Archives of the Balkan Medical Union
vol. 51, no. 2, pp. 282-285
June 2016

CASE REPORT

BILATERAL ADRENALECTOMY AND NELSON'S SYNDROME

Adriana Elena Nica[1], Mara Carsote[2*], Dan Nicolae Păduraru[1], Ana Valea[3]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Carol Davila University of Medicine and Pharmacy & C.I.Parhon National Institute of Endocrinology, Bucharest, Romania*
[3]*Iuliu Haţieganu University of Medicine and Pharmacy & Clinical County Hospital Cluj-Napoca, Romania*

Summary

Introduction: Nelson's syndrome (NS) represents a rare but severe, potentially life-threatening condition, displayed as a complication after bilateral adrenalectomy was done for Cushing's disease (CD), involving corticotropinoma increase and ACTH (Adrenocorticotropic Hormone) elevation.
Case report: This is the case of a 65-year old male diagnosed in 1987 with CD caused by a macrocorticotropinoma of 1 cm. Bilateral adrenalectomy was performed during the same year (classic approach with one month between sides) and external pituitary radiotherapy during next year. The patient was further under substitution for chronic adrenal insufficiency. In 2003 the adenoma was larger by 0.2 cm maximum diameter. In 2010, an extremely ACTH increase to 1250 pg/ml (Normal levels between 7.2 and 62.3 pg/mL) was consistent for NS without significant increase of the pituitary mass. For the next four years the annual assays showed a progression of ACTH with stationary pituitary imagery scan and normal eye field exam. The patient refused surgery so external pituitary radiation therapy was done once again. One year later, he was re-examined: normal body mass index was found in association with a blood pressure of 130/80 mmHg under daily prednisone 7.5 mg and fludrocortisone 0.1 mg; still associating skin and oral hyperpigmentation at the gingival level, palatal mucosa, and oral mucosa. ACTH responded to therapy and decreased to 715 pg/mL, showing a partial control of NS thus close follow-up is advised.
Conclusion: Currently, bilateral adrenalectomy is rarely used for CD compared to what was done three - four decades ago; the consecutive adrenal insufficiency in association with remaining hypophyseal tumor may complicate with NS, a condition with less described protocols of follow-up and treatment. However, if pituitary surgery which remains the first option is not feasible, radiotherapy, as mentioned case, improves the ACTH levels, especially if the tumor mass does not associate severe local anatomical compression.
Key words: adrenalectomy, Cushing's syndrome, Nelson syndrome

Résumé

Surrénalectomie bilatérale et syndrome de Nelson

Introduction: le syndrome de Nelson (NS) représente un état rare, mais grave, potentiellement mortel, déroulé comme une complication survenue après la surrénalectomie bilatérale faite pour la maladie de Cushing (CD), impliquant l'augmentation du corticotropinoma et la hausse de la hormone corticotrope (ACTH).
Présentation de cas: C'est le cas d'un patient mâle en âgé de 65 ans, diagnostiqué en 1987 avec CD causée par un macrocorticotropinoma de 1 cm. La surrénalectomie bilatérale a été réalisée au cours de la même année (la méthode classique avec un mois différence entre les deux planes) et la radiothérapie hypophysaire externe pendant l'année suivante. Le patient est entré depuis en substitution de l'insuffisance surrénale chronique. En 2003, l'adénome s'est agrandi de 0,2 cm en diamètre. En 2010, une augmentation extrême de l'ACTH à 1250 pg /ml (niveaux normaux entre 7,2 et 62,3 pg/ml) était compatible pour le NS, sans une croissance significative de la masse de l'hypophyse. Pour les quatre prochaines années, les essais annuels ont montré une progression de l'ACTH avec l'arrêt du balayage de l'imagerie pituitaire et l'examen normal du chanys visuel. Le patiente a refusé l'intervention chirurgicale de sorte que la radiothérapie externe pituitaire a été faite à nouveau. Un an plus tard, il a été réexaminé: l'indice de masse corporelle normale a été trouvé en association avec une pression artérielle de 130/80 mmHg sous prédnisone 7,5 mg/jour et fludrocortisone o,1 mg; cependant y sont associées l'hyperpigmentation de la peau et orale au niveau gingival, de la muqueuse palatine et de la muqueuse buccale. L'ACTH à répondu à la thérapie et a diminué à 715 pg/ml, montrant un contrôle partiel du NS; on recommande ainsi un suivi de près.
Conclusion: Habituellement, la surrénalectomie bilatérale est rarement utilisée pour les DD par rapport à ce qu'elle était - il y a trois-quatre décennies; l'insuffisance surrénale consécutive associée au reste de la tumeur hypophysaire peut se compliquer avec le NS, une complication aux protocoles moins bien décrits de suivi et de traitement. Néaumoins, si la chirurgie de l'hypophyse qui reste la première option, est impossible, la radiothérapie, comme dans le cas présenté, améliore les niveaux de l'ACTH, surtout si la masse tumorale n'associe pas une compression locale anatomique grane.
Mots clefs: surrénalectomie bilatérale, maladie de Cushing, syndrome de Nelson

