Reproductive disturbances in multiple neuroendocrine tumor syndromes

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Abstract

In the context of multiple neuroendocrine tumor syndromes, reproductive abnormalities may occur via a number of different mechanisms, such as hyperprolactinemia, increased GH/IGF-1 levels, hypogonadotropic hypogonadism, hypercortisolism, hyperandrogenism, hyperthyroidism, gonadotropin hypersecretion, as well as, tumorigenesis or functional disturbances in gonads or other reproductive organs. Precocious puberty and/or male feminization is a feature of McCune–Albright syndrome (MAS), neurofibromatosis type 1 (NF1), Carney complex (CNC), and Peutz–Jeghers syndrome (PJS), while sperm maturation and ovulation defects have been described in MAS and CNC. Although tumorigenesis of reproductive organs due to a multiple neuroendocrine tumor syndrome is very rare, certain lesions are characteristic and very unusual in the general population. Awareness leading to their recognition is important especially when other endocrine abnormalities coexist, as occasionally they may even be the first manifestation of a syndrome. Lesions such as certain types of ovarian cysts (MAS, CNC), pseudogynecomastia due to neurofibromas of the nipple–areola area (NF1), breast disease (CNC and Cowden disease (CD)), cysts and ‘hypernephroid’ tumors of the epididymis or bilateral papillary cystadenomas (mesosalpinx cysts) and endometrioid cystadenomas of the broad ligament (von Hippel–Lindau disease), testicular Sertoli calcifying tumors (CNC, PJS) monolateral or bilateral macroandroldism and microlithiasis (MAS) may offer diagnostic clues. In addition, multiple neuroendocrine tumor syndromes may be complicated by reproductive malignancies including ovarian cancer in CNC, breast and endometrial cancer in CD, breast malignancies in NF1, and malignant sex-cord stromal tumors in PJS.

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Introduction

Multiple neuroendocrine tumor syndromes may appear in a sporadic mode. The McCune–Albright syndrome (MAS; OMIM #174 800), a sporadic disease, representing a mosaic case of GNAS gene mutation leading to stimulatory G-protein subunit (G-s) activation, provides an example of a phenotype associated with a post zygotic gene alteration that is present in multiple but not in all tissues/cells. Mosaicism has been also reported for other syndromes such as the von Hippel–Lindau disease (VHLD; OMIM #193 300), which is primarily hereditary (Prowse et al. 1997, Murgia et al. 2000).

Hereditary multiple neuroendocrine tumor syndromes include multiple endocrine neoplasia (MEN) type 1, 2A, 2B and 4 (OMIM MEN1: #131 100; MEN2A: #171 400; MEN2B: #162 300; MEN4: #610 755), Carney complex (CNC; OMIM #160 980), von Recklinghausen disease (neurofibromatosis type 1, NF1; OMIM + 162 200), VHLD, paraganglioma/pheochromocytoma syndromes (PGL1, 2, 3, 4; OMIM PGL1: #168 000; PGL2: #605 373; PGL3: #605 373; PGL4: #115 310).

Hereditary multiple tumor syndromes with limited neuroendocrine involvement include the Peutz–Jeghers syndrome (PJS; OMIM #175 200) and Cowden disease (CD; OMIM #158 350).

In the context of multiple tumor syndromes, reproductive abnormalities may occur via a number of different mechanisms. The most frequent etiology is the presence of hyperprolactinemia, which may occur due to direct production by a prolactinoma or a mixed somatolactotrope tumor. MEN1, MAS, and rarely CNC may be accompanied by prolactinomas; however, other
large nonprolactin (PRL)-producing pituitary adenomas may lead to hyperprolactinemia when pressing on the optic chiasm resulting in stalk compression and blockade of the tonic inhibition of lactotropes by dopamine. Hyperprolactinemia will suppress LH levels and pulsatility, and reverse the LH/FSH ratio resulting in hypogonadotropic hypogonadism. A large pituitary tumor may also result in hypogonadotropic hypogonadism applying mechanical pressure and disrupting gonadotrope function. In addition, gonadotropin hypersecretion due to a LH/FSH-producing adenoma may also be part of pituitary pathology.

