Neurosurgical implications of Carney complex

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Object. The authors present their neurosurgical experience with Carney complex. Carney complex, characterized by spotty skin pigmentation, cardiac myxomas, primary pigmented nodular adrenocortical disease, pituitary tumors, and nerve sheath tumors (NSTs), is a recently described, rare, autosomal-dominant familial syndrome that is relatively unknown to neurosurgeons. Neurosurgery is required to treat pituitary adenomas and a rare NST, the psammomatous melanotic schwannoma (PMS), in patients with Carney complex. Cushing’s syndrome, a common component of the complex, is caused by primary pigmented nodular adrenocortical disease and is not secondary to an adrenocorticotropic hormone–secreting pituitary adenoma.

Methods. The authors reviewed 14 cases of Carney complex, five from the literature and nine from their own experience. Of the 14 pituitary adenomas recognized in association with Carney complex, 12 developed growth hormone (GH) hypersecretion (producing gigantism in two patients and acromegaly in 10), and results of immunohistochemical studies in one of the other two were positive for GH. The association of PMSs with Carney complex was established in 1990. Of the reported tumors, 28% were associated with spinal nerve sheaths. The spinal tumors occurred in adults (mean age 32 years, range 18–49 years) who presented with pain and radiculopathy. These NSTs may be malignant (10%) and, as with the cardiac myxomas, are associated with significant rates of morbidity and mortality.

Conclusions. Because of the surgical comorbidity associated with cardiac myxoma and/or Cushing’s syndrome, recognition of Carney complex has important implications for perisurgical patient management and family screening. Study of the genetics of Carney complex and of the biological abnormalities associated with the tumors may provide insight into the general pathobiological abnormalities associated with the tumors may provide insight into the general pathobiological features of pituitary adenomas and NSTs.

KEY WORDS • Carney complex • pituitary adenoma • schwannoma • acromegaly • Cushing’s syndrome

Carney complex is an autosomal-dominant, familial tumor syndrome first described by Carney, et al.9 This complex incorporated, expanded, and replaced the syndromes previously described by the acronyms NAME (nevi, atrial myxoma, myxoid neurofibromas, and ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxomas, and blue nevi).2,6 Since that first report, more than 300 patients with the disease have been identified. The initial description of the complex was of a triad of myxomas (cardiac, cutaneous, and mammary), mucocutaneous spotty pigmentation, and endocrine overactivity. The latter included primary pigmented nodular adrenocortical disease, which leads to an ACTH-independent form of Cushing’s syndrome.38,48 Acromegaly, caused by GH-producing adenomas,9 and, in some cases, male isosexual precocious puberty caused by testicular tumors. Description of the complex explained the coexistence, in individual patients or in kindred, of rare tumors such as cardiac myxoma, calcifying Sertoli cell tumors of the testes, and primary pigmented nodular adrenocortical disease. Within a few years it had become apparent that NSTs, described as calcified (psammomatous), melanotic variants of schwannomas, were also a component of the complex; these were seen in 14% of patients with Carney complex.7,8,16 Furthermore, four cases of other “unusual schwannomas” have been reported, including a pigmented cerebellopontine angle tumor.9 Thyroid abnormalities, from follicular hyperplasia to carcinoma, have also been linked to Carney complex,11 as have benign breast fibroadenomas and ductal adenomas.11,12,15

Neurosurgery was required for many of these patients. The surgical case studies of one patient with Carney complex who had a GH-secreting adenoma and one who had
a melanotic tumor of the S-2 nerve root are presented here as an introduction to, and a review of, the neurosurgical aspects of this genetic disorder.

**Pituitary Adenomas**

The adenomas identified thus far in Carney complex have been almost exclusively GH-secreting tumors. In the original report in 1985 Carney, et al., described four cases of GH adenomas, two from reports in the literature (including one case treated at our institution), one from their experience, and another as a personal communication. Of these patients, two presented with gigantism and two with acromegaly. Five more cases have been reported since that time, and to these we add five recent cases of our own (Table 1). Of these 14 patients, only three (Cases 4, 7, and 8) did not present with gigantism or acromegaly; on sellar tomography or computerized tomography imaging; on sellar tomography or computerized tomography in eight and on MR imaging in five.

The knowledge that patients with Carney complex are at risk for GH adenomas provides an exceptional opportunity to screen for the onset of somatotrophic abnormalities and for early radiological assessment of the pituitary gland, thus allowing for intervention before the onset of the clinical syndrome of gigantism or acromegaly. Such a patient, who developed a GH-secreting adenoma while being followed for Carney complex, is presented in Case 1.

