G Chir Vol. 36 - n. 4 - pp. 168-171
July-August 2015

clinical practice

Clinical problems in patient with Ehlers-Danlos syndrome and Multiple Chemical Sensitivity undergoing total thyroidectomy

V. PASTA[1]*, V. D'ORAZI[1,3]*, L. RUGGERI[2], M.F. TONI[2], P. URCIUOLI[1], G. TELLAN[2]

SUMMARY: **Clinical problems in patient with Ehlers-Danlos syndrome and Multiple Chemical Sensitivity undergoing total thyroidectomy.**

V. PASTA, V. D'ORAZI, L. RUGGERI, M.F. TONI, P. URCIUOLI, G. TELLAN

Clinical practice sometimes brings to face with situations quite peculiar, potentially dangerous for the patient's life. In the great majority of cases, pathologies associated with each other (cardiovascular, respiratory, neurological), while in other cases we can treat rare diseases or syndromes. It's considered exceptional the simultaneous presence of "rare" pathologies in a single patient. This exceptionality has been a push to treat a patient as a "unique" asking for help to deeper studies of pharmacogenetics. Our case reports the management of a patient with Ehlers-Danlos syndrome (EDS) and Multiple Chemical Sensitivity (MCS), undergoing a total thyroidectomy.

We found several problems, and we tried to find effective solutions for the management of the patient during the whole peri-operative process, from a clinical, pharmacological and also from a surgical point of view.

KEY WORDS: Multiple Chemical Sensitivity - Ehlers-Danlos Syndrome - Thyroidectomy - Pharmacogenetics.

Background

The Ehlers-Danlos syndrome (EDS) is a genetic disorder with autosomal dominant transmission that gives laxity in the ligaments, heart valve defects and impaired muscle contractility (1). To further complicate the picture there is a dysregulation of the autonomic nervous system (2).

We report a case of a patient of 57 years old affected by EDS associated with a serious drug intolerance (Multiple Chemical Sensitivity - MSC), candidate to total thyroidectomy for multinodular goiter disease, partially immersed in the upper left anterior mediastinum, with deviation and compression of the laryngotracheal axis.

We found several problems, and we tried to find effective solutions for the management of the patient during the whole peri-operative process, from a clinical, pharmacological and also from a surgical point of view.

Case report

The case object of our report represents an unusual condition, where a neuromuscular disease, the Ehlers-Danlos syndrome (EDS), is associated with a serious drug intolerance, the Multiple Chemical Sensitivity (MSC). The manifestations of this syndrome, with involvement of the cardiovascular and respiratory systems as well as integumentary, are secondary to exposure to substances found in everyday life or in response to common therapies.

The symptoms, reported even by the patient are the following: severe headache, intolerance to perfumes and for any type of cleanser, strong hyperosmia, muscle and joint pain of fibro-myalgic type, disturbance of sleep cycle with insomnia alternating with sudden drowsiness, cognitive disorders and memory deficits, dyspepsia, chronic fatigue, presence of tinnitus and dizziness (3). Among the events, often dramatic, are cited dyspnea related to laryngospasm and bronchospasm. The disease causes a deterioration of the patient's physical and psy-

[1] Department of Surgical Sciences, "Sapienza" University of Rome, Rome, Italy
[2] Department of Cardiovascular, Respiratory, Nephrological, Anaesthetic and Geriatric Sciences, "Sapienza" University of Rome, Rome, Italy
[3] Department of General Microsurgery and Hand Surgery, "Fabia Mater" Hospital, Rome, Italy

Corresponding author: Valerio D'Orazi, E-mail: info@valeriodorazi.com

* Co-first authors

© Copyright 2015, CIC Edizioni Internazionali, Roma

© CIC Edizioni Internazionali

chic status, forced to live dedicated to the control of the environment in which he carries out any type of activity (4). Furthermore, the inconstancy of manifestations exposes phenomena often unpredictable.

In particular, the patient reported a history of congenital joint hypermobility, muscles and skin weakness with slowed healing and tachycardia associated with palpitations. These symptoms were associated with the diagnosis of Elhers-Danlos hypermobile syndrome, defined according to the criteria of Brighton (5).

The patient reported multiple allergic reactions to environmental allergens, common nonionic surfactants present in detergents and soaps, disinfectant compounds and pharmaceutical preparations. Moreover, the treatment of these reactions, initially faced with a cortisone therapy, sparked repeated anaphylactoid reactions towards steroid anti-inflammatory drugs. In this framework, we found also the presence of gastroesophageal reflux disease, celiac disease, with iron deficiency anemia, and hyperinsulinism.