Correspondence address: *Mara Carsote, MD*
C. Davila University of Medicine and Pharmacy & C.I.Parhon National Institute of Endocrinology
Aviatorilor Ave 34-38, Bucharest, Romania *e-mail: carsote_m@hotmail.com*

Introduction

Nelson's syndrome (NS) represents a rare but severe, potentially life-threatening condition, displayed as a complication after bilaterally adrenalectomy was done for Cushing's disease, and associating the enlargement of the prior pituitary ACTH (Adrenocorticotropic Hormone) producing adenoma and elevated ACTH levels. (1,2) It is estimated that NS develops in about 8-44% of patients (depending on series cases) who have undergone this specific type of surgery related to both adrenals which is actually an unusual current therapeutically solution for a corticotropinoma since other options as pituitary surgery or pasireotide became much more important and efficient. (3,4,5) The first line therapy for Cushing disease is neurosurgical and adjuvant medication as pasireotide might help despite multiple side effects. (6,7) NS usually occurs 1 to 4 years after the procedure of bilateral adrenal removal was performed but the ranges vary from 2 months up to 24 years after surgery. (8,9) The clinical picture of NS is heterogeneous and it might be registered even in cases with a good surgical outcome which otherwise cannot predict the disease; most of symptoms are related to the local effects of the pituitary tumor on surrounding structures including secondary pituitary insufficiency, and diabetes insipidus, eye fields defects with various visual disturbances such as diplopia, bi-temporal hemianopsia or quadranopsia and increased intra-cranial pressure with associated headache. (10,11) A high level of ACTH may cause skin hyperpigmentation on different areas, not only on the sun-exposed surfaces. (12) The diagnosis NS is challenging and there are still some controversial criteria but one option is the confirmation of NS if a patient with adrenal insufficiency after bilateral adrenalectomy for Cushing's disease has minimum one of the following: an expanding pituitary mass lesion compared to pre-surgery image; an elevated plasma morning (8 a.m.) level of ACTH (above the level of 500 pg/mL) or progressive elevation of ACTH (a rise of more than 30% detected while the subject is followed-up having at least three consecutive assays with increasing ACTH). (13) The best therapy for cases with confirmation of clinical, hormonal and imagery aspects regarding NS is transsphenoidal surgery while radiotherapy and cabergoline are potential alternative options and only partially efficient; however, mild cases without classical picture may be conservatively treated for a long period of time. (14,15)

Case report

This is a case presentation of a Caucasian Romanian male with a history of bilateral surgery for Cushing's disease who was followed for almost three decades after this procedure and he developed in the mean time a mild phenotype of Nelson's syndrome.

