MANAGEMENT OF ENDOCRINE DISEASE

Carney complex: clinical and genetic update 20 years after the identification of the *CNC1* (*PRKAR1A*) gene

Lucas Bouys¹ and Jérôme Bertherat^{1,2}

¹Université de Paris, Institut Cochin, Inserm U1016, Paris, France and ²Department of Endocrinology and National Reference Center for Rare Adrenal Disorders, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, Paris, France

Correspondence should be addressed to J Bertherat
Email
jerome.bertherat@aphp.fr

Abstract

Described for the first time in 1985, Carney complex (CNC) is a rare dominantly inherited multiple neoplasia syndrome with almost full penetrance and characterized by both endocrine – primary pigmented nodular adrenocortical disease with Cushing's syndrome, acromegaly and thyroid tumors – and non-endocrine manifestations such as cardiac, cutaneous and mucosal myxomas, pigmented cutaneous lesions, psammomatous melanotic schwannoma, osteochondromyxoma and a wide range of other tumours with potential malignancy. The pathophysiology of CNC is a model of dysregulation of the cAMP/PKA signalling in human diseases. As described 20 years ago, inactivating heterozygous mutations of *PRKAR1A* formerly known as *CNC1*, encoding the regulatory subunit 1 α of protein kinase A, are identified in more than 70% of the index cases, while inactivating mutations of genes encoding phosphodiesterases are found in rare and particular forms of the complex. There is at present no medical specific treatment for CNC, every confirmed or suspected CNC patient should be managed by a multi-disciplinary team according to each manifestation of the disease and offered a long-term follow-up and genetic counselling. The better knowledge that we have now of this fascinating rare disease and its genetics will help to improve patients outcome.

European Journal of
Endocrinology
(2021) **184**, R99–R109

Introduction

In 1985, one year after he described bilateral primary pigmented nodular adrenocortical disease (PPNAD)

in four young patients with Cushing's syndrome (1), J A Carney, pathologist at the Mayo Clinic, described for the first time the 'complex of myxomas, spotty pigmentation and endocrine overactivity' (2), later named

Invited Author's profile

Jérôme Bertherat is professor of Endocrinology at Paris University, Chief of the Endocrinology Department of Cochin Hospital, head of the National Center for Rare Adrenal Diseases and of the research group 'Genomics and Signaling of Endocrine Tumors' at the Cochin Institute (INSERM), Paris, France. He serves as the coordinator of the French National Network for Rare Endocrine Disorders. His main research interests are Cushing's syndrome, the genetics of familial adrenal tumors and the molecular genetics of endocrine tumors. His laboratory has identified major genes involved in adrenocortical tumor formation as *ARMC5* and *ZNRF3* involved in primary bilateral macronodular adrenal hyperplasia and adrenal cancer, respectively.

after him, based on a retrospective study of 40 patients. The 'Carney complex' (CNC) was consistent with some cases reported in the literature in the previous 4 years as 'NAME syndrome' (3) or 'LAMB syndrome' (4) (for naevi, atrial myxoma, myxoid neurofibromata and ephelides and lentiginos, atrial myxoma, mucocutaneous myxomas and blue naevi, respectively), and probably consistent with a case of fatal bilateral atrial myxomas associated with 'many dark brown to black freckles on the skin, reported in 1960 (5); even evidence has been shown that Harvey Cushing treated the first known patient with Carney complex, more than 70 years before its first description (6).

Characterized by lentiginosis and multiple neoplasias – particularly Primary Pigmented Nodular Adrenal Disease (PPNAD) and myxomas – Carney complex (CNC) is rare, and its prevalence remains unknown. Considering the multiplicity of the manifestations of the disease and the broad variety of presentations in each patient, the diagnosis is challenging. It is possible that still today many patients are not diagnosed. The endocrinologist is probably one of the specialists in the best position to evoke the diagnosis in front of intriguing and quite specific manifestations such as PPNAD.

The largest international series reports 353 patients (7), and a recent national prospective study reports on 70 patients (8). In its initial description of CNC, Dr Carney speculated that the disease could be an autosomal dominantly inherited disorder (2). Indeed, about 70% of the cases are familial with an autosomal dominant transmission with almost full penetrance. According to the largest series of patients, CNC is more frequent in females than in males (63% vs 37%) (7).

Genetic findings

At the end of the 20th century, linkage analysis of kindreds with CNC identified two loci in 17q22-24 (9) and 2p16 (10, 11) containing the potential causing genes for the disease (initially named *CNC1* and *CNC2*, respectively).

CNC1

In 2000, 20 years ago and 15 years after the first description of the disease, the team of Dr Constantine Stratakis at the NIH discovered germline heterozygous inactivating mutations of *PRKARIA*, also known as *CNC1*, mapped at 17q22-24, encoding the protein kinase A regulatory subunit type 1 α , now considered as the main gene that causes CNC (12). The same gene was subsequently reported by Casey and collaborators at Cornell University (13).

To date, at least 130 different mutations have been described in more than 400 families from multiple ethnic origins, spread all over the ten coding exons (*PRKARIA* has 11 exons, but exon 1 is non-coding and rarely mutated) and in the adjacent intronic sequences (14). Exons 2, 3, 5 and 7 are more often mutated as represented in Fig. 1. In the largest series of 353 patients, 80 different *PRKARIA* mutations were found in 258 patients (73%). In this series, 80% of the mutations were exonic but 20% altered intronic splicing sites (7). Most of these mutations are private, except for the three clearly identified hot-spots: c.709-7del6 in intron 7, c.491-492delTG in exon 5, observed in 14 and 11 families, respectively, and c.82C > T in exon 2.

The mutations can be non-sense or missense substitutions, short frameshift insertions or deletions or more rarely large deletions. Most of these mutations lead

Figure 1

Representation of the *PRKARIA* gene and the number of unique identified mutations associated to each exon. Grey bars represent the exonic mutations (dotted grey bars represent frameshift deletions or insertions, crossed grey bars represent non-sense mutations, plain grey bars represent missense mutations), black bars represent the mutations in intronic splicing sites. Non-coding exons (exon 1 and the end of exon 11) are hatched. Exons' lengths are represented at scale (excepted for non-coding part of exon 11 which has been cut). Introns' lengths are not represented at scale.

to a non-sense mRNA, not translated into protein, by its degradation through the non-sense mediated mRNA decay (NMD) process. The NMD results in the absence of production of the mutant protein and in a reduction of 50% of total R1 α protein (encoded by the wild-type allele). However, some particular mutations are not subject to NMD and lead to the translation into an altered or shorter protein. This mechanism has been described for the first time in 2006 with the identification of an intronic mutation leading to exon 7 skipping (15). Currently, around 20% of *PRKAR1A* mutations are not subject to NMD. These mutations are often associated with a more severe phenotype.