The patient had a body weight of 78 kg and a height of 157 cm which led to a BMI of 31, attributable to the category of Obesity grade I or moderate.

Preoperative phoniatric evaluation showed edema at the level of the posterior laryngeal commissure and arytenoids, related to the gastro-esophageal reflux disease (GERD). The study of the cardiovascular system highlighted the presence of a sinus tachycardia, correlated to thyroid hyperfunction, further reason that indicated surgery. For these reasons, the patient was classified to the level 2 of the scale for cardiac risk stratification in non-cardiac surgery (6). The chest x-ray study showed a partial tracheal compression caused by thyroid disease. The patient had bilateral joint hypermobility, particularly marked at the level of the shoulder, which had resulted in repeated spontaneous dislocations. A psychological support and an adequate benzodiazepine therapy were preoperative keys for the approach to this patient (7).

For positioning on the operating table were used pillows, reinforcements and thicknesses in particular for the cervical portion of the spine. Thermal homeostasis has been guaranteed with a hot air system (Bair Hugger 3M) and monitored with esophageal probe in order to maintain body temperature at 37 degrees Celsius. The airway management was achieved with a face mask during induction and then we proceeded to oro-tracheal intubation, performed with the aid of a video-laryngoscope (Glidescope - Verathon Medical).

We have chosen a general balanced anesthesia with an induction performed by inhalation of sevoflurane. The opioid used was fentanyl, inductive dosage 3 μg/kg, and for muscle relaxation rocuronium at a dose of 0.6 mg/kg. We used a standard monitoring: ECG, SpO_2, NIBP, $ETCO_2$, body temperature, TOF in addition to the concentration of anesthetic gases and vapors. We proceeded to the periodic monitoring of blood glucose. During anesthesia the concentration of sevoflurane was kept at values of about 0.8 MAC.

The maintenance was monitored with Bi-Spectral-Index (BIS View- ASPECT), with parameters of anesthesia between 60 and 40. The gas exchange were guaranteed by a mechanical ventilation pressure controlled to obtain physiological values of SpO_2 and $ETCO_2$.

The awakening from anesthesia occurred gradually, seeking spontaneous breathing through a reduction in the concentration of sevoflurane. At that point a dose of 4 mg/kg sugammadex was administered and, achieved autonomy and respiratory reflexes, we proceeded to wake the patient up.

Discussion

The hemodynamic management has proven free from problems with this pharmacological approach. The maintenance of the thermal homeostasis had the theoretical basis of not to alter the metabolism of administered drugs.

In fact the whole choice of anesthetics and other drugs used has been based on a pharmacogenetic analysis of the patient, obtained thanks to the collaboration with specialists of the Laboratory of Medical Genetics and the Advanced Molecular Diagnostics of our University. Thanks to the study of genetic polymorphisms, particularly regarding the enzymes involved in the metabolism of drugs and substances commonly used in the perioperative period, it was possible to obtain the definition of the genotype associated with each enzyme and to perform, than, a prediction and estimate of the impact on the metabolism of each classes of drugs (8). In the study were also included some transporter proteins for drugs within the liver microsomes (ABCC1 and 2) and enzymes responsible for the control of intracellular oxidative stress, indirect indicator of metabolic overload. Specifically, the patient has been found to be abnormal, from a metabolic point of view, as regards CYP2C19, the CYP3A5 liver enzymes involved in the metabolism of Propofol, of gastroprotective H2 antagonists and proton pump inhibitors (even if the patient reported a history of cronic assumption of the latter). Deficits have been highlighted for the enzymes related to the glutathione metabolism (GSTM1, GSTP1, GSTT1) that directed the post-operative pain treatment, eliminating the choice of paracetamol, particularly not recommended in this case.

Using a drug-kinetic response profile was crucial in adapting the dose of drugs administered to the metabolising capacity of the patient, and to exclude those substances that would cause an accumulation and adverse reactions. For example, we obtained the recovery of neu-

© CIC Edizioni Internazionali

romuscular function by avoiding the use of anticholinesterase drugs, since their metabolism by the enzyme PON1 C108T, results lacking. An unexpected anomaly based on the genetic data was the manifested intolerance to corticosteroids, medications to which the patient in the genetic tests did not show alterations. Systemic reactions, that followed the administration of these drugs, were reported during passed admissions to treat reactions to other xenobiotics. Opposite situation was revealed as regards the proton pump inhibitors, in which case, the genetic profile deposed for altered metabolism and, instead, had not caused adverse reactions, during the chronic use at home. We have another confirmation of how the management of patients with MSC is sometimes unpredictable for the coexistence of a disease immunological based, investigable with direct immunoassay studies (9) and a selective dysmetabolism, predictable on the basis of some genetic known polymorphisms associated with key proteins (10). The clinical and management problem is manifest when these two methods of approach to disease, reveal data in contrast to one or more pharmaceutical species, as happened in the case we reported.