A 65-year old male patient was diagnosed in 1987 with Cushing's disease (complicated with high blood pressure and diabetes mellitus) caused by a macroadenoma of 1 centimeter (cm) maximum diameter. The therapy decided at that moment was bilateral adrenalectomy which was performed during the same year (classic approaches with a month between the two procedures). (fig. 1) The procedure was done without any complications and the patient was discharged with the recommendation of oral medication for chronic adrenal insufficiency caused by adrenals removal. Consecutively, he was offered external pituitary radiotherapy during next year (a procedure largely recommended in Romania at that time in order to prevent a potential pituitary tumor growth). He continued the adrenal substitution but he had a relatively poor compliance to periodic endocrine check-up. He was further admitted in 2003 and the pituitary adenoma seemed larger than initially based on magnetic resonance imagery scan (of 0.8 by 1 by 1.2 cm). No further treatment was recommended except for periodic endocrine control but he only had done some endocrine tests in 2008 showing, as expected, the persistence of central hypothyroidism but with controlled under daily orally levothyroxine substitution. (table 1) The patient returned for a complete assessment in 2010. At this moment, extremely elevation of ACTH level to 1250 pg/ml (Normal levels are between 7.2 and 62.3 pg/mL) was consistent for NS without significant increase of the pituitary mass. (table 1) For the next four years the annual assays showed a progression of ACTH with stationary pituitary imagery scan and normal eye field exam. The patient refused surgery so external pituitary radiation therapy was done once again. One year later, he was re-examined: normal body mass index was found in association with a blood pressure of 130/80 mmHg under daily prednisone 7.5 mg and fludrocortisone 0.1 mg; regular sinus rhythm of 60 beats per minute (with thyroid substitution of 125 μg levo-thyroxine per day), still associating skin and oral hyperpigmentation at the gingival level, palatal mucosa, and oral mucosa. The imagery was stationary pituitary. (fig. 2) The biochemical parameters revealed mild hypercholesterolemia of 209 mg/dL (normal levels less than 200 mg/dL), and high triglycerides of 174 mg/dL (normal levels less than 150 mg/dL). ACTH responded to therapy and decreased to 715 pg/mL, showing a partial control of NS thus close follow-up is advised. (table 1)

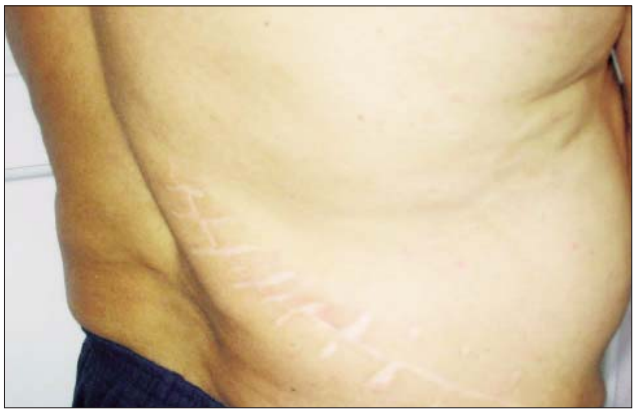

Figure 1 - The scar on the right side 28 years after bilateral adrenalectomy on a 65-year old male

Table 1 - Biochemical and hormonal values of a 65-year old male with bilateral adrenalectomy performed in 1987 for Cushing's disease (in association with external pituitary irradiation) who slowly developed Nelson's syndrome. Some of the data are not available (NA) because of endocrine testing done on different medical centers and poor patient's compliance to recommendation of periodic check-up during these three decades. In 2008, the blood ionogram shows an intermittent acute form of chronic adrenal insufficiency. In 2014 the patient had a second radiotherapy done

Parameter	The patient's assessment						Normal limits	Units	observation
Years since bilateral adrenalectomy (calendar)	21 (2008)	24 (2011)	25 (2012)	26 (2013)	27 (2014)	28 (2015)			
ACTH (Adrenocorticotropic Hormone)	NA	>1250	>1250	>1250	>2000	715	7.2-63.3	pg/mL	under prednisone 7.5 mg/day & fludrcortisone 0.1 mg/day
TSH (Thyroid stimulating hormone)	1.17	1.49	10.3	NA	3.28	3.39	0.4-4	μUI/mL	under Levo-thryoxine 125μg/day
FT4 (Free-levothyroxin)	1.20	1.27	1.13	NA	1.4	1.14	0.89-1.76	ng/mL	
Prolactin	NA	12.9	4.42	NA	NA	10.1	1.8-17	ng/mL	
Plasma testosterone	NA	NA	NA	NA	NA	5.87	1.8-9	ng/mL	
Plasma sodium	116	134	133	133		133	136-145	mEq/L	
Plasma potassium	5.8	4	4.5	4.5		4.1	3.5-5.1	mEq/L	

