



www.ijcci.info

International Journal of Clinical Cases and Investigations

Case Study

Management of Nelson's Syndrome with Persistent Hypercortisolism

Anurag R. Lila¹, ✉ Vijaya Sarathi¹, Varsha Jagtap¹, Tushar R. Bandgar², Padma S. Menon³, and Nalini S. Shah⁴

¹ Senior resident, ² Associate professor, ³ Professor, ⁴ Professor and head
Department of Endocrinology, Seth GSMC, KEM Hospital, Mumbai - 400012

International Journal of Clinical Cases and Investigations 2011. Volume 2 (Issue 4), 16:19, 6th May 2011

Abstract:

27 years old woman with Cushing's disease had persistent hypercortisolism despite two transsphenoidal surgeries and total bilateral adrenalectomy. Pituitary imaging revealed increase in size of corticotroph adenoma as compared to the pre-adrenalectomy scan and plasma ACTH value was 884 pg/ml. She was diagnosed to have Nelson's syndrome with persistent hypercortisolism. ACTH-stimulated ¹⁸F-FDG-PET/CT localized bilateral remnant and ectopic adrenal tissue. Hypercortisolism initially responded to cabergoline but later escaped at 6 months. Conventional pituitary radiotherapy effectively controlled hypercortisolism and progression of pituitary adenoma over a period of one year. We discuss the difficulties in diagnosis and management in this case of Nelson's Syndrome with persistent hypercortisolism.

Case report:

27 years old woman presented to us (year: 2008) with complaints of weight gain with mooning of face, generalized hyperpigmentation, stretch marks and secondary amenorrhea. She was diagnosed as Cushing's disease (CD) (histopathologically proven) and had undergone transsphenoidal pituitary adenomectomy on two occasions (year: 2003 and 2005). Later for the persistent disease she underwent total bilateral adrenalectomy (TBA) (year: 2005). After the adrenal surgery hypocortisolism was documented and she was put on steroids replacements. 18 months later, her 8.00 am serum cortisol was normal and steroid replacement was stopped. Her investigations in September 2008 (8.00 am serum cortisol - 29.1 µg/dl, 8.00 am plasma ACTH - 884 pg/ml, midnight serum cortisol - 22.4 µg/dl, 2 days standard 2mg dexamethasone suppressed cortisol - 17.0 µg/dl) proved ACTH dependent endogenous hypercortisolism. Magnetic resonance imaging (MRI) of pituitary revealed significant increase in size of corticotroph adenoma (8 x 8 mm) as compared to the pre-adrenalectomy scan (Fig 1). 8.00 am plasma ACTH value was 884 pg/ml and was significantly higher than pre-adrenalectomy value (8.00 am plasma ACTH value - 98 pg/ml). She was diagnosed to have Nelson's syndrome (NS) with persistent hypercortisolism. Computerized tomography scan abdomen was negative for residual or

ectopic adrenal tissues. Since ido-cholesterol scan was not available, 2-(¹⁸F)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) was done which showed bilateral adrenal remnants and an ectopic adrenal tissue near left renal hilum. The management options were either pituitary adenoma directed (surgery/radiation/drugs) or adrenal remnant directed (surgery/drugs). Adrenal directed treatment was deferred for the fear of the central tumor growth with loss of endogenous cortisol feed back. The patient declined a repeat pituitary adenomectomy or radiotherapy so was put on cabergoline (3.5 mg/week). Three months later she presented with hypocortisolemic symptoms with 8.00 am serum cortisol – 3 µg/dl and plasma ACTH - 119.6pg/ml. MRI of pituitary was same as compared to the previous scan. Cabergoline was stopped and she was put on steroid replacement. One month later her 8.00 am serum cortisol was 10.5 µg/dl and steroid replacement was withheld. Again for the persistent symptoms, reevaluation in April 2009 showed hypercortisolism (8.00 am serum cortisol- 17.8 µg/dl, midnight serum cortisol - 13.6 µg/dl, 2 days standard 2mg dexamethasone suppressed cortisol - 14.6 µg/dl). MRI of pituitary was unaltered. She was put on oral cabergoline 3.5 mg/week and prednisolone 2.5 mg/day from April 2009 to August 2009. Initially she lost weight and her menstrual cycles regularized and had hypocortisolism (8.00 am cortisol – 3.0 µg/dl) on this regimen. Symptoms recurred and investigation in August 2009 showed treatment escape (8.00 am serum cortisol 15.5 µg/dl, midnight serum cortisol - 14.7 µg/dl, 2 days 2mg standard dexamethasone suppressed cortisol -10.8 µg/dl) with unchanged MRI pituitary findings. Patient was counseled regarding the treatment options. She declined repeat pituitary surgery and opted pituitary radiotherapy. She received sellar irradiation in December 2009 (45 grays in 25 fractions). Follow up 1 year later showed improvement in her health. She lost 9 kg of weight and is cycling regularly. Latest investigations are 8.00 am serum cortisol – 12.6 µg/dl, 8.00 am plasma ACTH - 145 pg/ml, midnight serum cortisol - 4.4 µg/dl, and 2 days 2mg standard dexamethasone suppressed cortisol – 1.3 µg/dl.