**Melanotic Schwannomas**

Psammomatous melanotic schwannomas are visually striking tumors, distinguished from typical schwannomas at surgery by black pigmentation. The characteristic pathologic features have been defined by Carney; in addition to melanin content, the tumor features psammoma bodies and fat, Carney considered these tumors to be schwannomas based on their gross association with nerves, their S-100 protein positivity, and the presence of a basal lamina around the tumor cells seen on electron microscopy studies. However, areas of Antoni Types A and B tissue, typical of sporadic schwannomas, are not a common finding. Thus, a primary consideration in the differential diagnosis is a melanoma of the dura. Melanomas may originate in the melanocytes of the dura and cranial melanotic schwannomas occurred before Carney’s description of the association of these tumors to his eponymous syndrome. In a 1990 review of reported cases of melanotic schwannomas in which calcification

**TABLE 1**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Clinical Presentation</th>
<th>Tumor Size</th>
<th>Invasion of Dura/CS</th>
<th>Immunostaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propp &amp; Scully, 1980</td>
<td>1</td>
<td>11, M giant</td>
<td>NR</td>
<td>NR</td>
<td>acidophilic</td>
<td>NR</td>
</tr>
<tr>
<td>Rosenzweig, et al., 1982</td>
<td>2</td>
<td>16, M giant</td>
<td>macro</td>
<td>UK</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Carney, et al., 1985</td>
<td>3</td>
<td>21, M acro</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gorman &amp; Hewer, 1985</td>
<td>5</td>
<td>28, F acro</td>
<td>macro</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Leedman, et al., 1986</td>
<td>6</td>
<td>40, F acro</td>
<td>macro</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Carson, et al., 1988</td>
<td>7</td>
<td>13, M CS</td>
<td>micro</td>
<td>NR</td>
<td>neg</td>
<td>ACTH</td>
</tr>
<tr>
<td>Handley, et al., 1992</td>
<td>8</td>
<td>14, F HA</td>
<td>macro</td>
<td>UK</td>
<td>PRL/GH</td>
<td>NR</td>
</tr>
<tr>
<td>Yen, et al., 1992</td>
<td>9</td>
<td>22, F acro</td>
<td>macro</td>
<td>NR</td>
<td>PRL/GH</td>
<td>NR</td>
</tr>
<tr>
<td>Present study†</td>
<td>10</td>
<td>20, M acro</td>
<td>macro</td>
<td>yes</td>
<td>PRL/GH</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>19, F acro</td>
<td>macro</td>
<td>NR</td>
<td>PRL/GH</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>37, F acro</td>
<td>macro</td>
<td>NR</td>
<td>PRL/GH</td>
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<td>macro</td>
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<td>PRL/GH</td>
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<tr>
<td></td>
<td>14</td>
<td>39, F acro</td>
<td>macro</td>
<td>yes</td>
<td>PRL/GH</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Acro = acromegaly; CS = Cushing’s syndrome; giant = gigantism; HA = headache; macro = macroadenoma; micro = microadenoma; neg = negative; NR = not recorded; UK = unknown.
† These five patients underwent surgery performed by two of the authors (E.H.O. and J.C.W.).

**TABLE 2**

<table>
<thead>
<tr>
<th>Date of Assay</th>
<th>GH (ng/ml; norm 0–10)</th>
<th>IGF-I (ng/ml; norm 40–112)</th>
<th>OGTT: GH at 90 Mins (ng/ml; norm &lt;1)</th>
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<tr>
<td>December 1995</td>
<td>5.6</td>
<td>211</td>
<td>3.3</td>
</tr>
<tr>
<td>May 1996</td>
<td>ND</td>
<td>253</td>
<td>ND</td>
</tr>
<tr>
<td>August 1996</td>
<td>4.1–14.6</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>November 1997</td>
<td>3.1–14.7</td>
<td>ND</td>
<td>6.7</td>
</tr>
<tr>
<td>July 1998</td>
<td>31†</td>
<td>ND</td>
<td>15†</td>
</tr>
</tbody>
</table>

* The abnormal IGF-I values are notable in the face of normal GH values (December 1995, May 1996). Not until the July 1998 follow up was an adenoma demonstrated on MR imaging. Abbreviations: ND = not done; norm = normal; OGTT = oral glucose tolerance test.
† By radioimmunoassay (ng/ml).
was reported (that is, PMSs only), Carney found that more than half (55%) were associated with Carney complex, with an average patient age at diagnosis of 22.5 years. Psammomatous melanotic schwannomas were located on the spinal nerve roots in 28% of patients and were in a location related to the gastrointestinal tract (esophagus, stomach, rectum) in another 28%. Although cranial schwannomas have been described in patients with Carney complex (four by Carney, two of which were melanotic, and all without psammoma bodies, and another typical acoustic schwannoma), their numbers are too small to be considered a definitive part of the complex.