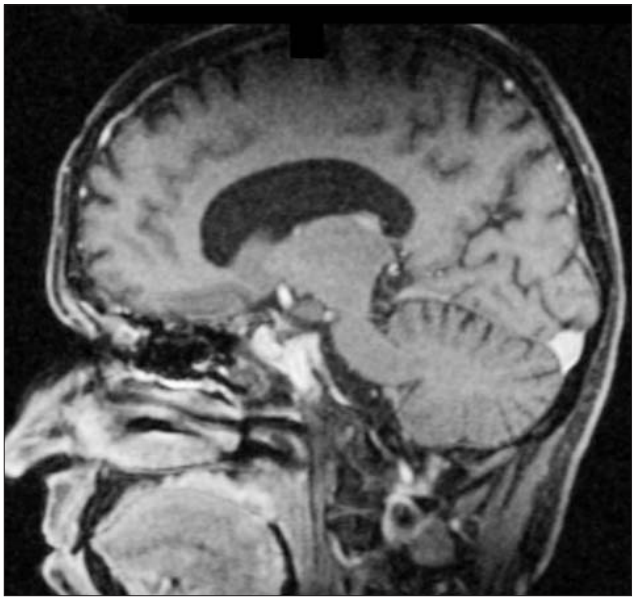

Figure 2 - Pituitary Magnetic Resonance Imagery on a 65-year old male diagnosed with Nelson's syndrome (presented scan is from 2015, 28 years after bilateral adrenalectomy)

Discussion

Some observations are necessary in correlation with the long medical history of this male case. First, the clinical phenotype of bilateral adrenalectomy-related NS was suggestive in this particular situation based on persistent and intermittently exacerbated skin and mucosal hyperpigmentation which may actually be found frequent. (16,17) Secondly, the therapeutically options for NS are limited especially if pituitary surgery was refused by the patient. The pituitary neurosurgical procedure might be successful and currently it represents the first line therapy for NS especially if optic chiasm is compressed (which was not registered on this case). (18) Some authors recommend as alternative the therapy with dopamine agonist cabergoline. (19,20) Pituitary radiotherapy immediately after bilateral adrenalectomy lowers the risk of NS in some cases but no in all (21). Currently, there is no standard procedure and schedule of check-up for patients with NS since the complication after bilateral surgery varies as timing, clinical and endocrine presentation and there are no clear risk factors for developing the condition; moreover bilateral adrenal removal is regarded as palliative. (22,23). Thirdly, in cases with slow progression, a long-term survival is seen, as this presented man case. Related to adrenal approach, currently the laparoscopic procedure (including one time for both adrenals) offers a better outcome. (24)

Conclusion

Currently, bilateral adrenalectomy is a rare therapeutically option for Cushing's disease compared to what was done three - four decades ago; the consecutive adrenal insufficiency in association with remaining hypophyseal tumor may complicate with Nelson's syndrome, a condition with less described protocols of follow-up and treatment. However, if pituitary surgery which remains the first option is not feasible, radiotherapy, as mentioned case, improves the ACTH levels, especially if the tumor mass does not associate severe local anatomical compression.

Conflict of interest

The authors have nothing to declare.

Acknowledgement

We thank the medical team and the patient.