The clinical assessment of large series of patients allowed genotype/phenotype correlations. Exonic mutations are significantly associated with lentiginos, cardiac myxomas, acromegaly and psammomatous melanotic schwannoma. Some mutations are associated with a peculiar phenotype: c.709-7del6 is mostly associated with isolated PPNAD as described by Groussin *et al.* (15); c.491-492del is associated with more frequent cardiac myxomas, lentiginos and thyroid tumours.

Other genes

In 2014, a germline triplication of the 1p31.1 region including the *PRKACB* gene, encoding the catalytic subunit β of the PKA, has been identified in a 19-year-old woman diagnosed with Carney complex with acromegaly, lentiginos and myxomas, who did not harbour a *PRKAR1A* mutation (16).

In isolated PPNAD, without any other neoplasia classically observed in CNC, germline mutations of the genes encoding main actors of the PKA pathway have been described: germline copy-number gains in the 19p region including the *PRKACA* gene, encoding the catalytic subunit α of PKA, have been described in five patients with bilateral adrenal hyperplasia including isolated micronodular adrenal hyperplasia (17); germline inactivating heterozygous mutations of *PDE11A*, encoding a phosphodiesterase expressed in adrenal cortex, have been described in four patients (out of three families) with PPNAD (18). Deleterious *PDE11A* variants have also been described in patients with Carney complex associated with a *PRKAR1A* mutation, these patients had more frequent PPNAD and testicular tumours (19). A germline inactivating heterozygous mutation of *PDE8B*, encoding another phosphodiesterase, has been described once in one young female patient diagnosed with severe Cushing's syndrome at the age of 2 (20).

To date, *CNC2* (potentially mapped at 2p16) has never been identified and its existence remains discussed.

Pathophysiology of the cAMP/PKA pathway

Until now, all the genes implicated in CNC encode the main actors of the cAMP/PKA pathway, which is a ubiquitous signaling pathway involved in a wide range of cell functions such as proliferation, differentiation and apoptosis. Activation of the cAMP/PKA pathway is triggered by the binding of a ligand with its specific seven-domain transmembrane receptor. The intracellular domain of the receptor is coupled to Gs protein, consisting of three subunits (α , β , γ). Its activation leads to the stimulation of adenylyl cyclase, which is the enzyme catalysing the dephosphorylation of ATP into the second messenger: cAMP. In its inactive state, protein kinase A (PKA) is a heterotetramer consisting of two regulatory and two catalytic subunits. Four subtypes of regulatory subunit (R1 α , R1 β , R2 α and R2 β) and three subtypes of catalytic subunit (C α , C β , C γ) have been identified. The binding of cAMP to the regulatory subunits leads to their dissociation from catalytic subunits, enabling them to phosphorylate many targets such as the nuclear transcription factor CREB (cAMP responsive element binding protein) resulting in the transcription of genes containing a CRE domain. Phosphodiesterases (PDEs) are negative regulators of the cAMP/PKA pathway by converting the cAMP into inactive AMP (21, 22, 23, 24). Therefore, inactivating mutations of *PRKAR1A*, *PDE8B* or *PDE11A* are proven to increase cAMP signaling, as well as copy-number gains of genes encoding the catalytic subunits. The physiological cAMP/PKA pathway and its alterations in case of *PRKAR1A* and *PDEs* mutations are illustrated in Fig. 2, using ACTH and its receptor as an example in adrenal cortex.

Murine models

The first *Prkar1a* knock-out murine model has been described in 2002 by Amieux *et al.* (25). All homozygous mutant embryos failed to develop a functional heart tube with a constant foetal lethality, suggesting that the other regulatory subunits of PKA could not rescue *Prkar1a* function.

A transgenic mouse carrying an antisense transgene for *Prkar1a* exon 2 has been established in 2003, associated with a lowered R1 α activity, and developed adrenocortical hyperplasia with Cushing's syndrome, thyroid follicular

Figure 2

Physiological activation and pathological activation of the cAMP/PKA pathway due to *PRKAR1A* and *PDEs* inactivating mutations. (A) Physiological activation of the cAMP/PKA pathway. (B) Increased PKA catalytic subunit dissociation due to *PRKAR1A* inactivating mutations. (C) Increased levels of cAMP due to impaired degradation into AMP because of inactivating mutations of genes encoding the phosphodiesterases. R, regulatory subunit of PKA; C, catalytic subunit of PKA; PDE, phosphodiesterase; AKAP, A Kinase Anchoring Protein; AC, adenylyl cyclase; CREB, cAMP Response Element Binding Protein.

hyperplasia and adenomas and other mesenchymal tumours (26).

Numerous tissue-specific *Prkar1a* knock-out mouse models have been generated, most of them are sufficient to reproduce a human manifestation. Among them we can cite the adrenal-specific KO (AdKO) leading to an adrenal hyperplasia with ACTH-independent Cushing's syndrome (27), the pituitary-specific invalidation inducing pituitary tumorigenesis and abnormalities of the GH axis (28) or the thyroid-specific KO, associated with hyperthyroidism and follicular neoplasms including carcinomas (29).

Clinical features

Considering the numerous manifestations of CNC and their variability among patients, simple and homogenous diagnostic criteria are difficult to establish in an index case. However, some manifestations are rare and highly specific of the disease while other that are more frequent are less specific and clearly need to be associated with others manifestation to be suggestive of the diagnosis. Therefore, according to the recommendations for CNC diagnosis, diagnostic criteria are classified as major (for more specific manifestations), supplementary or suggestive. The diagnosis is made if two major features are present, or one major feature with a supplementary criterion, such as a proven *PRKAR1A* inactivating heterozygous germline mutation or an affected first-degree relative (30). The diagnostic criteria are summarized in Table 1.

Major criteria

Frequencies of the major clinical features met in CNC are summarized in Table 2. We focused on three different series of CNC patients: the original retrospective series described by Carney *et al.* in 1985 (2), the largest retrospective series investigating retrospectively patients that were all genotyped at the NIH or Cochin Hospital published in 2009 (7), and the only prospective series of CNC patients to date, conducted at the national level in France and recently published (8).

Cardiac myxomas

Cardiac myxomas are benign tumours characterized by stellate mesenchymal cells in a myxoid stroma. With a penetrance of 20 to 40% of patients (7, 8), they are not the most frequent feature diagnosed in CNC patients, but their diagnosis is crucial because of its high morbidity and lethality. In CNC, cardiac myxomas can arise in any cardiac cavity, are often multiple and/or recurrent (31, 32) and occur at a median age of 50 (7); on the contrary, isolated cardiac myxomas grow much later in life, classically in the sixth or seventh decade, mostly in left atria, and are generally unique, recurrence being exceptional (33). However, histological features are strictly identical in the two conditions. Due to their complications, typically embolism, heart failure and sudden death, cardiac myxomas require surgical treatment.