The occurrence of PMS of the nerve roots may cause the presenting symptoms of Carney complex. Carney complex–associated PMSs have been seen associated with cervical, thoracic, lumbar, and sacral nerve roots. Three cases of tumors arising from the S-2 root make this single location the most common. In patients with spinal Carney complex, presenting symptoms have consisted exclusively of pain and radiculopathy, although myelopathy has been described in patients with non–Carney complex involving melanotic schwannomas. Multiple PMSs of the nerve sheath are possible and have been thought to be synchronous or metachronous tumors of different origins rather than metastatic foci. However, to our knowledge no genetic studies have been conducted to conclude definitively whether they are de novo or metastatic tumors.

The PMS of Carney complex is a potentially malignant tumor; it was the cause of death in four of Carney’s 31 patients in his 1990 report. Since then, three other cases of malignant PMS and Carney complex have been reported (including one arising from a sacral root), and we recently treated another such patient. The lung was the most common site of metastasis. There are no definitive histological findings that indicate malignancy. However, the combination of mitoses, large nuclei with huge nucleoli, and necrosis is suggestive of a malignant tumor. In the limited experience with metastatic PMSs, chemotherapy and radiation treatment have failed to prevent a fatal outcome. A patient with Carney complex and a sacral root NST is presented in Case 2.

Illustrative Cases

Case 1

This 39-year-old woman with Carney complex, who manifested spotty skin and labial pigmented lesions, multiple cutaneous myxomas, recurrent atrial myxoma, follicular thyroid carcinoma, and primary pigmented nodular adrenocortical disease, was found to have increased levels of GH and IGF-I. The results on an oral glucose tolerance test conducted as part of a screening examination more than 2 years before surgery were abnormal. There was no clinical evidence of acromegaly and an MR image of the sella turcica was nondiagnostic. Biochemical data are presented in Table 2.

Only at the end of a 2.5-year period of observation was a pituitary tumor observed on MR imaging. At the time the abnormality was demonstrated on MR imaging, the patient had developed mild physical signs associated with acromegaly, limited to thickening of the tip of her nose and widening of the gap between her front incisors. Other symptoms were limited to a 4-month history of decreased libido and intermittent, bilateral carpal tunnel syndrome. She underwent transthyroidal resection of a discrete 6-mm adenoma. At surgery, no dural or cavernous sinus invasion was seen. Results of immunohistochemical studies of the specimen revealed the typical pattern seen with Carney complex GH tumors (Table 1), displaying both PRL and GH positivity. Plasma levels of GH and IGF-I were normal 4 months after surgery (GH = 3 ng/ml, IGF-I = 126 ng/ml).

Case 2

This 44-year-old woman with Carney complex, manifested by primary pigmented nodular adrenocortical disease, thyroid adenoma, breast myxoid fibroadenomas, and previous gastric, pulmonary, and perirenal PMSs, presented with a 6-month history of progressive low-back pain and intermittent leg pain, greater on the right side than on the left. Her only neurological deficit was right-sided perineal sensory loss. Sacral spine MR imaging revealed a large, right-sided, bilobed, inhomogeneously enhancing mass at the S-2 level that expanded the bone in this region (Fig. 1). Preoperative lower-extremity electromyography studies demonstrated mild evidence of denervation in the left S-1 muscle groups. Surgical excision of the tumor was accomplished via a midline sacral approach and a left-sided sacral hemilaminectomy. The tumor could be seen through the attenuated lamina as a dark mass. Spinal fluid, removed with a needle puncture above the tumor before
the tumor was manipulated, had a brown discoloration, which had been caused by melanotic cellular debris according to results of cytological studies. Dural opening revealed a dumbbell-shaped mass that enveloped the entire S-2 root. The S-1 root was compressed but not incorporated in the tumor. A gross-total excision of that tumor was performed (Fig. 2). Pathological study results revealed large, atypical, epithelioid cells with heavy cytoplasmic pigmentation, vesicular nuclei, and prominent nucleoli. The tumor stained positively for S-100 protein, synaptophysin, HMB-45, MART-1 and was weakly positive for vimentin, whereas it stained negative for cytokeratin, neuron-specific enolase, chromogranin, and KBA-62. The tumor invaded the perineurium of S-2. Postoperatively, the patient experienced resolution of her pain and no new neurological symptoms. A lumbar puncture performed 3 weeks postoperatively revealed clear cerebrospinal fluid and no tumor cells were found on cytological studies. Twelve months later, she has had no clinical or radiological evidence of tumor recurrence in the spine. However, she has developed multiple new lung lesions. Fine-needle aspiration removed the same kind of large, heavily pigmented cells that were present in her sacral NST. The immunohistochemical profile of these cells was identical to that of the sacral tumor. The patient was referred for systemic treatment of the metastatic disease.