References

1. Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ. Long-term results of total adrenalectomy for Cushing's disease. World J Surg. 2000; 24:108–113.
2. Van Aken MO, Pereira AM, van den Berg G, Romijn JA, Veldhuis JD, Roelfsema. Profound amplification of secretory-burst mass and anomalous regularity of ACTH secretory process in patients with Nelson's syndrome compared with Cushing's disease. Clin Endocrinol (Oxf). 2004; 60:765–772.
3. Chapuis Y, Pitre J, Conti F, et al. Role and operative risk of bilateral adrenalectomy in hypercortisolism.World J Surg. 1996. 20(7):775-9; discussion 779-80.
4. Tiyadatah BN, Kalavampara SV, Sukumar S, Mathew G, Pooleri GK, Prasanna AT, et al. Bilateral Simultaneous Laparoscopic Adrenalectomy in Cushing's Syndrome: Safe, Effective, and Curative. J Endourol. 2012; (2):157-63.
5. Rizk A, Honegger J, Milian M, Psaras T. Treatment Options in Cushing's Disease. Clin Med Insights Oncol. 2012. 6:75-84.
6. Valea A, Morar A, Pop D, Carsote M, Ghemigian A, Dumitrache C. Infertility as the onset of Cushing's disease: is pasireotide a treatment option?. Ars Medica Tomitana. 2015;3(21);128-131.
7. Valea A, Carsote M, Ghemigian A, Morar A, Dumitru DP, Georgescu CE. Severe hepatocytolisis syndrome – a challange in medical therapy of Cushing's disease. Ars Medica Tomitana. 2015;3(21);132-136.
8. Gil-Cárdenas A, Herrera MF, Díaz-Polanco A, Rios JM, Pantoja J. Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. Surgery. 2007;141:147–152.
9. Arshad F, Laway BA, Ahmad M, Showkat HI, Kotwal S, Ahmad Mir S.. Leksell Gamma Knife: An Effective Non Invasive Treatment for Rare Case of Nelson's Syndrome. Int J Endocrinol Metab. 2013 Summer; 11(3): 195–198.
10. Thomas CG Jr, Smith AT, Benson M, Griffith J. Nelson's syndrome after Cushing's disease in childhood: a continuing problem. Surgery. 1984;96(6):1067-77.
11. Assié G, Bahurel H, Bertherat J, Kujas M, Legmann P, Bertagna X. The Nelson's syndrome... revisited. Pituitary. 2004;7(4):209-15.
12. Munir A, Newell-Price J. Nelson's Syndrome. Arq Bras Endocrinol Metabol. 2007;51(8):1392-6.
13. Barber TM, E Adams, O Ansorge J V Byrne, N Karavitaki, Wass AH. Nelson's syndrome. Eur J Endocrinol. 2010;163(4):495-507.
14. Kemink SA, Grotenhuis JA, De Vries J, Pieters GF, Hermus AR, Smals AG. Management of Nelson's syndrome: observations in fifteen patients. Clin Endocrinol (Oxf). 2001;54(1):45-52.
15. Howlett TA, Plowman PN, Wass JA, Rees LH, Jones AE, Besser GM. Megavoltage pituitary irradiation in the management of Cushing's disease and Nelson's syndrome: long-term follow-up. Clin Endocrinol (Oxf). 1989;31(3):309-23.
16. Ernest I, Ekman H. Adrenalectomy in Cushing's disease. A long-term follow-up. Acta Endocrinologica Supplement.1972; 160:3–41.
17. Kasperlik-Załuska AA, Nielubowicz J, Wisławski J, Hartwig W, Załuska J, Jeske W, Midalska B . Nelson's syndrome: incidence and prognosis. Clinical Endocrinology. 1983;19: 693–698.
18. Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ. Neurosurgical treatment of Nelson's syndrome. Journal of Clinical Endocrinology and Metabolism. 2002;87: 5465–5469.
19. Casulari LA, Naves LA, Mello PA, Pereira Neto A, Papadia C. Nelson's syndrome: complete remission with cabergoline but not with bromocriptine or cyproheptadine treatment. Horm Res. 2004; 62(6):300-5.
20. Shraga-Slutzky I, Shimon I, Weinshtein R. Clinical and biochemical stabilization of Nelson's syndrome with long-term low-dose cabergoline treatment. Pituitary. 2006; 9(2):151-4.
21. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, et al. The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab. 1995; 80: 165–171.
22. Assié G, Bahurel H, Coste J, Silvera S, Kujas M, Dugué MA, et al. Corticotroph tumor progression after adrenalectomy in Cushing's Disease: a reappraisal of Nelson's Syndrome. J Clin Endocrinol Metab. 2007; 92:172–179.
23. Prajapati OP, Verma AK, Mishra A, Agarwal G, Agarwal A, Mishra SK. Bilateral adrenalectomy for Cushing's syndrome: Pros and cons. Indian J Endocrinol Metab. 2015;19(6):834-40.
24. Lezoche G, Baldarelli M, Cappelletti Trombettoni MM, Polenta V, Ortenzi M, Tuttolomondo A, Guerrieri M. Two Decades of Laparoscopic Adrenalectomy: 326 Procedures in a Single-Center Experience. Surg Laparosc Endosc Percutan Tech. 2016;26(2): 128-32.