CASE REPORT

Nelson Syndrome: A Rare Cause of Generalized Hyperpigmentation of the Skin

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Abstract

Nelson syndrome is a rare cause of generalized mucocutaneous hyperpigmentation. Its clinical manifestations are due to excessive secretion of adrenocorticotropic hormone from a pituitary adenoma, which develops after bilateral therapeutic adrenalectomy. As this operation has fallen into disuse, Nelson syndrome is now extremely rare and difficult to recognize. We present a very severe case of generalized hyperpigmentation due to Nelson syndrome in a 37-year-old woman.

KEYWORDS
Nelson syndrome; Hyperpigmentation; Adrenalectomy

PALABRAS CLAVE
Síndrome de Nelson; Hiperpigmentación; Suprarrenalectomía

Introduction

Nelson syndrome refers to a set of clinical manifestations caused by hypersecretion of adrenocorticotropic hormone (ACTH) by a pituitary adenoma which develops after bilateral therapeutic adrenalectomy to treat Cushing disease. In 1958 Nelson described the first case of this disorder, which is an extremely rare cause of generalized skin hyperpigmentation.

Clinically, the syndrome is characterized by mucocutaneous hyperpigmentation caused by α-melanocyte-stimulating hormone (MSH). Both MSH and ACTH rise simultaneously, as both are derived from a precursor peptide commonly designated proopiomelanocortin (POMC).
Because bilateral adrenalectomy is the last therapeutic option in patients with Cushing disease who have not responded to other measures, Nelson syndrome is now extremely uncommon.\textsuperscript{5,17} We describe a rare, very severe case in a 37-year-old woman.

Case Description

A 37-year-old white woman with no relevant personal or family history was referred to our outpatient clinic for generalized, progressive, and very pronounced increase in mucocutaneous pigmentation, to the point that she resembled a person of black race.

At age 27 the patient had initiated with severe headache and diplopia. The study revealed apoplexy of a pituitary macroadenoma. Following transsphenoidal hypophysectomy, she maintained normal hormone levels, and the only symptom was secondary amenorrhea of hypophyseal origin.

At age 30 the patient underwent fertility treatment and developed a clear case of Cushing syndrome with hyperglycemia, hypertension, and characteristic phenotype, accompanied by an increase in ACTH levels (1000 pg/mL). Petrosal sinus catheterization confirmed abnormal ACTH secretion of hypophyseal origin and Cushing disease.

The neurosurgery department ruled out another operation, and therapeutic attempts consisting of stereotactic radiotherapy and hormone replacement therapy were unable to control ACTH hypersecretion by the tumor.

At age 31, the patient underwent therapeutic bilateral adrenalectomy to eliminate the effect of ACTH on the adrenal glands. The clinical symptoms of Cushing disease gradually disappeared and the ACTH levels increased (1500-1800 pg/mL).

Symptoms of Nelson syndrome started to develop 2 months after the operation. Physical examination showed very intense generalized hyperpigmentation which was more pronounced in areas exposed to sunlight, such as the face, arms, and neck (Figure 1). A brownish-black coloring was also observed on all mucosas, but was particularly noticeable on the labial mucosa, gums, and hard palate, with scattered brownish macules (Figure 2). Nail pigmentation was also observed (Figure 3).

Histology of an excisional biopsy from the abdominal area showed prominent basal hyperpigmentation and presence of abundant dermal melanophages (Figure 4).
function consists of stimulating melanocyte growth and binding to melanocyte membrane receptors, and its biologic activity contains the MSH amino acid sequence, it stimulates skin melanogenesis in humans. Because the ACTH molecule is derived from POMC, whose secretion by the pituitary gland is stimulated by hypothalamic CRH secretion and, consequently, ACTH secretion by the pituitary gland, which keeps serum levels of the hormone and its precursor peptides within normal limits or slightly elevated. The surgical elimination of adrenocortical secretion also removes the inhibitory effect on hypothalamic CRH secretion and, consequently, ACTH and CRH and their effects increase. The result will be evident, generalized hyperpigmentation not limited to (although more severe in) areas exposed to the sun. The degree of pigmentation will depend on the patient’s race and the type of skin pigmentation will depend on the patient’s race and the type of skin (e.g., the key enzyme in melanogenesis. Moreover, the drug is nontoxic. It has been used in topical and oral form in various hyperpigmentation disorders, such as melasma, lentigo maligna, or melanoma.

In addition to hormone replacement therapy with hydrocortisone (20 mg/12 h), levothyroxine (50 µg/24 h), cabergoline (2 mg/wk), and lanreotide (120 mg/mo), adequate full sun protection and azelaic acid capsules (500 mg/8 h) were prescribed. After 7 months of treatment, the patient experienced a slight decrease in generalized hyperpigmentation. Despite hormone replacement therapy and stereotactic radiotherapy sessions of the pituitary gland, ACTH levels remained above 1000 pg/mL and, consequently, MSH levels remained elevated.

Discussion

Nelson syndrome is an extremely rare disorder (incidence, 8%-42% of patients who have undergone adrenalectomy) because bilateral adrenalectomy is now performed only very occasionally. The condition is more common among women in the third and fourth decades of life. It tends to occur 1 to 4 years after therapeutic bilateral adrenalectomy and has an iatrogenic origin.

