Case Report

Nelson's syndrome presenting as bilateral oculomotor palsy

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ABSTRACT

Nelson's syndrome refers to a clinical spectrum arising from progressive enlargement of pituitary adenoma and elevated adrenocorticotrophic hormone after total bilateral adrenalectomy for Cushing's disease comprising of hyperpigmentation, visual field defects which can be life threatening. We report here a 50-year male presenting with rapid onset of Nelson's syndrome with an unusual finding of bilateral oculomotor palsy mistakenly treated as ocular myasthenia.

Key words: Cushing's disease, Nelson's syndrome, oculomotor palsy

Introduction

Don Nelson first described a syndrome which consisted of visual field defects, hyperpigmentation, elevated plasma ACTH levels and a large sellar mass which is now named after him.[1] Nelson's syndrome (NS) refers to a clinical spectrum arising from progressive enlargement of pituitary adenoma and elevated adrenocorticotrophic hormone after total bilateral adrenalectomy for Cushing's disease (CD) and can be life threatening.[2] We report here a 50-year male presenting with rapid onset of NS with an unusual finding of bilateral oculomotor palsy and the management strategies.

Case Report

A 50-year male presented initially seven years back with right renal calculi, multiple dorso-lumbar vertebral fractures, progressive centripetal obesity, wide violaceous striae over abdomen and axilla, proximal myopathy, diabetes mellitus and hypertension. Evaluation was suggestive of CD – [overnight dexamethasone suppression test: Serum cortisol – 23 μg/dL; low dose DST – 16 μg/dL; morning plasma adrenocorticotrophic hormone (ACTH) of 123 pg/mL]. Magnetic resonant imaging (MRI) of sella showed a pituitary macroadenoma measuring 14×15×18 mm with minimal suprasellar extension. He underwent sublabial endonasal transsphenoidal excision of macroadenoma. Histopathology confirmed ACTH secreting pituitary adenoma. Post-operative evaluation showed persistent hypercortisolism and a residual lesion in sella for which he received fractionated conventional radiotherapy of 5400 Gy and initiated on ketoconazole. The patient was subsequently lost to follow up. He again reported 30 months back with worsening of his initial symptoms; however he had noticed improvement in his symptomatology three years following radiotherapy. He noticed increasing abdominal girth, generalised weakness, easy fatigability, proximal muscle weakness, decreased libido, erectile dysfunction, loss of pubic and axillary hairs and worsening of proximal muscle weakness, diabetes and hypertension. Evaluation at this stage revealed recurrence of hypercortisolism, secondary hypothyroidism, secondary hypogonadism and secondary osteoporosis. MRI sella showed a recurrent pituitary macroadenoma with minimal suprasellar extension [Figure 1a and b]. Computed

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.122643

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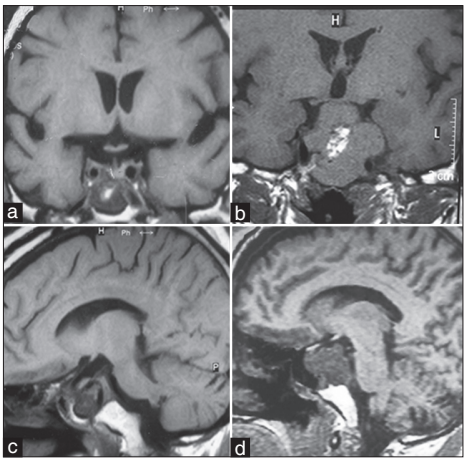

Figure 1: T1 weighted magnetic resonant imaging of sellar region. (a) and (c) are pre-total bilateral adrenalectomy (TBA) images showing pituitary macroadenoma with minimal suprasellar extension. (b) and (d) are post-TBA images showing asymmetrical suprasellar enlargement of the tumor with invasion into bilateral cavernous sinus

tomography (CT) showed bilateral enlarged adrenals. The patient underwent total bilateral adrenalectomy (TBA) with prophylactic gamma knife irradiation for the pituitary macroadenoma. Post-operatively he was started on hydrocortisone, fluodrocortisone, thyroxin and testosterone replacement. He was discharged with the advice of periodic follow up. Ten months after TBA he presented to a local clinician with complains of progressive drooping of right eye. He was subsequently evaluated by a neurologist and a diagnosis of 'ocular myasthenia' was made and treated with pyridostigmine. With no relief of symptoms he reported to us two months later. He again complained of reappearance of his initial symptoms, worsening of proximal muscle weakness, drooping of eyelids, visual field defects and darkening of skin. Examination revealed Cushingoid habitus, hyperpigmented TBA scar, bilateral ptosis [right more than left, Figure 2], restriction of extra-ocular movements, bitemporal hemianopia and proximal muscle weakness. Hydrocortisone, fluodrocortisone and pyridostigmine tablets were stopped. His 0800 hours cortisol was 36 μg/dL and plasma ACTH was 774 pg/mL. MRI sella showed enlargement of macroadenoma-measuring 26×30×29 mm extending into bilateral cavernous sinus, completely encasing right internal carotid artery (ICA) and abutting left ICA [Figure 1b and d]. CT of abdomen showed adrenal rest hyperplasia [Figure 3]. Ultrasound scrotum showed no abnormality. There was no evidence of any metastases. He underwent transnasal transsphenoidal debulking of recurrent lesion. Histopathology was consistent with ACTH secreting pituitary adenoma. Comparing the Ki-67 labelling index (LI), it was 4% after first transsphenoidal excision and 8% after second transsphenoidal excision. He has been counseled for periodic follow up.