Increased GH/insulin-like growth factor-1 (IGF-1) levels due to a GH-secreting pituitary adenoma may lead to insulin resistance and hyperinsulinemia inducing a polycystic ovary syndrome (PCOS) phenotype affecting ovulatory function. Hypercortisolism and/or hyperandrogenism due to a pituitary ACTH adenoma, ectopic production of ACTH or increased cortisol/androgen production by adrenal tumor(s) may result in metabolic disturbances affecting general health and/or reproductive function. Similarly, hyperthyroidism that may result from thyroid toxic adenoma(s) or a pituitary TSH adenoma will affect metabolic status and induce menstrual disturbances and increased rate of first trimester abortions.

Finally, tumorigenesis or functional disturbances in gonads or other reproductive organs complicate more or less frequently these syndromes.

**Endocrine hormonal disturbances in the context of a multiple endocrine syndrome**

**Pituitary hormones**

Hormonal disturbances are very frequent in multiple endocrine tumor syndromes.

Excess of all pituitary hormones has been described in the context of MEN1. Anterior pituitary adenomas (2/3 of the cases are microadenomas) are most frequently PRL (may be the presenting feature in up to 15% and may affect up to 35% of patients in the course of their lives), GH (may be the presenting feature in up to 5% and may affect up to 12% of patients in the course of their lives), and ACTH secreting. A few gonadotrope tumors, TSH-secreting adenomas, and a TSH carcinoma have been also reported (Socin et al. 2003, Benito et al. 2005, Sztal-Mazer et al. 2008, Scheithauer et al. 2009). Apart from mono- or plurihormonal pituitary adenomas, ectopic GHRH production may be another hormonal manifestation in MEN1 that may affect pituitary function-stimulating GH secretion by somatotropes (Trouillas et al. 2008).

In MAS, the most usual pituitary abnormalities include GH excess (4–5% of the cases) and hyperprolactinemia (3–4% of the cases); however, ACTH- and TSH-secreting tumors have been described (Gessl et al. 1994, Riminucci et al. 2002).

In CNC, increased activity of the GH axis has been reported in up to 75% of patients, and pituitary tumors are most often somatotropinomas (10% of the patients are acromegalic at presentation) with rare cases of prolactinomas (Handley et al. 1992, Stratakis et al. 2001).

In NF1, cases of GH hypersecretion have been attributed to the disruption of the somatostatin tone by optic nerve gliomas (Drake et al. 2000, Drimmie et al. 2000). Central activation of pituitary gonadotrope function, mostly, but not solely, due to the presence of optic pathway tumors or hypothalamic involvement, may induce central precocious puberty in young NF1 patients. In NF1, precocious puberty has been reported in 2.4% of the patients, while delayed puberty may also occur (Carmi et al. 1999, Virdis et al. 2000, 2003).

**Target organ hormones**

Target organ hormone hypersecretion is usually secondary to pituitary hormonal excess; however, in MAS autonomous thyroid, adrenal and gonadal hyperactivity is a much more frequent cause of hormonal overproduction.

In CNC, adrenal and gonadal hyperactivity is quite frequent. Many cases of PJS, MAS and CNC are accompanied by autonomous peripheral steroid hormone hypersecretion and may present with peripheral precocious puberty.

In addition, a rare case of Cushing syndrome caused by a cortisol-producing adrenal adenoma presenting as the first manifestation of MEN1, due to MEN1 gene mutation at a splicing site, has been reported recently (Alzahrani et al. 2008).

Parathyroid hormone (PTH) hypersecretion is mainly a feature of the MEN syndromes, although some cases have been described in NF1 (Altinova et al. 2007, Kodama et al. 2007). PTH-related protein has been implicated as a possible etiologic factor for bone fibrous dysplasia in MAS (Fraser et al. 2000).

Pathophysiology and clinical presentation of reproductive disturbances in hormone excess

Hyperprolactinemia, as has been demonstrated almost three decades ago, suppresses LH levels and pulsatility, leading to hypogonadotropism and reversal of the LH/FSH ratio (Tolis 1980). As a result, patients may present with amenorrhea, galactorrhea, infertility, or impotence in males.

Aside from PRL excess, GH hypersecretion also affects menstrual cyclicity. Menstrual disturbances may be the first manifestation of acromegaly, while menstrual irregularity may affect 40–84% of female patients in the course of the disease (Kaltsas et al. 1999). A small percentage of patients present with amenorrhea, galactorrhea, infertility, or impotence in males.