Around 7% of cardiac myxomas are associated with CNC, a recent genetic study found a *PRKAR1A* somatic

Table 1 Frequency of the most frequent clinical features of CNC, according to three series: the first described series by Carney *et al.* in 1985, the largest retrospective series reported by Bertherat *et al.* in 2009 and the prospective series published by Espiard *et al.* in 2020.

	Carney <i>et al.</i> (2), n = 40	Bertherat <i>et al.</i> (7), n = 353	Espiard <i>et al.</i> (8), n = 70
Pigmented cutaneous lesions	26 (65.0)	—	—
Lentigines	—	248 (70.3)	39 (55.7)
Blue naevi	—	177 (50.1)	12 (17.1)
Cardiac myxoma	29 (72.5)	112 (31.7)	16 (22.9)
PPNAD	18 (45.0)	212 (60.1)	48 (68.6)
Cutaneous myxoma	18 (45.0)	69 (19.5)	14 (20.0)
Thyroid tumours	3 (7.5)	88 (24.9)	8 (11.4)
Acromegaly	4 (10.0)	42 (11.9)	13 (18.6)
Psammomatous melanotic schwannoma	—	28 (7.9)	7 (10.0)
Osteochondromyxoma	—	—	4 (5.7)
Breast lesions	10 (41.7)	42 (19.0)	21 (42.0)
Ovarian lesions	2 (8.3)	31 (14.0)	—
LCCSCT	9 (56.3)	54 (40.9)	7 (35.0)

mutation in 64% out of 61 isolated cardiac myxomas, without any germline alteration (33).

Cutaneous manifestations

Three types of benign cutaneous lesions represent the most common features met in CNC, occurring early in life (7, 30, 34).

Lentigines, present in 60 to 80% of CNC patients, are small, flat and pigmented hamartomatous melanocytic macules, brown or black coloured, poorly delimited, with a specific peri-orificial distribution in CNC, classically seen around the lips, the eyes (including on the eyelids), the ears and the genital areas. Mucosal lentigines are often observed with vaginal, oral or conjunctival localizations (7, 8, 34). They usually appear in early childhood, increase in number and pigment intensity during puberty, and sometimes fade in old age (35, 36, 37).

Epithelioid blue naevi are a subtype of blue naevi, rarely met in the general population but observed in 20 to 50% of CNC patients (7, 8). They are small, circular or star-shaped, pigmented and poorly delimited lesions, blue to black coloured, with a variable distribution, usually associated with a dermal fibrosis (38, 39).

Cutaneous myxomas are usually non-pigmented sessile or pedunculated infra-centimetric lesions, with a classic distribution in the eyelids, nipples, external ear canal or genitalia (40) and are present in 20 to 50% of CNC patients (2, 7, 8). Interestingly, cutaneous myxomas are predictive of cardiac myxomas, since a study showed that cutaneous myxomas were present earlier in life in 80% of patients with cardiac myxomas (40).

Skin lesions should be excised only when malignant degeneration is suspected or to confirm the diagnosis of atypical lesions (34). Otherwise, simple clinical monitoring is recommended.

Endocrine features

Primary Pigmented Nodular Adrenal Disease (PPNAD) PPNAD is the most common endocrine feature met in CNC, present in 45 to 70% of patients (2, 7, 8), with an increased frequency in female (71% are women and 29% are men), with a median age at diagnosis of 34 years (7). Nevertheless, PPNAD can arise in early childhood in some cases. In autopsy series, histological evidence of PPNAD was present in almost all patients (2).

On CT scan imaging, adrenals can appear normal or moderately enlarged. But higher definition (CT slice thickness less than 5 mm) allows to visualize small round hypodense nodules, usually smaller than 10 mm (41). However, a retrospective analysis of 17 patients with PPNAD showed adrenal macronodules associated with micronodules in three patients (17.6%) (42), confirmed by histopathological findings. They recorded also the adrenal NP-59 uptake in scintigraphy, which was asymmetric in ten patients (58.8%) and symmetric in the seven others (41.2%). The presence of unilateral macronodule was correlated with asymmetric adrenal uptake (42).

PPNAD histological characteristics are quite unique already from the macroscopic examination: the adrenal cortex is dotted with numerous small pigmented nodules, classically less than 10 mm in their greatest diameter and usually surrounded by atrophic adrenocortical tissue (1).

Table 2 Diagnostic criteria and supplemental criteria for CNC and suggestive but not diagnostic findings (adapted from Stratakis *et al.* (63)). Diagnosis of CNC is made if the patient exhibits two of the diagnostic criteria or one diagnostic criterion and one of the supplemental criteria (30).

Diagnostic criteria for CNC

- 1 Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
- 2 Myxoma (cutaneous and mucosal)*
- 3 Cardiac myxoma*
- 4 Breast myxomatosis* or fat-suppressed MRI findings suggestive of this diagnosis
- 5 PPNAD* paradoxical positive response of urinary glucocorticosteroids to dexamethasone administration during Liddle's test
- 6 Acromegaly due to GH-producing adenoma*
- 7 LCCSCT* or characteristic calcification on testicular ultrasonography, in a young patient
- 8 Thyroid carcinoma* or multiple hypoechoic nodules on thyroid ultrasonography
- 9 Psammomatous melanotic schwannoma*
- 10 Blue nevus, epithelioid blue nevus (multiple)*
- 11 Breast ductal adenoma (multiple)*
- 12 Osteochondromyxoma*

Supplemental criteria

- 1 Affected first-degree relative
- 2 Inactivating mutation of the *PRKAR1A* gene

Findings suggestive or possibly associated with CNC but not diagnostic for the disease

- 1 Intense freckling (without darkly pigmented spots or typical distribution)
- 2 Blue nevus, usual type (if multiple)
- 3 Café-au-lait spots or other 'birthmarks'
- 4 Elevated IGF-I levels, abnormal oGTT, or paradoxical GH response to TRH testing in the absence of clinical acromegaly
- 5 Cardiomyopathy
- 6 Pilonidal sinus
- 7 History of Cushing's syndrome, acromegaly or sudden death in extended family
- 8 Multiple skin tags and other skin lesions; lipomas
- 9 Colonic polyps (usually in association with acromegaly)
- 10 Hyperprolactinemia (usually mild and associated with clinical or subclinical acromegaly)
- 11 Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient
- 12 Family history of carcinoma, in particular of the thyroid, colon, pancreas and the ovary; other multiple benign or malignant tumours

*With histological confirmation.