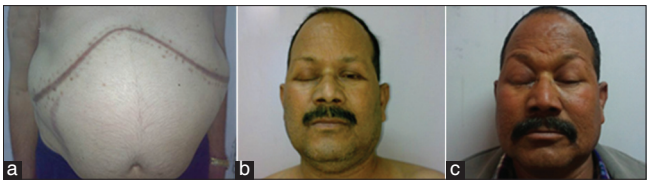

Figure 2: (a) Photograph showing the hyperpigmented scar mark of total bilateral adrenalectomy (TBA), also note the hyperpigmentation of upper limb; (b) Bilateral ptosis of both eyes; right more than left ten months after TBA; (c) Complete ptosis of both eyes 12 months after TBA, note the rapid progression of hyperpigmentation over two months

Discussion

Post-operative hypercortisolism in CD is managed with redo excision of pituitary adenoma, radiotherapy, medical therapy or at times TBA. TBA offers immediate reversal of hypercortisolism and is often a definitive procedure for CD. However, TBA is associated with two potential complications-adrenal insufficiency and NS. The former can be managed successfully with steroid replacement and patient education. Management of later is challenging. NS occurs after CD in about 8-43% adult CD patient and is more frequent in children.[2] A case series from India found NS in two out of their 16 patients and was suspected in eight other patients.[3]

Our patient presented about 10 months after TBA, which is very short duration for development of NS. NS can appear as early as 2 months[4] or as late as 24 years[5] after TBA with an average of about 6 years.[6] Hyperpigmentation is seen in about 50% of patients with NS in present series and is no longer an essential feature of NS.[6] About 19% of post-TBA patients can have hyperpigmentation without evidence of NS.[7]

Our patient had an unusual presentation in the form of bilateral progressive oculomotor palsy presenting as ptosis. The classical visual disturbance in NS is visual field defects. Oculomotor palsy has been infrequently reported in literature.[8] However, the diagnosis was delayed due the presentation of the patient with ptosis to neurologist and being treated as ocular myasthenia.

Recent evidence suggests pituitary radiotherapy prior to TBA decreases the incidence of NS. Those who receive prophylactic conventional radiotherapy 25% go on to develop NS while those who don't about 50% develop.[9] About 65% of the patients who received prophylactic gamma knife radiosurgery (GKS) showed decreasing trends of plasma ACTH, however 35% had increasing trend of ACTH.[10] Though our patient received prophylactic GKS he still went on to develop NS over a very short period of time.

Another aspect notable in our patient was adrenal enlargement after TBA. This could have been due to stimulation by ACTH of some adrenal tissue left during

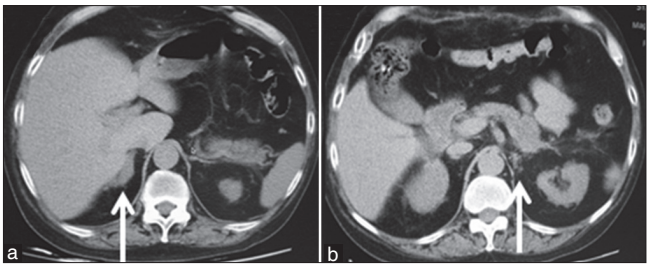

Figure 3: (a and b) Computed tomography of abdomen showing bilateral adrenal rest enlargement

surgery or more likely due to hyperplasia of adrenal rest tissue. This can lead to eucortisolism or recurrence of hypercortisolism.[11] Adrenal rest tissue can be seen in the adrenal bed or in para-testicular and para-ovarian tissue.[11] However scrotal ultrasound performed didn't show any testicular adrenal rest tissue (TART). TART can be cause of testicular pain or infertility in NS.

There are many postulated predictors of NS development - young age at TBA, pregnancy, insufficient steroid replacement, fulminant course of CD[12] and more recently Ki-67 LI.[13] Ki-67 LI is marker for proliferation which gives an estimate for aggressiveness of the tumor. Ki-67 LI of >3% is associated with aggressive tumors and which in turn predict the development of NS.[13] Ki-67 LI after the first tumor excision was 4% while that after the second debulking surgery was 8%. This explains the rapid onset of NS in our patient.

The patient is planned for frequent follow ups. In case the patient has progressive course he is planned for alternate forms of therapy like dopamine agonist, somatostatin analogues, sodium valproate or PPARγ agonists.[6] Recently temozolamide has shown promising results in treatment for NS.[14]

Approach to patient being considered for TBA for CD:

1. Prophylactic radiotherapy to pituitary.
2. Optimal steroid replacement.
3. Visual field charting once in 6 months and subsequently decrease the frequency.
4. Periodic plasma ACTH levels-once in 3 months in the first year and subsequently decrease the frequency.
5. MRI sella once in 6 months in the first year then annually.
6. Evaluation for testicular adrenal rest tissue-testicular ultrasound.

Recently a new diagnostic criteria for NS has been proposed which should satisfy either of the following components:[6]

1. An expanding pituitary mass lesion post-TBA surgery (shown on MRI or CT scan) compared with MRI of the pituitary prior to TBA surgery.
2. An elevated level of ACTH to >500 ng/l from a single plasma sample taken at 0800 h prior to steroid administration and post-TBA surgery, in addition to progressive elevations of ACTH levels from plasma samples taken on at least three consecutive occasions at different time-points post-TBA surgery (a rise of ACTH by >30% of the initial post-TBA sample).

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Cite this article as: Gundgurthi A, Kharb S, Garg MK, Brar KS, Bharwaj R, Pathak HC, *et al*. Nelson's syndrome presenting as bilateral oculomotor palsy. Indian J Endocr Metab 2013;17:1114-6.

Source of Support: Nil, **Conflicting Interest:** None declared.