

NELSON'S SYNDROME: A GIANT PITUITARY

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ABSTRACT

Nelson's syndrome is a pituitary mass that develops following total bilateral adrenalectomy (TBA) for the treatment of Cushing's disease. It is one of the most challenging of all endocrine conditions. The frequent aggressiveness of the underlying ACTH-secreting pituitary adenoma (corticotrophinoma) necessitates regular biochemical and radiological screening. Failure to administer prophylactic neoadjuvant pituitary radiotherapy at the time of TBA and a rapid rise of ACTH levels during the first year following TBA are the main factors that may predict the occurrence of Nelson's syndrome. Though, computerized tomography (CT) and magnetic resonance imaging (MRI) have led to the early diagnosis and improvement in management, these tumours are sometimes detected late, through clinical manifestations of invasion and compression of the surrounding structures. With this perspective in mind, we describe a 22-year-old gentleman who presented 10 years after TBA with right sided hemiparesis caused by a corticotroph adenoma.

Key words: Nelson's syndrome, radiotherapy, bilateral adrenalectomy

INTRODUCTION

Nelson's syndrome is due to a pituitary mass that develops following total bilateral adrenalectomy (TBA) for the treatment of Cushing's disease. It is one of the most challenging of all endocrine conditions. In 1958, Don Nelson described the first case in a 33-year-old woman who had undergone total bilateral adrenalectomy (TBA) for the treatment of refractory Cushing's disease. With an incidence of 8–43% in adults and 25–66% in children, Nelson's syndrome can develop up to 24 years after TBA (1, 2). The central pathological feature of Nelson's syndrome is the underlying ACTH-secreting pituitary adenoma (corticotrophinoma). The aggressiveness of the underlying corticotrophinoma justify the need for close monitoring. Current evidence suggests that the failure of administering prophylactic neoadjuvant pituitary radiotherapy at the time of TBA, a rapid rise of ACTH levels during the 1st year after total bilateral adrenalectomy, the presence of residual pituitary tumour on magnetic resonance imaging (MRI) after transsphenoidal surgery (TSS) as the main risk factors for developing Nelson's syndrome.

The current management of this condition is centered on surgery and radiotherapy. In recent times the alkylating agent, Temozolomide, has shown a promise as a novel and effective therapeutic agent in the treatment of associated aggressive corticotroph tumours. Though, computerized tomography (CT) and magnetic resonance imaging (MRI) have led to an earlier diagnosis and improved management, Nelson's tumours are sometimes detected very late through clinical manifestations of invasion and compression of surrounding structures. With this background, we report a 22-year gentleman, who presented with right sided hemiparesis as a result of a corticotroph adenoma, 10 years after total bilateral adrenalectomy.

CASE REPORT

In 2004, a 23-year-old man was diagnosed with adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome. His ACTH value was 154pg/ml (normal < 46pg/ml). However, the source of ACTH was not localized during the initial workup. Radiological evaluation with a magnetic resonance imaging (MRI)

had revealed a normal pituitary gland without any evidence of an ectopic source of ACTH (Fig.1a, b). In view of refractory hypokalemia and progressive symptoms, he underwent bilateral adrenalectomy. After the surgery, he was well on oral prednisolone and fludrocortisone replacement therapy.

Subsequent follow up after one year revealed progressive hyperpigmentation of the skin and mucous membranes with an ACTH level of 850pg/ml. Even during this visit, the source of ACTH was not found. He was lost to follow up and returned for re-evaluation after a period of 7 years, when he noticed a weakness of the right upper and lower limb, which had progressed over a period of three weeks. He could not walk or write without support. Subsequently, he developed urinary incontinence, headache and recurrent vomiting.

On examination, his Glasgow coma score (GCS) was 15/15 and vital signs were normal. He had generalized hyperpigmentation of the skin, surgical scars and the mucous membranes (Fig. 2a, b). He also had right sided hemiparesis with facial nerve involvement. Perimetry revealed evidence of bitemporal hemianopia. His ACTH levels were >1250pg/ml (normal <46). MRI of the brain demonstrated a sellar mass with suprasellar extension into the third ventricle, causing hydrocephalus (Fig. 3a, b). He underwent a biventricular peritoneal shunt insertion for hydrocephalus and focused radiotherapy (5400 cGy in 30 fractions) to the giant supra-sellar mass. There was a gradual improvement with treatment. After a year later, he was symptomatically better and there was a resolution of his hemiparesis. His subsequent MRI showed partial regression of the mass (Fig. 4a, b). However, he had persistently elevated ACTH levels with compressive symptoms due to a giant pituitary mass. He was subjected to radiotherapy alone, as surgery was not considered as the appropriate primary choice of treatment in view of the extensive invasion into the surrounding structures.

DISCUSSION

Although, trans-sphenoidal pituitary surgery is the first line of treatment for Cushing's disease, recurrences are observed in about 20% of patients (3). Total bilateral adrenalectomy may be proposed to patient with Cushing's disease where the pituitary source of ACTH is not localized, to patients with failed pituitary surgery and those refractory to medical therapy. However, the occurrence of Nelson's syndrome (NS), a corticotroph adenoma with concomitantly high ACTH levels is a major concern.