The syndrome is an unusual cause of diffuse skin hyperpigmentation, and the differential diagnosis should include other conditions that provoke similar skin symptoms, particularly those with hormone disturbances (Table). The pathophysiology of Nelson syndrome is clearly identified. ACTH is derived from POMC, whose secretion from the pituitary gland is stimulated by hypothalamic corticotropin-releasing hormone (CRH). POMC is also the common peptide precursor of MSH, β-lipotropin, and β-endorphin. When its levels rise, all derivative hormones also rise and their effects on skin therefore increase. Both ACTH and MSH (α, β, and γ) increase melanogenesis in humans. Because the ACTH molecule contains the MSH amino acid sequence, it stimulates skin pigmentation. On the other hand, α-MSH acts by binding to melanocyte membrane receptors, and its biologic function consists of stimulating melanocyte growth and proliferation, while also favoring melanin synthesis and dispersion of its granules and thus increasing pigmentation. The other melanocortins, β-MSH and γ-MSH, have much weaker melanin-stimulating activity than α-MSH.

Before therapeutic bilateral adrenalectomy, the cortisol produced by the adrenal glands works to suppress hypothalamic CRH secretion and, consequently, ACTH secretion by the pituitary gland, which keeps serum levels of the hormone and its precursor peptides within normal limits or slightly elevated. The surgical elimination of adrenocortical secretion also removes the inhibitory effect on hypothalamic CRH secretion and, consequently, ACTH and CRH and their effects increase. The result will be evident, generalized hyperpigmentation not limited to (although more severe in) areas exposed to the sun. The degree of pigmentation will depend on the patient’s race and the type of skin (e.g., the key enzyme in melanogenesis. Moreover, the drug is nontoxic. It has been used in topical and oral form in various hyperpigmentation disorders, such as melasma, lentigo maligna, or melanoma.

In our patient, the agent was the key enzyme in melanogenesis. Moreover, the drug is nontoxic. It has been used in topical and oral form in various hyperpigmentation disorders, such as melasma, lentigo maligna, or melanoma.

Figure 4 Histologic study showing hyperpigmentation of the basal layer of the epidermis and presence of abundant dermal melanophages (hematoxylin-eosin, ×100).

A type of stereotactic radiosurgery known as the gamma knife has proven to be successful in pituitary adenomas refractory to other surgical techniques. Transsphenoidal radiotherapy has also shown its usefulness when surgery is contraindicated. Effective pharmacological therapy does not exist, although drugs have been used to lower plasma levels (e.g., dopamine antagonists such as bromocriptine and cabergoline and somatostatin analogs, such as octreotide and lanreotide), to shrink the tumor (e.g., valproic acid and rosiglitazone), and to avoid altering circadian rhythm (e.g., 4 doses of hydrocortisone).

Dermatologic treatments in this syndrome alone are not encouraging. Our patient was given azelaic acid (500 mg/8 h) based on literature reports regarding its use. Azelaic acid is a 9-carbon dicarboxylic acid obtained by oxidation of oleic acid with nitric acid. The drug has been used to treat hyperpigmentation disorders from the time in vitro tests showed that it was a competitive inhibitor of tyrosinase, the key enzyme in melanogenesis. Moreover, the drug is nontoxic. It has been used in topical and oral form in various hyperpigmentation disorders, such as melasma, lentigo maligna, or melanoma.

In our patient, the agent was the only treatment that proved to be effective in reducing the pigmentation of Nelson syndrome without presenting, to date, any kind of adverse effect. Hence, we suggest that the drug should be considered in these cases and in other conditions with generalized skin hyperpigmentation.
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Conflicts of Interest

The authors declare no conflicts of interest.

References


Table 1  Diffuse Skin Hyperpigmentation: Differential Diagnosis

<table>
<thead>
<tr>
<th>Cutaneous Symptoms</th>
<th>Systemic Symptoms</th>
<th>Type of Pigment</th>
<th>Histologic Site</th>
<th>Laboratory Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison disease</td>
<td>Generalized pigmentation</td>
<td>Melanin</td>
<td>↑ Melanin in basal layer of the epidermis</td>
<td>↓ Plasma cortisol</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>More pronounced in areas exposed to sunlight, palmar-plantar folds, mucosas, nails, recent scars, and areas exposed to friction</td>
<td>Melanin</td>
<td>↑↑ Melanin in basal layer of the epidermis</td>
<td>↑↑ ACTH</td>
</tr>
<tr>
<td>Nelson syndrome</td>
<td>None, due to hormone replacement therapy</td>
<td>Melanin</td>
<td>↓ Melanin in superficial dermis</td>
<td>↑↑ MSH</td>
</tr>
<tr>
<td>Hyperthyroidism (Graves disease)</td>
<td>Similar to Addison disease, but less pronounced and in high phototypes</td>
<td>Melanin</td>
<td>↑↓ Melanin in basal layer of the epidermis</td>
<td>↓ MSH</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Grayish pigmentation</td>
<td>Hemosiderin</td>
<td>Deposits in basal layer, dermal macrophages, and extracellular matrix in the dermis</td>
<td>↑↑↑ MSH</td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, adrenocorticotropic hormone; MSH, melanocyte-stimulating hormone; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.