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Gonadotropin hypersecretion due to a gonadotrope adenoma is rare among patients with multiple neuroendocrine tumor syndromes. In general, gonadotrope tumors may be complicated by ovarian hyperstimulation even in the absence of continually elevated FSH levels (Kihara et al. 2006). In a 40-year-old woman with a FSH-producing pituitary microadenoma, the serum concentration of E2 and the size of her multicystic ovaries fluctuated dramatically and were transiently normalized (Maruyama et al. 2005).

A characteristic case of a woman with MEN1 and a gonadotrope tumor has been described (Benito et al. 2005). She originally presented with amenorrhea and was treated at age 31 by transsphenoidal surgery, which was repeated 5 years later. Elevated plasma E2 (>1840 pmol/l) and endometrial hyperplasia persisted after the second transphenoidal surgery. At the age of 39, ovarian stimulation, multiple ovarian cysts, and endometrial hyperplasia were observed as a result of persistent mild elevation of plasma FSH (approximately twofold higher than the upper limit of

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<td>PTH/PTHrP</td>
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●, Frequent syndrome feature; ○, rare syndrome feature; □, in transgenic animal model; ▽, PTHrP. Estrogen and androgen excess in MEN1 may be observed in women either as a consequence of an FSH adenoma and ovarian hyperstimulation (estrogen excess), or due to acromegaly and increased free androgen levels due to lower steroid hormone-binding globulin (SHBG) levels. In CNC, PJS and MAS peripheral steroid production may be observed. In NF1, usually central precocious puberty is the cause of steroid hormone excess. Elevated secretion of PTHrP has been reported to be possibly associated with bone fibrous dysplasia in MAS. For references, please see text. PRL, prolactin; GC, glucocorticoids; TH, thyroid hormone; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; MEN, multiple endocrine neoplasia; CNC, Carney Complex; PJS, Peutz–Jeghers syndrome; NF1, neurofibromatosis type 1 (von Recklinghausen disease); MAS, McCune–Albright syndrome.
normal (2×ULN) and markedly elevated plasma E₂ concentrations (Djerassi et al. 1995). She subsequently developed hyperparathyroidism, while later a temporal lobe metastasis indicated that the tumor was a gonadotrope carcinoma (Benito et al. 2005).

However, in a woman with a gonadotrope tumor, the extent of reproductive disturbances is dependent on the remaining pituitary function and the presence of sufficient pituitary LH production capable of supporting estrogen secretion by the ovary. High PRL and E₂, and low LH occur in most cases, although E₂ may remain within normal limits for the corresponding menstrual cycle phases. However, in cases with essentially absent LH, the ovarian hyperstimulation profile associated with a FSH-secreting adenoma is not accompanied by high estrogen levels and endometrial hyperplasia. As an example, in a 28-year-old woman with abdominal pain and large ovaries with multiple follicular cysts, a FSH-secreting pituitary macroadenoma (not in the context of a MEN1 phenotype) was not accompanied by high levels of serum E₂, probably due to insufficient LH production (Shimon et al. 2001).

In a man with MEN1, a FSH-secreting gonadotrope macroadenoma encircling both carotid arteries and compressing the optic chiasm was accompanied by reduced libido and erectile function in the presence of a typical hormonal profile with high FSH (~3×ULN) and α-subunit, moderately high PRL, and normal LH in spite of low total testosterone (Sztal-Mazer et al. 2008).

**Fertility, gestation, parturition, and postdelivery health issues of mother, fetus, and newborn**

Hyperthyroidism, hypercortisolism, hyperandrogenism, and hyperparathyroidism have been associated with severe adverse effects on fertility, pregnancy progression, and pregnancy outcome. Maternal hyperthyroidism, especially when poorly controlled, is associated with an increased risk of miscarriage, medically indicated preterm delivery, preeclampsia, congestive heart failure, thyroid storm, intrauterine growth retardation, low birth weight or fetal loss and stillbirth (Abalovich et al. 2007). Women with hyperandrogenism and PCOS, apart from subfertility, have a significantly higher risk of developing gestational diabetes, pregnancy-induced hypertension, preeclampsia and preterm birth, risk of neonatal intensive care unit admission, and perinatal mortality (Boomsma et al. 2006, Martin et al. 2008). Hypercortisolism is associated with maternal and fetal morbidity and/or mortality including hypertension, gestational diabetes or impaired glucose tolerance, impaired wound healing, osteoporosis, bone fractures, psychiatric complications, maternal cardiac failure, premature birth, stillbirth, intrauterine deaths, or spontaneous abortions (Bronstein et al. 2002, Lindsay & Nieman 2005). Hyperparathyroidism may result in hypercalcemic crisis of the mother during pregnancy and neonatal hypocalcemia, especially when hyperparathyroidism has been undiagnosed (Higgins & Hisley 1988, Hsieh et al. 1998, Schnatz & Thaxton 2005, Pieringer et al. 2007).