PPNAD can be responsible for an ACTH-independent Cushing's syndrome (CS), which can be overt or subclinical. Its diagnosis is made with the usual tools such as 24 h urinary free cortisol (UFC) and midnight plasma or salivary cortisol. However in the CS due to PPNAD, a paradoxical UFC increase on the second day of the high-dose dexamethasone test is quite specific (43, 44), probably due to an increased expression of the glucocorticoid receptor (45). This test is particularly useful in patients without CS or with subclinical CS or when the diagnosis of CNC has not been established in a patient with adrenal Cushing and no tumour visible on imaging. However, Espiard *et al.* described recently a poor sensitivity of 39% in a prospective series of 70 CNC patients (8). Cyclical or atypical CS are common in PPNAD.

The classical treatment for patients with overt CS is bilateral adrenalectomy (46). Anticortisol drugs such as ketoconazole, metyrapone or mitotane (47, 48) can be

temporarily used but none of them have been reported successful on long-term treatment.

To date, two very rare cases of adrenocortical carcinoma have been described in CNC patients, characterized by androgen and cortisol co-secretion and rapid metastatic evolution or local recurrence in both cases (49, 50, 51).

Thyroid tumors Thyroid disorders are more frequent in CNC patients than in the general population. Cystic and nodular lesions are present in 75% of patients on systematic ultrasonography series (52). Thyroid tumours occur in 10 to 25% of patients (2, 7, 8) with a median age at diagnosis ranging from 40 to 70. Follicular adenomas are the most common manifestation, but according to the largest series of 353 CNC patients, follicular or papillary thyroid cancer occurs in 2.5% of them (7). Recently, Carney *et al.* described a series of 26 CNC patients with thyroid disorders (53): seven with follicular carcinoma – fatal in three of them,

three with papillary carcinoma, seven with follicular adenoma and five with nodular hyperplasia. Surprisingly, four patients had hyperthyroidism: two patients with toxic adenoma and two other patients with follicular hyperplasia mimicking a Graves' disease. Hyperthyroidism has been described in a mouse model of thyroid-specific *Prkar1a* invalidation (29).

Regarding thyroid tumours, current guidelines by the American Thyroid Association and the American College of Radiology Thyroid Imaging Criteria should be utilized to select thyroid nodules in patients with CNC for fine needle aspiration biopsy and decide on surgical removal. Typically, fine needle aspiration biopsy is recommended for thyroid nodules classified as TIRADS5 (if size > 10mm) or ATA highly suspicious (54, 55).

Pituitary manifestations Whereas only 10 to 19% of CNC patients develop an overt acromegaly (2, 7, 8), around 75% of them show a disturbed GH and/or prolactin axis such as elevated insulin-growth factor 1 (IGF1), abnormal GH response to oral-glucose tolerance test or paradoxical response to TRH stimulation, without any pituitary adenoma identified on MRI (56, 57, 58). Acromegaly due to a pituitary adenoma can occur during or after the third decade of life. Transsphenoidal removal of the adenoma remains the better treatment for these patients (59). Somatostatin analogs or GH receptor antagonists can be considered if the surgical treatment is not sufficient or for patients with no detectable adenoma. Histological analysis often reveals a somatomammotroph hyperplasia surrounding the adenoma (57). Hyperprolactinemia has been reported in 64% of CNC patients, contrasting with the rare occurrence of prolactinoma (56).

Gonadal manifestations

Testicular lesions Large Cell-Calci-fying Sertoli Cell Tumors (LCCSCT) are the most frequent testicular tumors occurring in 35 to 60% of CNC male patients (2, 7, 8), usually at young age. They present as bilateral and multifocal calcifying lesions, progressively replacing the normal testicular tissue, causing the obstruction of seminiferous tubules resulting in an abnormal sperm morphology and a reduced sperm count thus leading to an impaired fertility (60). Diagnosis is easily made by ultrasonography. The malignant potential of these tumors is very low and metastatic evolution remains exceptional (61, 62) so that most patients are managed by simple monitoring.

Ovarian lesions Ovarian lesions occur in 8 to 14% of female CNC patients (2, 7), mostly represented by ovarian cysts, but benign tumours of the ovarian surface epithelium are frequent, such as serous cystadenomas and cystic teratomas, easily identified by ultrasonography, presented as hypoechoic lesions. The heterogeneity of these ovarian lesions could question the association with CNC but their frequency suggests that pelvic ultrasonographic should be done in the initial evaluation of CNC female patients. In some rare cases, these tumours can evolve into ovarian carcinoma such as mucinous adenocarcinoma or endometrioid carcinoma (63), requiring a oncology referral and management including surgical removal when possible.

Other sites of involvement

Breast lesions Benign breast tumours are frequent in CNC, with an estimated frequency of 20 to 40% in female patients (2, 7, 8). The typical lesions are breast or nipple myxomas, myxoid fibroadenomas and ductal adenomas. These tumours are classically bilateral and multicentric and rise after puberty. Both male and female patients are concerned by nipple myxomas. Espiard *et al.* described for the first time a possible association with CNC and breast carcinomas, occurring in 13.5% of the female patients under 50 in their series (8). Systematic ultrasonography or MRI evaluation should be recommended. Surgical removal should be considered only for suspicion of breast carcinoma, while simple monitoring is indicated in other breast lesions.

Bone lesions Osteochondromyxomas are rare and benign myxomatous bone tumours, occurring in 1 to 5% of CNC patients (8, 64), classically before the age of 2. They are localized preferentially in the diaphysis of long bones and nasal sinuses. The surgical removal is usually curative, but some cases of local invasiveness or recurrence after surgery have been reported.

Espiard *et al.* reviewed the skeletal MRI of 20 CNC patients, revealing vertebral nodular lesions in 50% of them, compatible with osteochondromyxomas but for whom atypical haemangiomas could not be excluded (8). This suggests asymptomatic osteochondromyxomas could be much more frequent in CNC patients than described so far.

Psammomatous melanotic schwannoma
Psammomatous melanotic schwannomas are nerve sheath-derived tumours occurring in 5 to 10% of CNC

patients (7, 8) with a median age at diagnosis of 32. Brown pigmentation, calcifications and multicentric nature are characteristic of these CNC-associated tumors (65). They can grow anywhere in the central or peripheral nervous system but preferentially in the gastrointestinal tract, the paraspinal sympathetic chain and the chest wall (41). Malignancy has been reported, occurring probably in less than 10% of affected patients, with a classical metastatic progression in liver, lung and brain (66). Due to their localization, these tumours are often symptomatic and the treatment should be surgical when possible (58), but their potential invasiveness can lead to a difficult removal. To date, no medical treatment has been proven to be effective in metastatic tumours.