The incidence of Nelson's syndrome is about 8-43% in adults and 25-66% in children. The time interval between adrenalectomy and the diagnosis of Nelson's syndrome is from 6 months to 24 years (4). The usual presentation involves progressive hyperpigmentation of the skin and mucous membranes with very high ACTH levels (>500pg/ml) despite adequate corticosteroid supplementation. Visual field defects and cranial nerve palsies that could occur due to the mass effects of the tumor invading adjacent structures as was seen in the present case are uncommon in modern clinical practice (4, 5).

Dopamine agonist such as Cabergoline have been documented to induce remission and tumour reduction in some patients with NS (4). Selective somatostatin analogues such as Octreotide may decrease plasma ACTH levels and reduce tumour volume in some patients with Nelson's syndrome (5). In refractory cases, newer somatostatin analogues such as pasireotide and the alkylating agent, Temozolomide hold promise as therapeutic agents in reducing plasma ACTH levels and regression of these tumours (2) Pituitary surgery should be the first-line of treatment for Cushing's disease. However, when total bilateral adrenalectomy is offered, considering the aggressiveness of the underlying corticotrophinoma in Nelson's syndrome, adjuvant pituitary radiotherapy should be considered for all the patients who undergo TBA.

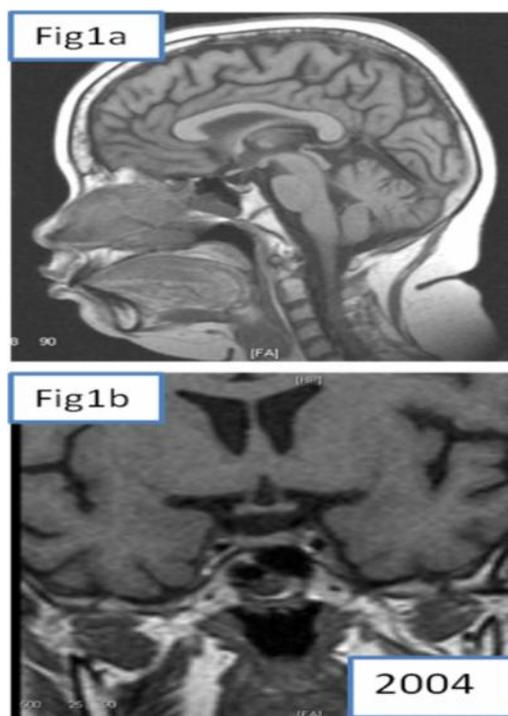
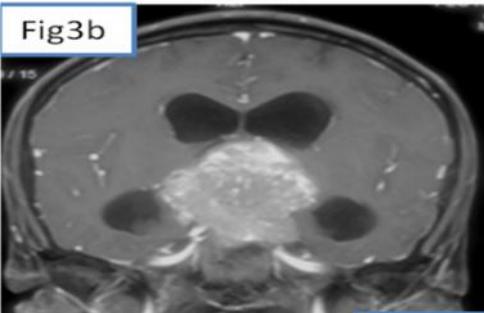
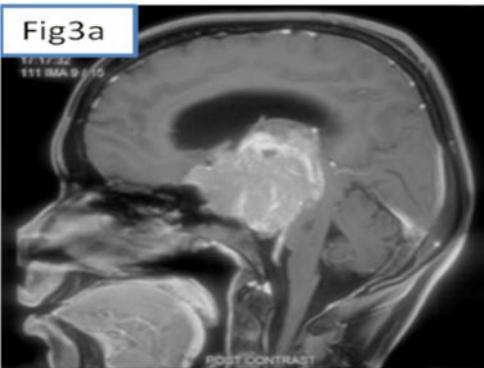


Fig 1a, 1b: T1W sagittal and coronal MRI images showing normal pituitary gland.



Fig2a: Hyperpigmentation of the scars over the back and Fig2b: Hyperpigmentation of knuckles of hands.



Fig; 3a, 3b: T1W sagittal and coronal contrast MRI images showing 61 x 60 x 49mm (Transverse /Coronary/ Sagittal) sella-suprasellar mass extending into the supra-sellar cistern and the third ventricle, causing obstruction of the 3rd ventricle and hydrocephalus, performed when the patient had symptoms in 2012.

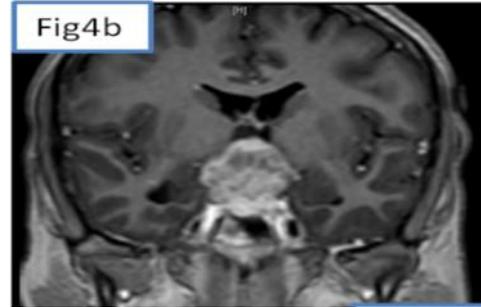
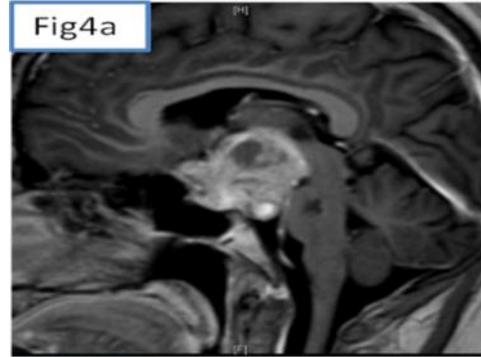


Fig 4a, 4b: T1W sagittal and coronal contrast MRI images showing a giant pituitary adenoma in 2014 but with a reduction in size 42x41x30mm (Transverse/Coronary/Transverse) 1 year after radiotherapy, when compared to the previous MRI done in 2012.

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