**Tumorigenesis, hyperplasia, architectural, or functional disturbances in reproductive organs in the context of a multiple endocrine tumor syndrome**

In everyday practice, tumorigenesis of reproductive organs due to a multiple tumor syndrome is rare. However, certain lesions appear characteristic, and the occurrence of unusual types of tumors in patients with other known endocrine abnormalities may occasionally point at the direction of a multiple endocrine tumor syndrome.

Summaries of male and female reproductive organ tumors that may occur in the context of multiple neuroendocrine tumor syndromes are presented in Tables 2 and 3.

**Multiple endocrine neoplasia syndrome-1**

The presence of uterine leiomyomas has been described in a number of female MEN1 patients. Uterine smooth muscle tumors have been linked with loss of heterozygosity in 11q13, i.e. the locus that contains the MEN1 gene (McKeeby et al. 2001), and recently to a new mutation of the MEN1 gene, in a case also manifesting a bladder leiomyoma (Choi et al. 2008). Other genitourinary leiomyomas, such as the case of a ureteral leiomyoma causing hydronephrosis (Ikota et al. 2004), have also been described in MEN1 patients. However, due to the high frequency of these lesions in the general population, their presence does not offer any diagnostic help unless they coexist with other tumors. Regardless, the possible coexistence of leiomyomas should be considered in female MEN1 patients.

A case of an ovarian gastrinoma has also been described in a MEN1 patient, while carcinoids of the ovary have been reported in MEN1 and MEN2A cases (Abboud et al. 2001, Papageorgiou & Stratakis 2002).

Interestingly, heterozygous MEN1 mutant mice show a high incidence of gonadal tumors of endocrine
Table 2 Male reproductive organ involvement in multiple tumor syndromes

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<th>MEN</th>
<th>CNC</th>
<th>PJS</th>
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<td>Testicular Sertoli cells</td>
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<td>Large-cell calcifying tumors</td>
<td>Bilateral multicentric tumors (most calcifying)</td>
<td>Isolated mono/bilateral testicular enlargement</td>
<td>Leydig cell tumors</td>
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<td>Testicular Leydig cells</td>
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<td>Other testicular involvement</td>
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<td>Testicular cancer in MEN4?</td>
<td>Adrenocortical rest tumors</td>
<td>Interstitial cell tumors</td>
<td>Testicular microlithiasis</td>
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<td>Other male organ involvement</td>
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<td>Prostate neuroendocrine tumors and carcinoids (MEN2B)</td>
<td>Aggressive prostate cancer 11q13.1 gain (MEN1 gene?)</td>
<td>Cysts and ‘hyper-nephroid’ tumors of epididymis</td>
<td>Bilateral papillary cystadenomas of epididymis</td>
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McCune–Albright syndrome

In MAS, large ovarian cysts producing estrogen (as a result of Gs activation in ovarian cells) are responsible for the episodic increases in serum estrogen levels and a parallel reduction in gonadotropin secretion. Very frequently, these changes result in sexual precocity. Precocious puberty is part of the characteristic triad of MAS that also includes cafe au lait spots and polyostotic fibrous dysplasia. Autonomous ovarian function persists during puberty and early adult life. Precocious puberty is less frequent in males occurring in ~15% of the patients (de Sanctis et al. 2003, Matarazzo et al. 2006).

Secondary central precocious puberty following exposure to the peripherally derived sex steroids and responding to therapy with GnRH analogs has been suggested to occur in a subgroup of patients with MAS (Schmidt & Kiess 1998).

As the ovarian cysts develop in very young girls prior to the diagnosis of MAS, some of these patients are subjected to oophorectomy for presumed ovarian tumors. A recent study that assessed medical records of an 18-year period (1988–2005) revealed that four out of nine MAS female patients with sudden onset of vaginal bleeding at an age range of 6 months to 7 years underwent salpingo-oophorectomy before the first diagnosis of MAS. Histology revealed benign ovarian cysts in these four patients (Nabhan et al. 2007).

