

Visual Vignette- Nelson's syndrome: a Giant Pituitary

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Abstract

Nelson's syndrome is an infrequent pituitary mass with an incidence of 8–43% in adults and 25–66% in children 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. Current evidence favours a lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA and a rapid rise of ACTH levels in the year post TBA as factors that may predict the occurrence of Nelson's syndrome. Though, computerized tomography (CT)/magnetic resonance imaging (MRI) have led to the early diagnosis and improvement in management. Nelson's related 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 10 years after TBA who presented with right sided hemiparesis due to a corticotroph adenoma.

Running Title: Nelson syndrome

Key terms: Nelson syndrome, radiotherapy, bilateral adrenalectomy

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Introduction

Nelson's syndrome is an infrequent 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 post TBA (1, 2). The central pathological feature of Nelson's syndrome is an underlying ACTH-secreting pituitary adenoma (corticotrophinoma). The frequent aggressiveness of the underlying corticotrophinoma justifiably necessitates close screening. Current evidence suggests risk factors that include a lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA and a rapid rise of ACTH levels in the first year post TBA as factors that may predict the occurrence of Nelson's syndrome. The current management is centered on surgery and radiotherapy. In recent times the alkylating agent, Temozolomide, holds 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 late through clinical manifestations of invasion and compression of surrounding structures. With this background, we report a 22 year gentleman, 10 years after TBA who presented with right sided hemiparesis as a result of a corticotroph adenoma.

Case

In 2004, a 23 year old man was diagnosed to have adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome. The source of ACTH was not localized during the initial workup. His evaluation had revealed a normal pituitary gland on magnetic resonance imaging (MRI). (Fig.1a, b) and there wasn't any evidence of an ectopic source of ACTH. In view of refractory hypokalemia and progressive symptoms, he underwent bilateral adrenalectomy. Preoperatively his ACTH value was

154pg/ml (normal < 46pg/ml). After 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. Screening for the source of ACTH was negative. He was lost to follow up and returned for re-evaluation after a period of 7 years, when he noticed weakness of the right upper and lower limb which had progressed over three weeks. He could not walk without support or write. Subsequently, he developed urinary incontinence, headache and recurrent vomiting. On examination, his GCS (Glasgow coma score) was 15/15 and vital signs were normal. He had generalized hyperpigmentation of the skin, old scars of surgery and the mucous membranes (Fig.2a, b). Systemic examination revealed right sided hemiparesis with facial nerve involvement. Perimetry revealed had bitemporal hemianopia. 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 for hydrocephalus and focused radiotherapy (5400 cGy in 30 fractions) was administered to the giant suprasellar mass. After a year, he was symptomatically better with resolution of hemiparesis. His subsequent MRI showed partial regression of the mass (Fig. 4a,b).

The present subject 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 the appropriate primary choice in view of extensive invasion of the surrounding structures.

Transsphenoidal pituitary surgery is the first line of treatment for Cushing's disease; though recurrence has been observed in about 20% of patients (3). In 1958, Don Nelson et al were the first to report a corticotroph macroadenoma

in a 33 year old lady who had underwent total bilateral adrenalectomy (TBA) for refractory Cushing's syndrome(4). TBA may be proposed in any patient with a non-localized pituitary source of ACTH or failure of pituitary surgery and those refractory to medical therapy. However, the major concern following adrenalectomy is the occurrence of Nelson's syndrome (NS), a corticotroph adenoma with concomitantly high ACTH levels.

This syndrome does not occur infrequently and has an incidence of 8–43% in adults and 25–66% in children, with a time interval between adrenalectomy and NS diagnosis of 6 months to 24 years (4). The usual presentation involves progressive hyperpigmentation of the skin and mucous membranes with ACTH levels >500pg/ml despite adequate corticosteroid supplementation. Visual field defects and cranial nerve palsies were additional presenting features due to the mass effects of the tumor invading adjacent structures as was seen in the present case, but are uncommon in recent years (4,5). Dopamine agonist like Cabergoline have been documented to induce remission and tumour reduction in some patients with NS (4). Selective somatostatin analogues (SSAs) like Octreotide may decrease plasma ACTH levels and reduce tumour volume in some patients with Nelson's syndrome (5). In refractory cases newer somatostatin analogues like Pasireotide or the alkylating agent: Temozolomide hold promise as therapeutic agents in reducing plasma ACTH and causing regression of the tumor (2). Current evidence suggests that lack of prophylactic neoadjuvant pituitary radiotherapy at the time of TBA, a rapid rise of ACTH levels in a year post TBA, the presence of residual pituitary tumour on magnetic resonance imaging (MRI) and post transsphenoidal surgery (TSS) as common risk factors for NS. Pituitary surgery should be the first-line of treatment and in view of the aggressiveness of the underlying corticotrophinoma in NS, adjuvant radiotherapy should be considered in most patients.

References

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Figures

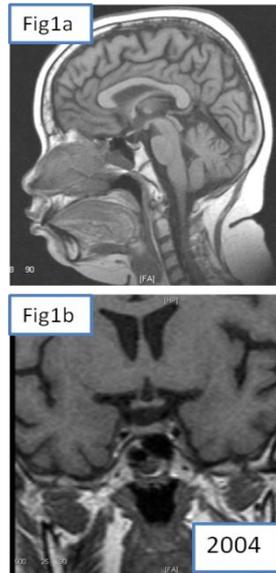


Figure 1a, Figure 1b: T1W sagittal and coronal MRI images showing normal pituitary gland.



Figure 2a: Hyperpigmentation of the scars over the back and Figure 2b: Hyperpigmentation of knuckles of hands.

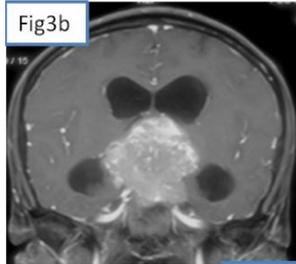
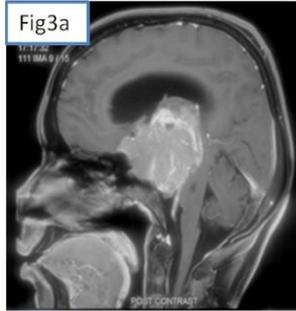


Figure 3a, b: T1W sagittal and coronal contrast MRI images showing 61 x 60 x 49 mm (Transverse x Coronal x Sagittal) sella-suprasellar mass extending into the suprasellar cistern and the third ventricle, causing obstruction of the 3rd ventricle and hydrocephalus, performed when the patient had symptoms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

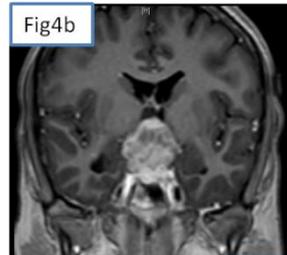
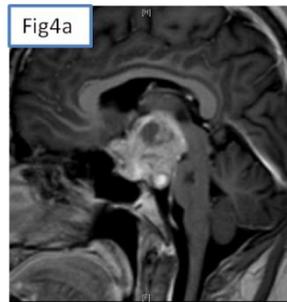


Figure 4a, b: T1W sagittal and coronal contrast MRI images showing a giant pituitary adenoma in 2014 but with a reduction in size 42 x 41 x 30 mm (Transverse x Coronal x Transverse) 1 year after radiotherapy, when compared to the previous MRI done in 2012.