Discussion

Carney complex is a hereditary tumor syndrome of considerable importance to the neurosurgeon. In many ways, Carney complex is similar to more familiar genetic tumor syndromes. For instance, patients with this complex may present with cutaneous manifestations such as spotty skin pigmentation and skin lesions, including melanotic schwannoma, findings that are reminiscent of the neurocutaneous syndromes:1,5,6,10,19,20,31,44 the phacomatoses, such as neurofibromatosis, tuberous sclerosis, von Hippel–Lindau disease; the neurocutaneous angiomatosis; and neurocutaneous melanomatosis. The endocrine tumors (pituitary, adrenal, thyroid, testicular) that arise with Carney complex, are reminiscent of tumor combinations of the multiple endocrine neoplasia syndromes.

Surgical removal of the pituitary adenomas and schwannomas is the treatment of choice. Because patients with Carney complex may initially present with either of these lesions, the original diagnosis of the complex may be made by the neurosurgeon. Identifying patients with Carney complex has important implications for perioperative management, particularly for recognizing an adrenal cause of Cushing’s syndrome and for ruling out the coexistence of a cardiac myxoma with its subsequent risk of hemodynamic or embolic complications, including stroke. Furthermore, accurate diagnosis has implications for genetic counseling and screening of the patient’s relatives. Once the genetic abnormality has been well characterized, screening and diagnosis based on DNA analysis should be possible.

Elucidating the genetic abnormality that is transferred in a familial syndrome that predisposes a patient to certain tumors also provides the opportunity to understand the pathophysiological aspects of tumor formation in general. For instance, genetic abnormalities found in pituitary adenomas of multiple endocrine neoplasia I and McCune–Albright syndrome also have been identified in sporadic tumors.19,47,48,49 Two loci have been linked to Carney complex (chromosome 2 [2p16] and chromosome 17 [17q]), but the responsible gene(s) has yet to be identified and is the subject of ongoing research.14,40,42,43

Pituitary Adenomas

Recognition of the risk of developing a GH adenoma in the presence of Carney complex provided the unique opportunity to observe the development of acromegaly in the patient in Case 1 by demonstrating the temporal relationship among the onset of biochemical abnormalities, radiological evidence of abnormalities, and clinical manifestations (Case 14, Table 1). In this case, the serum IGF-I was abnormal years before a tumor appeared on MR imaging, and, even when the 6-mm lesion was identified on an MR image, only subtle clinical findings were suggestive of acromegaly. Consequently, by the time there are overt clinical manifestations, some adenomas have grown into large and potentially invasive tumors.

Furthermore, surgical intervention based on biochemical evidence alone, despite a nondiagnostic MR image such as commonly occurs in Cushing’s disease, may be considered. We have experience treating one patient with Carney complex (Case 12, Table 1) who had elevated IGF-I, subtle acromegalic features, and a nondiagnostic MR image, and who underwent elective surgical exploration. Discovery and removal of a microadenoma has provided biochemically confirmed tumor remission for this patient at 2 years postoperatively. The advantage of early surgery is the removal of the tumor before it becomes locally invasive (which carries a poorer prognosis) and before irreversible consequences of elevated GH occur (arthritis, atherosclerosis, cardiomyopathy, and cosmetic deformity). Early treatment of elevated GH and IGF-I levels also may prevent the promotion of secondary tumors.33 Therefore, it seems appropriate to follow patients with Carney complex carefully to detect early evidence of excess GH secretion.

Melanotic Schwannomas

Neurosurgeons should be familiar with the association
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of PMSs—the peculiar, pigmented, neural crest–derived tumors of the nerve sheath—with Carney complex because more than half of the reported cases of these schwannomas have been found in the context of this syndrome. The neurosurgeon also must be aware of the possible malignancy of PMSs. It was previously thought that melanotic schwannomas were benign lesions, but metastases may arise from sporadic melanotic schwannomas as well as from the PMSs of Carney complex, as demonstrated in Case 2. Unfortunately, there is currently no reliable histopathological indicator of malignancy. Although some aggressive and metastasizing melanotic schwannomas have demonstrated marked pleomorphism, high mitotic activity, and a malignant peripheral NST-like schwannomas have demonstrated marked pleomorphism, high mitotic activity, and a malignant peripheral NST-like schwannoma.

References


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