Suggestive criteria

Many other manifestations have been observed in CNC patients and are summarized in Table 1. These criteria are suggestive for CNC diagnosis but not sufficient.

Around 2.5% of CNC patients develop pancreatic tumours, including adenocarcinoma, acinar cell carcinoma and intraductal pancreatic mucinous neoplasia (30, 67).

CNC patients may have predisposition for other malignancies in rare cases.

Screening recommendations

For manifestations requiring specific follow-up and treatment, early and regular monitoring is a key feature in order to allow early diagnosis and management. Patients should be seen at least annually with a detailed clinical examination for all the manifestations of CNC. Despite a late median age at diagnosis of cardiac myxomas in CNC patients, they may occur in early childhood. In a recent study, four patients developed cardiac myxomas before the age of 5, the younger one was 4 (32). Cardiac myxoma can occur even earlier since it has been described in a 3-year-old child (7). In the only prospective study about CNC patients, cardiac myxomas led to complications for 68.8% of patients, including stroke in 7 of 16 affected patients. PPNAD can appear in early childhood as well with earliest detections around the age of 2. We recommend an annual assessment of echocardiography, beginning in the first 2 years of life in CNC children with *PRKAR1A* germline mutation. Twenty-four hour urinary free cortisol (UFC) and 1 mg dexamethasone suppression test should theoretically be recommended according

to the same time frame than for cardiac myxomas, but because of the poor feasibility of these investigations in early infancy, it can be guided by clinical examination, including growth curve faltering and/or excessive weight gain.

Because of the later onset of thyroid nodules (53), the first cervical ultrasonography should be performed in the first 10 years of age, while ovarian and breast imaging could begin after puberty in female patients.

The earliest reported detection of LCCSCT was made in a 2-yr-old boy (30), but systematic testicular ultrasonography should not be recommended at such a young age because of the usual therapeutic abstention.

For patients diagnosed with CNC after puberty or in adulthood, we recommend to perform the following explorations immediately at initial diagnosis of CNC: echocardiography, 24-h UFC, 1 mg dexamethasone suppression test, serum IGF1 and prolactin, thyroid ultrasonography, pituitary, spine and abdominal MRI, pelvic ultrasonography and MRI or mammography in female patients, testicular ultrasonography in male patients. Echocardiography, 24-h UFC, 1 mg dexamethasone suppression test, serum IGF1 and prolactin can be repeated annually, but there is no consensus regarding the frequency of the other explorations; the results of initial investigations and clinical examination should guide their frequency. For patients with an history of cardiac myxoma, echocardiography should be performed twice a year (30) because of its frequent recurrence after surgery, recently estimated at 44% and even more frequent in women (32).

Osteochondromyxomas and PMS are less frequent clinical features and then should not be systematically looked for apart from the initial spine MRI, and imaging should be guided on the result of the initial imaging and on the annual clinical signs and examination.

Treatment

There is not yet a systemic medical treatment developed according to genetic defect or targeting the cAMP/PKA signaling in CNC. Each manifestation is treated individually. In most of the manifestations, surgical treatment is usually discussed in a multi-disciplinary setting, particularly cardiac myxomas, PPNAD, thyroid carcinomas, PMS and often acromegaly. For the other clinical features, surgical removal can be discussed but therapeutic abstention and simple monitoring are often proposed in the absence of symptoms or patient complaint.

Genetic counselling

PRKARIA sequencing and copy-number variation analysis is indicated for each patient presenting with CNC diagnostic criteria without any family history of CNC, as well as for every first-degree relative. For patients without any identified *PRKARIA* alteration, analysis of *PRKACA*, *PRKACB* and phosphodiesterases genes can be discussed, particularly in isolated PPNAD. In first-degree relative of mutation carriers, genetic analysis should be offered and can be discussed in the first 2 years of life in infants in order to plan appropriately the follow-up since CNC manifestations may appear before the age of 3.

Conclusion

Described 35 years ago, CNC is a rare disease with numerous manifestations. Its diagnosis might be difficult in many cases, despite its various characteristic endocrine and non-endocrine features. However, the more detailed description of all the manifestations of the disease in various retrospective and now prospective cohorts is very helpful to improve both diagnosis and management of CNC by multi-disciplinary teams based on each diagnosed manifestation of the disease. Long-term follow-up, at least annually, is clearly needed and the clearer description of the disease and its evolution that we have today should help to develop better recommendations. The identification of the *CNC1* gene 20 years ago was instrumental to better understand the pathophysiology of this disease, that is a major example of dysregulation of the cAMP/PKA pathway in human disease. It has already led to genetic counselling offerings and family screenings that will ultimately improve the outcome by earlier diagnosis. On the long-term understanding, the molecular mechanisms of the disease will hopefully open the way to specific medical therapies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

Lucas Bouys is recipient of research fellowships from the CARPEM and the ARC Foundation, J B laboratory is supported by the Agence Nationale pour la Recherche grant ANR-18-CE14-0008-01 and the Fondation pour la Recherche Médicale (EQU201903007854).

Acknowledgement

The authors thank Aparna Mazumdar for helping in manuscript editing.

