfunction in patients with chronic low back pain and failed back surgery syndrome. Clin J Pain 2016; 32: 226–31.
11. Bordoni B, Marelli F. Failed back surgery syndrome: review and new hypotheses. J Pain Res 2016; 9: 17-22.
12. Hallman DM, Lyskov E. Autonomic regulation in musculoskeletal pain. Pain in Perspective, 2012.
13. Djuric V. Pulsed radiofrequency treatment of complex regional pain syndrome: A case series. Pain Res Manag 2014; 19: 186-90.
14. Buchan JG, Alvarado DM, Haller GE, et al. Rare variants in FBN1 and FBN2 are associated with severe adolescent idiopathic scoliosis. Hum Mol Genet 2014; 23: 5271-82.
15. Velvin G, Bathen T, Rand-Hendriksen S, Geirdal A. Systematic review of chronic pain in persons with Marfan syndrome. Clin Genet 2016; 22: 647-58.
16. Babcock D, Gasner C, Francke U, Maslen C. A single mutation that results in an Asp to His substitution and partial exon skipping in a family with congenital contractural arachnodactyly. Hum Genet 1998; 103: 22-8.
17. Kou I, Takahashi Y, Johnson TA, et al. Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. Nat Genet 2013; 6: 676-9.
18. Baschal EE, Wethey CI, Swindle K, et al. Exome sequencing identifies a rare HSPG2 variant associated with familial idiopathic scoliosis. G3 (Bethesda) 2015; 5: 167-74.
19. Bogduk N. Pulsed radiofrequency. Pain Med 2006; 7: 396-407.
20. Harper WL, Schmidt WK, Kubat NJ, Isenberg RA. An open-label pilot study of pulsed electromagnetic field therapy in the treatment of failed back surgery syndrome pain. Int Med Case Rep J 2015; 8: 13-22.
21. Freitas TS, Fonoff ET, Neto ORM, Deusdará RM, Waihrich ES, Kessler I. Pulsed radiofrequency of sympathetic lumbar plexus versus sympathetic block in the management of lower limb complex regional pain syndrome type 1. Journal of Pain & Relief 2014; 3: 3-7.
22. Owens EF, Hosek RS, Sullivan SGB, Russell BS, Mullin LE, Dever LL. Establishing force and speed training targets for lumbar spine high-velocity, low-amplitude chiropractic adjustments. J Chiropr Educ 2016; 30: 7-13.
23. Jia Z, Ren H, Li Q, Ji N, Luo F. Pulsed radiofrequency reduced neuropathic pain behavior in rats associated with upregulation of GDNF expression. Pain Physician 2016; 19: 49–58.
24. Baronio M, Sadia H, Paolacci S, et al. Molecular aspects of regional pain syndrome. Pain Res Manag 2020; 3: 1-10.

Received: 3 September 2020
Accepted: 14 October 2020
Correspondence:
Stefano Paolacci
Via delle Maioliche, 57/D, Rovereto (TN), Italy
E-mail: stefano.paolacci@assomagi.org