The surgical procedure lasted about 90 minutes and, after having performed an exasperated prior hemostasis, during the surgical procedure has not been present any particular difficulties and/or complications. Despite the dip in the anterior superior mediastinum of the left lobe and the poor extensione of the neck, the relative laxity of the prethyroidal muscles facilitated the surgical approach. The only difference of note, was the evidence of numerous small abnormal bridge vessels that linked the parenchyma of the thyroid gland to the carotid artery and jugular vein. For this reason, we paid particular attention to preventive hemostasis during surgical dissection. In fact one of the peculiarities of the ED syndrome is the tendency to bleeding even after minor trauma thus increased in surgery (11). Even the protection and dressing of the wound has been chosen with care, opting for a type of patch to which the patient had not previously shown any reaction. The management of postoperative period, characterized by headache and muscle stiffness, has been entrusted only to physiotherapy.

Conclusions

The rational management of the patient with Ehlers-Danlos Syndrome (EDS) and Multiple Chemical Sensitivity (MCS), undergoing a total thyroidectomy, requires that the anesthesiologist, which compares with the disease, has clear which are the roads on which the pathology bases its complexity, so that he will be able to manage one by one, individually, with as many tools he possesses.

The pharmacogenetic study was the plus value of this treatment. In fact, it can be the future of the clinic, especially as regards the anesthetic management, for patients at risk for drug-related diseases.

Conflict of interest statement

The authors declare that they have no competing interests.

Acknowledgements

We would like to thank the patient who participated in this study. No financial support was received for this study.

Consent

Written informed consent was obtained from the patients for publication of this manuscript.

Author's contributions

VP, GT and VD designed and wrote the paper; VP, VD and PU performed the surgery; GT, LR and MFT performed general anesthesia and followed the patient in the postoperative period; VP, PU and VD performed the literature search and supported the writing of the paper.

All authors read and approved the final manuscript.

References

1. Malfait F, Wenstrup RJ, De Paepe A. Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type. Genet Med. 2010;12 (10):597-605. doi: 10.1097/GIM.0b013e3181eed412.
2. Johnston BA, Occhipinti KE, Baluch A, Kaye AD. Ehlers-Danlos syndrome: complications and solutions concerning anesthetic management. Middle East J Anaesthesiol. 2006;18(6):1171-84.
3. Bell IR, Miller CS, Schwartz GE, Peterson JM, Amend D. Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odor intolerance and chemical sensitivity. Arch Environ Health. 1996;51:9-21.
4. Black DW, Doebbeling BN, Voelker MD, Clark WR, Woolson RF, Barrett DH, Schwartz DA. Quality of life and health-services utilization in population-based sample of military personnel reporting multiple chemical sensitivity. J Occup Environ Med. 1999;41:928-33.
5. Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol. 2000;27(7):1777-9.
6. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med. 1977 Oct 20;297(16):845-50.
7. Guglielmi RS, Cox DJ, Spyker DA. Behavioral treatment of pho-

© CIC Edizioni Internazionali

bic avoidance in multiple chemical sensitivity. J Behav Ther Exp Psychiatry. 1994;25(3):197-209.

8. McKeown-Eyssen G, Baines C, Cole DE, Riley N, Tyndale RF, Marshall L, Jazmaji V. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. Int J Epidemiol. 2004;33(5):971-8. Epub 2004 Jul 15.
9. De Luca C, Scordo MG, Cesareo E, Pastore S, Mariani S, Maiani G, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. Toxicol Appl Pharmacol. 2010;1;248(3):285-92. doi: 10.1016/j.taap.2010.04.017. Epub 2010 Apr 27.
10. Meggs WJ. Mechanisms of allergy and chemical sensitivity. Toxicol Ind Health. 1999;15:331-338.
11. Wiesmann T, Castori M, Malfait F, Wulf H. Recommendations for anesthesia and perioperative management in patients with Ehlers-Danlos syndrome(s). Orphanet J Rare Dis. 2014;23(9):109. doi: 10.1186/s13023-014-0109-5.

© CIC Edizioni Internazionali