References

- Shenoy BV, Carpenter PC & Carney JA. Bilateral primary pigmented nodular adrenocortical disease: rare cause of the Cushing syndrome. *American Journal of Surgical Pathology* 1984 **8** 335–344. (<https://doi.org/10.1097/0000478-198405000-00002>)
- Carney JA, Gordon H, Carpenter PC, Shenoy BV & Go VL. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine* 1985 **64** 270–283. (<https://doi.org/10.1097/00005792-198507000-00007>)
- Atherton DJ, Pitcher DW, Wells RS & Macdonald DM. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. *British Journal of Dermatology* 1980 **103** 421–429. (<https://doi.org/10.1111/j.1365-2133.1980.tb07266.x>)
- Rhodes AR, Silverman RA, Harriest TJ & Perez-Atayde AR. Mucocutaneous lentigines, cardiomyocutaneous myxomas, and multiple blue nevi: the 'LAMB' syndrome. *Journal of the American Academy of Dermatology* 1984 **10** 72–82. ([https://doi.org/10.1016/s0190-9622\(84\)80047-x](https://doi.org/10.1016/s0190-9622(84)80047-x))
- Frankenfeld RH, Waters CH & Steiner RC. Bilateral myxomas of the heart. *Annals of Internal Medicine* 1960 **53** 827–838. (<https://doi.org/10.7326/0003-4819-53-4-827>)
- Tsay CJ, Stratakis CA, Fauch FR, London E, Stathopoulou C, Allgauer M, Quezado M, Dagradi T, Spencer DD & Lodish M. Harvey Cushing treated the first known patient with Carney complex. *Journal of the Endocrine Society* 2017 **1** 1312–1321. (<https://doi.org/10.1210/js.2017-00283>)
- Bertherat J, Horvath A, Groussin L, Grabar S, Boikos S, Cazabat L, Libe R, René-Corail F, Stergiopoulos S, Bourdeau I *et al.* Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (*PRKAR1A*): phenotype analysis in 353 patients and 80 different genotypes. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2085–2091. (<https://doi.org/10.1210/jc.2008-2333>)
- Espiard S, Vantyghem MC, Assié G, Cardot-Bauters C, Raverot G, Brucker-Davis F, Archambeaud-Mouveroux F, Lefebvre H, Nunes ML, Tabarin A *et al.* Frequency and incidence of Carney complex manifestations: a prospective multicenter study with a three-year follow-up. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** e436–e446. (<https://doi.org/10.1210/clinem/dgaa002>)
- Casey M, Mah C, Merliss AD, Kirschner LS, Taymans SE, Denio AE, Korf B, Irvine AD, Hughes A, Carney JA *et al.* Identification of a novel genetic locus for familial cardiac myxomas and Carney complex. *Circulation* 1998 **98** 2560–2566. (<https://doi.org/10.1161/01.cir.98.23.2560>)
- Stratakis CA, Carney JA, Lin JP, Papanicolaou DA, Karl M, Kastner DL, Pras E & Chrousos GP. Carney complex, a familial multiple neoplasia and lentiginosis syndrome: analysis of 11 kindreds and linkage to the short arm of chromosome 2. *Journal of Clinical Investigation* 1996 **97** 699–705. (<https://doi.org/10.1172/JCI118467>)
- Matyakhina L, Pack S, Kirschner LS, Pak E, Mannan P, Jaikumar J, Taymans SE, Sandrini F, Carney JA & Stratakis CA. Chromosome 2 (2p16) abnormalities in Carney complex tumours. *Journal of Medical Genetics* 2003 **40** 268–277. (<https://doi.org/10.1136/jmg.40.4.268>)
- Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS & Stratakis CA. Mutations of the gene encoding the protein kinase A type I- α regulatory subunit cause familial cardiac myxomas and Carney complex. *Nature Genetics* 2000 **26** 89–92. (<https://doi.org/10.1038/79238>)
- Casey M, Vaughan CJ, He J, Hatcher CJ, Winter JM, Weremowicz S, Montgomery K, Kucherlapati R, Morton CC & Basson CT. Mutations in the protein kinase A R1 α regulatory subunit cause familial cardiac myxomas and Carney complex. *Journal of Clinical Investigation* 2000 **106** R31–R38. (<https://doi.org/10.1172/JCI10841>)
- <http://prkar1a.nichd.nih.gov>.