Discussion:

Nelson's syndrome was defined in an earlier era using sellar radiograms as proof of an enlarging pituitary tumor with progressive hyperpigmentation after TBA for Cushing's syndrome. In recent times, using MRI as proof of corticotroph tumor progression and due to the availability of sensitive ACTH assays (cut off > 200 pg/ml), the pathology can be indentified early¹. Our patient showed both corticotroph progression and plasma ACTH values > 200 pg/ml after TBA. In addition our patient was Cushingoid and had endogenous hypercortisolism demonstrated by altered cortisol circadian rhythm and unsuppressed post dexamethasone cortisol values.

Residual adrenocortical function have been demonstrated in 9/37(25%) after TBA for CD (2). In this series only one single case (1/37) was reported to have NS with hypercortisolemia similar to our case. Another large study of CD patients treated with TBA in which 12 (27%) had adrenal remnants. Of these 12 patients, 2 developed early recurrence of CD from hyperfunctioning adrenal remnant tissue³. The possibility of residual adrenocortical function after TBA should be considered and steroid replacements should be tailored accordingly to prevent exogenous steroid excess. In rare case scenario like our case NS may present as endogenous hypercortisolism.

In ¹⁸F-FDG-PET/CT study hypermetabolism was seen at the right and left suprarenal regions and at a focus near the left renal hilum. The increment in the metabolic activity after 30 min of cosyntropin administration (250 µg) proved the areas as adrenal tissue⁴. To the best of our knowledge use of ACTH-stimulated ¹⁸F-FDG-PET/CT as diagnostic modality to localize adrenal tissue has not been described earlier.

Pituitary adenomas express dopamine receptors ubiquitously. There are reports of cabergoline induced remission of NS⁵ and tumor resolution⁶. There is no report of its usage in NS with persistent hypercortisolism. In our case pituitary adenoma was responsive to cabergoline by decreasing the ACTH drive lead to hypocortisolism. MRI of pituitary was same as compared to the previous scan ruling out any tumor infarct or hemorrhage. For safety small dose of steroid replacement was added later. After initial response, treatment escape occurred at 6 months and drug was stopped. Pivonello et al reported treatment escape in 5/15 (33%) of cabergoline responsive CD patients after 6–18 months of drug administration⁷.

Pituitary surgery should be the first-line treatment option for NS⁸. Progression of corticotroph adenoma in NS may occur, despite surgical intervention in some patients and adjuvant radiotherapy may be required in 20–30% of such patients^{8,9}. Pituitary radiation has been used as preventive mean, but data on use of radiotherapy as first line option in NS is limited. In our case the patient declined repeat pituitary directed surgery. Conventional fractionated radiotherapy proved to be efficacious in term of control of hypercortisolism and non progression of pituitary adenoma over a period of one year.

Conclusion:

Nelson's syndrome may coexist with endogenous hypercortisolism. ACTH-stimulated ¹⁸F-FDG-PET/CT may be helpful in localizing adrenal tissue. Cabergoline may be used as bridge management till the radiotherapy shows its effect.