As in many MAS patients, the ovaries may be unequally affected, due to the mosaic distribution of GNAS mutation, and this may offer the possibility of therapeutic intervention. Follow-up of a 33-year-old patient...
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<td><strong>Low levels of VHL in aggressive breast tumors</strong></td>
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*Table 3 Female reproductive organ involvement in multiple tumor syndromes*
MAS patient (with irregular menstrual cycles of 30–180 days, monophasic temperature curves, and severe pelvic pain) with transvaginal ultrasound and blood tests, at 3-day intervals for 3 months, indicated a persistently quiescent left ovary, a persistently polycystic right ovary, constantly high E₂, and very low FSH and LH levels. A regular monthly menstrual cycle was restored soon after right ovariectomy, in spite of the fact that GNAS1 gene mutation was present in both ovaries, as documented by bilateral biopsies (Lavoué et al. 2008). In addition, even in cases where both ovaries appear morphologically affected, a therapeutic approach may be suitable. In a characteristic case report, the least affected ovary of a MAS patient became quiescent with GnRH agonist-induced gonadotropin suppression. Normal ovulation resumed after removal of the affected right ovary and a pregnancy occurred within 3 months reaching term without complications. DNA analysis showed no GNAS mutation in the placenta, umbilical cord structures, or umbilical cord blood indicating an unaffected offspring (Laven et al. 2004).

In male patients, testicular involvement may result in different profiles depending on the extent of Gₐα activation in Sertoli and Leydig cells. Thus, isolated nonsecretory Sertoli cell defect may present with mono- or bilateral macroorchidism without precocious puberty (Coutant et al. 2001, Arrigo et al. 2006, Rey et al. 2006). If a Leydig cell defect is present, androgen secretion occurs and precocious puberty appears in about 15% of male patients. Interstitial cell tumors are rare among MAS patients, while testicular micro-lithiasis has been suggested to be characteristic feature in this syndrome (Wasniewska et al. 2004, 2006).

Interestingly, despite long-term FSH suppression and a very low sperm count, spermatogenesis was active in a 18-year-old MAS patient who first presented with sexual precocity, monolateral macroorchidism, increased testosterone levels, and suppressed gonadotropins 15 years earlier (De Luca et al. 2008).

Breast cancer and a case of a 27-year-old woman with ductal carcinoma in situ and Paget’s disease of the nipple have been reported, and it has been suggested that MAS patients may be at an increased risk for breast cancer possibly associated with estrogen hypersecretion and/or GH excess (Tanabe et al. 1998, Huston & Simmons 2004, Dumitrescu & Collins 2008).

**Carney complex**

In the context of CNC, frequent female reproductive organ manifestations include ovarian benign or malignant tumors (such as serous cystadenomas, cystic teratomas, mucinous adenocarcinomas, endometrioid carcinomas) and myxoid uterine leiomyomas, while an atypical mesenchymal neoplasm of the uterine cervix has also been reported (Nwokoro et al. 1997, Stratakis et al. 2000, Papageorgiou & Stratakis 2002). Male reproductive organ manifestations include testicular large-cell calcifying Sertoli cell tumors (LCCSCT), Leydig cell tumors (LCT), and adrenocortical rest tumors of the testes (Carney et al. 1985). Androgen secreting LCT or LCCSCT may cause precocious puberty in boys, while LCCSCT tumors may also be estrogen secreting occasionally accompanied by male feminization (Stratakis et al. 2001, Brown et al. 2007). Apart from the tumorigenesis aspects, recent data suggest that sperm abnormalities are present in CNC. Male mice heterozygous for the protein kinase A type 1-α regulatory subunit (PRKAR1A) gene have severely reduced fertility, and these mice, as well as, CNC patients heterozygous for PRKAR1A mutations have morphologically abnormal sperm and reduced sperm number. This is likely due to elevated protein kinase A catalytic activity in male meiotic or postmeiotic germ cells leading to structural defects in mature sperm explaining the reduced transmission of PRKAR1A inactivating mutations by male patients with CNC. In light of these observations, male infertility should be considered in the context of CNC (Burton et al. 2006, Wieacker et al. 2007).

Breast tissue characteristic lesions in CNC include lobular or nodular myxomatosis, myxoid fibroadenomas, and ductal adenomas (Carney & Toorkey 1991a,b, Courcoutsakis et al. 1997).