- 15 Groussin L, Horvath A, Jullian E, Boikos S, Rene-Corail F, Lefebvre H, Cepheise-Velayoudom FL, Vantyghem MC, Chanson P, Conte-Devolx B *et al.* A PRKARIA mutation associated with primary pigmented nodular adrenocortical disease in 12 kindreds. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1943–1949. (<https://doi.org/10.1210/jc.2005-2708>)
- 16 Forlino A, Vetro A, Garavelli L, Ciccone R, London E, Stratakis CA & Zuffardi O. PRKACB and Carney complex. *New England Journal of Medicine* 2014 **370** 1065–1067. (<https://doi.org/10.1056/NEJMc1309730>)
- 17 Beuschlein F, Fassnacht M, Assié G, Calebiro D, Stratakis CA, Osswald A, Ronchi CL, Wieland T, Sbiera S, Faucz FR *et al.* Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *New England Journal of Medicine* 2014 **370** 1019–1028. (<https://doi.org/10.1056/NEJMoa1310359>)
- 18 Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, Stein E, Levine E, Delimpasi G, Hsiao HP *et al.* A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. *Nature Genetics* 2006 **38** 794–800. (<https://doi.org/10.1038/ng1809>)
- 19 Libé R, Horvath A, Vezzosi D, Fratticci A, Coste J, Perlemon K, Ragazzon B, Guillaud-Bataille M, Groussin L, Clauser E *et al.* Frequent phosphodiesterase 11A gene (PDE11A) defects in patients with Carney complex (CNC) caused by PRKARIA mutations: PDE11A may contribute to adrenal and testicular tumors in CNC as a modifier of the phenotype. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** E208–E214. (<https://doi.org/10.1210/jc.2010-1704>)
- 20 Horvath A, Mericq V & Stratakis CA. Mutation in PDE8B, a cyclic AMP-specific phosphodiesterase in adrenal hyperplasia. *New England Journal of Medicine* 2008 **358** 750–752. (<https://doi.org/10.1056/NEJMc0706182>)
- 21 Taylor SS, Ilouz R, Zhang P & Kornev AP. Assembly of allosteric macromolecular switches: lessons from PKA. *Nature Reviews: Molecular Cell Biology* 2012 **13** 646–658. (<https://doi.org/10.1038/nrm3432>)
- 22 Taylor SS, Zhang P, Steichen JM, Keshwani MM & Kornev AP. PKA: lessons learned after twenty years. *Biochimica et Biophysica Acta* 2013 **1834** 1271–1278. (<https://doi.org/10.1016/j.bbapap.2013.03.007>)
- 23 Yu B, Ragazzon B, Rizk-Rabin M & Bertherat J. Protein kinase A alterations in endocrine tumors. *Hormone and Metabolic Research* 2012 **44** 741–748. (<https://doi.org/10.1055/s-0032-1316292>)
- 24 Vezzosi D & Bertherat J. Phosphodiesterases in endocrine physiology and disease. *European Journal of Endocrinology* 2011 **165** 177–188. (<https://doi.org/10.1530/EJE-10-1123>)
- 25 Amieux PS, Howe DG, Knickerbocker H, Lee DC, Su T, Laszlo GS, Idzerda RL & McKnight GS. Increased basal cAMP-dependent protein kinase activity inhibits the formation of mesoderm-derived structures in the developing mouse embryo. *Journal of Biological Chemistry* 2002 **277** 27294–27304. (<https://doi.org/10.1074/jbc.M200302200>)
- 26 Griffin KJ, Kirschner LS, Matyakhina L, Stergiopoulos SG, Robinson-White A, Lenherr SM, Weinberg FD, Claflin ES, Batista D, Bourdeau I *et al.* A transgenic mouse bearing an antisense construct of regulatory subunit type 1A of protein kinase A develops endocrine and other tumours: comparison with Carney complex and other PRKARIA induced lesions. *Journal of Medical Genetics* 2004 **41** 923–931. (<https://doi.org/10.1136/jmg.2004.028043>)
- 27 Sahut-Barnola I, de Jossineau C, Val P, Lambert-Langlais S, Damon C, Lefrançois-Martinez AM, Pointud JC, Marceau G, Sapin V, Tissier F *et al.* Cushing's syndrome and fetal features resurgence in adrenal cortex-specific Prkar1a knockout mice. *PLoS Genetics* 2010 **6** e1000980. (available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2883593/>) (<https://doi.org/10.1371/journal.pgen.1000980>)
- 28 Yin Z, Williams-Simons L, Parlow AF, Asa S & Kirschner LS. Pituitary-specific knockout of the Carney complex gene Prkar1a leads to pituitary tumorigenesis. *Molecular Endocrinology* 2008 **22** 380–387. (<https://doi.org/10.1210/me.2006-0428>)
- 29 Pringle DR, Yin Z, Lee AA, Manchanda PK, Yu L, Parlow AF, Jarjoura D, La Perle KMD & Kirschner LS. Thyroid specific ablation of the Carney complex gene, PRKARIA, results in hyperthyroidism and follicular thyroid cancer. *Endocrine-Related Cancer* 2012 **19** 435–446. (<https://doi.org/10.1530/ERC-11-0306>)
- 30 Stratakis CA, Kirschner LS & Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4041–4046. (<https://doi.org/10.1210/jcem.86.9.7903>)
- 31 Wei K, Guo HW, Fan SY, Sun XG & Hu SS. Clinical features and surgical results of cardiac myxoma in Carney complex. *Journal of Cardiac Surgery* 2019 **34** 14–19. (<https://doi.org/10.1111/jocs.13980>)
- 32 Pitsava G, Zhu C, Sundaram R, Mills JL & Stratakis CA. Predicting the risk of cardiac myxoma in Carney complex. *Genetics in Medicine* 2021 **23** 80–85. (<https://doi.org/10.1038/s41436-020-00956-3>)
- 33 Maleszewski JJ, Larsen BT, Kip NS, Castonguay MC, Edwards WD, Carney JA & Kipp BR. PRKARIA in the development of cardiac myxoma: a study of 110 cases including isolated and syndromic tumors. *American Journal of Surgical Pathology* 2014 **38** 1079–1087. (<https://doi.org/10.1097/PAS.0000000000000202>)
- 34 Mateus C, Palangié A, Franck N, Groussin L, Bertagna X, Avril MF, Bertherat J & Dupin N. Heterogeneity of skin manifestations in patients with Carney complex. *Journal of the American Academy of Dermatology* 2008 **59** 801–810. (<https://doi.org/10.1016/j.jaad.2008.07.032>)
- 35 Vandersteen A, Turnbull J, Jan W, Simpson J, Lucas S, Anderson D, Lin JP, Stratakis C, Pichert G & Lim M. Cutaneous signs are important in the diagnosis of the rare neoplasia syndrome Carney complex. *European Journal of Pediatrics* 2009 **168** 1401–1404. (<https://doi.org/10.1007/s00431-009-0935-y>)
- 36 Stratakis CA. Genetics of Peutz-Jeghers syndrome, Carney complex and other familial lentiginoses. *Hormone Research* 2000 **54** 334–343. (<https://doi.org/10.1159/000053283>)
- 37 Horvath A & Stratakis CA. Carney complex and lentiginosis. *Pigment Cell and Melanoma Research* 2009 **22** 580–587. (<https://doi.org/10.1111/j.1755-148X.2009.00613.x>)
- 38 Carney JA & Stratakis CA. Epithelioid blue nevus and psammomatous melanotic schwannoma: the unusual pigmented skin tumors of the Carney complex. *Seminars in Diagnostic Pathology* 1998 **15** 216–224.
- 39 Carney JA & Ferreiro JA. The epithelioid blue nevus: a multicentric familial tumor with important associations, including cardiac myxoma and psammomatous melanotic schwannoma. *American Journal of Surgical Pathology* 1996 **20** 259–272. (<https://doi.org/10.1097/00000478-199603000-00001>)
- 40 Carney JA, Headington JT & Su WP. Cutaneous myxomas: a major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Archives of Dermatology* 1986 **122** 790–798. (<https://doi.org/10.1001/archderm.122.7.790>)
- 41 Courcoutsakis NA, Tatsi C, Patronas NJ, Lee CC, Prassopoulos PK & Stratakis CA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation. *Insights into Imaging* 2013 **4** 119–133. (<https://doi.org/10.1007/s13244-012-0208-6>)
- 42 Vezzosi D, Tenenbaum F, Cazabat L, Tissier F, Bienvenu M, Carrasco CA, Laloi-Michelin M, Barraud G, Lefebvre H, Hiéronimus S *et al.* Hormonal, radiological, NP-59 scintigraphy, and pathological correlations in patients with Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD). *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 4332–4338. (<https://doi.org/10.1210/jc.2015-2174>)
- 43 Koch CA, Bornstein SR, Chrousos GP & Stratakis CA. Primary pigmented nodular adrenocortical dysplasia (PPNAD) within the scope of Carney complex as the etiology of Cushing syndrome. *Medizinische Klinik* 2000 **95** 224–230.