References:

1. **Assié G, Bahurel H, Coste J, Silvera S, Kujas M, Dugué MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X.** Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome. *J Clin Endocrinol Metab.* 2007; 92:172–179.
2. **Kemink L, Hermus A, Pieters G, Benraad T, Smals A, Kloppenborg P.** Residual adrenocortical function after bilateral adrenalectomy for pituitary-dependent Cushing's syndrome. *J Clin Endocrinol Metab.* 1992; 75:1211–1214.
3. **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.
4. **Lila AR, Malhotra G, Sarathi V, Bandgar TR, Menon PS, Shah NS.** Localization of remnant and ectopic adrenal tissues with cosyntropin-stimulated ¹⁸F-FDG-PET/CT in a patient with Nelson syndrome with persistent hypercortisolism. *J Clin Endocrinol Metab.* 2010; 95:5172–5173.
5. **Pivonello R, Faggiano A, Di Salle F, Filippella M, Lombardi G, Colao A.** Complete remission of Nelson's syndrome after 1-year treatment with cabergoline. *J Endocrinol Invest.* 1999; 22:860–865.
6. **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; 62:300–305.
7. **Pivonello R, De Martino MC, Cappabianca P, De Leo M, Faggiano A, Lombardi G, Hofland LJ, Lamberts SW, Colao A.** The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *J Clin Endocrinol Metab.* 2009; 94:223–30.

8. **Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ.** Neurosurgical treatment of Nelson's syndrome. *J Clin Endocrinol Metab.* 2002; 87:5465–5469.
9. **Kemink SA, Grotenhuis JA, De Vries J, Pieters GF, Hermus AR, Smals AG.** 2001
10. Management of Nelson's syndrome: observations in fifteen patients. *Clin Endocrinol (Oxf).*2001; 54:45-52.

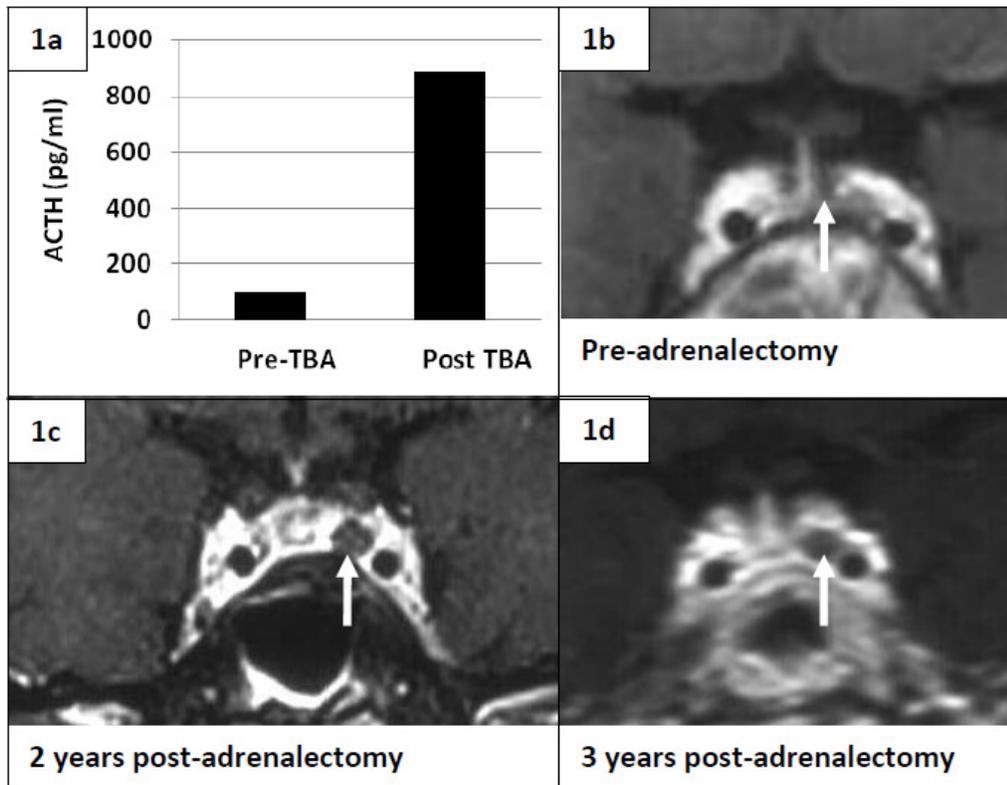


Fig 1: Comparison of pre- and post total bilateral adrenalectomy (TBA) 8:00 am plasma ACTH values (1a) and pre-TBA MRI (1b) with that after 2 years (1c) and 3 years (1d) of post-TBA.