- 44 Stratakis CA, Sarlis N, Kirschner LS, Carney JA, Doppman JL, Nieman LK, Chrousos GP & Papanicolaou DA. Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. *Annals of Internal Medicine* 1999 **131** 585–591. (<https://doi.org/10.7326/0003-4819-131-8-199910190-00006>)
- 45 Louiset E, Stratakis CA, Perraudin V, Griffin KJ, Libé R, Cabrol S, Fève B, Young J, Groussin L, Bertherat J *et al.* The paradoxical increase in cortisol secretion induced by dexamethasone in primary pigmented nodular adrenocortical disease involves a glucocorticoid receptor-mediated effect of dexamethasone on protein kinase A catalytic subunits. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2406–2413. (<https://doi.org/10.1210/jc.2009-0031>)
- 46 Lowe KM, Young WF, Lyssikatos C, Stratakis CA & Carney JA. Cushing syndrome in Carney complex: clinical, pathological, and molecular genetic findings in the 17 affected Mayo Clinic patients. *American Journal of Surgical Pathology* 2017 **41** 171–181. (<https://doi.org/10.1097/PAS.0000000000000748>)
- 47 Cignarelli M, Picca G, Campo M, Margaglione M, Marino A, Logoluso F & Giorgino F. A six month mitotane course induced sustained correction of hypercortisolism in a young woman with PP2AD and Carney complex. *Journal of Endocrinological Investigation* 2005 **28** 54–60. (<https://doi.org/10.1007/BF03345530>)
- 48 Campo MR, Lamacchia O, Farese A, Conserva A, Picca G, Grilli G & Cignarelli M. Mitotane and Carney complex: ten years follow-up of a low-dose mitotane regimen inducing a sustained correction of hypercortisolism. *Hormones* 2015 **14** 300–304. (available at: <http://www.hormones.gr/8518/article/preview.html>) (<https://doi.org/10.14310/horm.2002.1514>)
- 49 Anselmo J, Medeiros S, Carneiro V, Greene E, Levy I, Nesterova M, Lyssikatos C, Horvath A, Carney JA & Stratakis CA. A large family with Carney complex caused by the S147G PRKARIA mutation shows a unique spectrum of disease including adrenocortical cancer. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 351–359. (<https://doi.org/10.1210/jc.2011-2244>)
- 50 Morin E, Mete O, Wasserman JD, Joshua AM, Asa SL & Ezzat S. Carney complex with adrenal cortical carcinoma. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E202–E206. (<https://doi.org/10.1210/jc.2011-2321>)
- 51 Bertherat J. Adrenocortical cancer in Carney complex: a paradigm of endocrine tumor progression or an Association of Genetic Predisposing Factors? *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 387–390. (<https://doi.org/10.1210/jc.2011-3327>)
- 52 Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA & Shawker T. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 2037–2043. (<https://doi.org/10.1210/jcem.82.7.4079>)
- 53 Carney JA, Lyssikatos C, Seethala RR, Lakatos P, Perez-Atayde A, Lahner H & Stratakis CA. The spectrum of thyroid gland pathology in Carney complex: the importance of follicular carcinoma. *American Journal of Surgical Pathology* 2018 **42** 587–594. (<https://doi.org/10.1097/PAS.0000000000000975>)
- 54 Zhang Q, Ma J, Sun W & Zhang L. Comparison of diagnostic performance BETWEEN the American College of Radiology thyroid imaging reporting and data system and American Thyroid Association guidelines: a systematic review. *Endocrine Practice* 2020 **26** 552–563. (<https://doi.org/10.4158/EP-2019-0237>)
- 55 Castellana M, Castellana C, Treglia G, Giorgino F, Giovannella L, Russ G & Trimboli P. Performance of five ultrasound risk stratification systems in selecting thyroid nodules for FNA. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** dgz170. (<https://doi.org/10.1210/clinem/dgz170>)
- 56 Raff SB, Carney JA, Krugman D, Doppman JL & Stratakis CA. Prolactin secretion abnormalities in patients with the ‘syndrome of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas’ (Carney complex). *Journal of Pediatric Endocrinology and Metabolism* 2000 **13** 373–379. (<https://doi.org/10.1515/JPEM.2000.13.4.374>)
- 57 Pack SD, Kirschner LS, Pak E, Zhuang Z, Carney JA & Stratakis CA. Genetic and histologic studies of somatomammotropic pituitary tumors in patients with the ‘complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas’ (Carney complex). *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 3860–3865. (<https://doi.org/10.1210/jcem.85.10.6875>)
- 58 Watson JC, Stratakis CA, Bryant-Greenwood PK, Koch CA, Kirschner LS, Nguyen T, Carney JA & Oldfield EH. Neurosurgical implications of Carney complex. *Journal of Neurosurgery* 2000 **92** 413–418. (<https://doi.org/10.3171/jns.2000.92.3.0413>)
- 59 Lonser RR, Mehta GU, Kindzelski BA, Ray-Chaudhury A, Vortmeyer AO, Dickerman R & Oldfield EH. Surgical management of Carney complex-associated pituitary pathology. *Neurosurgery* 2017 **80** 780–786. (<https://doi.org/10.1227/NEU.0000000000001384>)
- 60 Burton KA, McDermott DA, Wilkes D, Poulsen MN, Nolan MA, Goldstein M, Basson CT & McKnight GS. Haploinsufficiency at the protein kinase A α gene locus leads to fertility defects in male mice and men. *Molecular Endocrinology* 2006 **20** 2504–2513. (<https://doi.org/10.1210/me.2006-0060>)
- 61 Nogales FF, Andujar M, Zuluaga A & García-Puche JL. Malignant large cell calcifying Sertoli cell tumor of the testis. *Journal of Urology* 1995 **153** 1935–1937. ([https://doi.org/10.1016/S0022-5347\(01\)67361-0](https://doi.org/10.1016/S0022-5347(01)67361-0))
- 62 Koopman RJ & Happle R. Autosomal dominant transmission of the NAME syndrome (nevi, atrial myxoma, mucinosis of the skin and endocrine overactivity). *Human Genetics* 1991 **86** 300–304. (<https://doi.org/10.1007/BF00202415>)
- 63 Stratakis CA, Papageorgiou T, Premkumar A, Pack S, Kirschner LS, Taymans SE, Zhuang Z, Oelkers WH & Carney JA. Ovarian lesions in Carney complex: clinical genetics and possible predisposition to malignancy. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 4359–4366. (<https://doi.org/10.1210/jcem.85.11.6921>)
- 64 Carney JA, Boccon-Gibod L, Jarka DE, Tanaka Y, Sweet RG, Unni KK & Stratakis CA. Osteochondromyxoma of bone: a congenital tumor associated with lentiginos and other unusual disorders. *American Journal of Surgical Pathology* 2001 **25** 164–176. (<https://doi.org/10.1097/0000478-200102000-00004>)
- 65 Carney JA. Psammomatous melanotic schwannoma: a distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. *American Journal of Surgical Pathology* 1990 **14** 206–222. (<https://doi.org/10.1097/0000478-199003000-00002>)
- 66 Shields LBE, Glassman SD, Raque GH & Shields CB. Malignant psammomatous melanotic schwannoma of the spine: a component of Carney complex. *Surgical Neurology International* 2011 **2** 136. (available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205494/>) (<https://doi.org/10.4103/2152-7806.85609>)
- 67 Gaujoux S, Tissier F, Ragazzon B, Rebours V, Saloustros E, Perlemonne K, Vincent-Dejean C, Meurette G, Cassagnau E, Dousset B *et al.* Pancreatic ductal and acinar cell neoplasms in Carney complex: a possible new association. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** E1888–E1895. (<https://doi.org/10.1210/jc.2011-1433>)

Received 28 September 2020

Revised version received 25 November 2020

Accepted 5 January 2021