**Neurofibromatosis type 1**


In addition, there are several case reports describing the presence of reproductive organ (ovarian and uterine) neurofibromas, which, however, do not always appear associated with other manifestations of neurofibromatosis (Horyn et al. 1988, Gersell & Fulling 1989, Nortier et al. 1989, Gordon et al. 1996, Nunes et al. 2005, Wei et al. 2005). Whether some of these cases represent manifestations of a distinct entity (rather a result of a somatic or mosaic defect) is not known.

Breast disease includes either true gynecomastia, a rather frequent finding among NF1 patients associated with precocious puberty, or pseudogynecomastia associated with neurofibromas, mainly of the

Increased relative risk for breast malignancy (by approximately fivefold) has been reported in female NF1 patients (Sharif et al. 2007). Ductal, scirrhous, and metaplastic carcinomas, as well as Paget’s disease of the breast, malignant schwannoma, and neurofibrosarcoma, have been described in patients with NF1 who appear to manifest rather unusual breast malignancies compared with the general population (Cox & Hudson 1956, Malas et al. 1995, Nakamura et al. 1998, Murayama et al. 1999, Güran & Safali 2005, Kawawa et al. 2007, Natsiopoulos et al. 2007, Invernizzi et al. 2008). A case of male adenocarcinoma and bilateral ductal in situ carcinomas have also been reported (Ronchese 1953, Wilson et al. 2004).

**von Hippel–Lindau disease**

In VHLD, characteristic reproductive organ features include epididymal cysts, bilateral papillary cystadenomas and ‘hypermephroid’ tumors, as well as bilateral papillary cystadenomas (mesosalpinx cysts) and endometrioid cystadenomas of the broad ligament (the developmental equivalent of epididymis in females; Nicolaj et al. 1979, Gruber et al. 1980, Witten et al. 1985, Gersell & King 1988, Zbar et al. 1999, Shen et al. 2000, Aydin et al. 2005, Mehta et al. 2007).

Vascular ovarian and uterine lesions, including angiectasia, angiomas and hemangiosarcomas, have been observed in a heterozygous VHL mutant animal model of carcinogen exposure (Kleymenova et al. 2004).

Interestingly, low levels of VHL have been detected in cases of aggressive breast tumors (not associated with VHLD and with negative mutation and loss of heterozygosity analysis), suggesting a defect that results in disruption of the normal VHL expression pattern (Sourvinos et al. 2001, Zia et al. 2007). Whether the VHL defect in VHLD patients may contribute to breast cancer progression is presently unknown.

**Peutz–Jeghers syndrome**

In PJS, bilateral multicentric Sertoli cell testicular tumors (most calcifying) in boys have been found in cases of rapid growth and advanced bone age associated with markedly elevated serum levels of E₂ and gynecomastia/feminization. High aromatase activity is responsible for the oversecretion of estrogen by these tumors (Coen et al. 1991, Young et al. 1995, Lefevre et al. 2006).

The occurrence of ovarian granulosa cell tumors is much more frequent than that of testicular tumors, and the appearance of isosexual precocity in girls with PJS is consistent with the production of estrogen by these tumors (Solh et al. 1983). Ovarian Sertoli cell tumors may also develop rarely (Ferry et al. 1994, Zung et al. 1998).

**Cowden disease**

Hamartomas of the genitourinary tract, uterine fibroids, and endometrial carcinoma have been reported, while only few patients with CD have ovarian disease, such as ovarian cystadenomas (Papageorgiou & Stratakis 2002, Scheper et al. 2006, Blumenthal & Dennis 2008).

Regarding breast disease, typical lesions include mammary ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, fibroadenomas, fibrocystic change, breast hamartoma, densely fibrotic hyalinized nodules, as shown by a detailed study of 19 women with CD. Among these patients, evidence of breast hamartoma was found in 17 and of malignancy, mainly ductal carcinoma, in 14 out of 19 women (Schrager et al. 1998). Male breast cancer has also been reported (Fackenthal et al. 2001).

**Paragangioma/pheochromocytoma syndromes**

In general, PGL syndromes are not associated with reproductive organ involvement. However, a number of case reports describe the presence of ovarian and vaginal paragangiomas, although no linkage to the PGL syndromes has been documented for these cases, as no SDH gene mutations have been detected (Hassan et al. 2003, Kuscu et al. 2005, McCluggage & Young 2006, Bacha et al. 2007).

Interestingly, a recent report raises the possibility of contribution of SDH mutations to the development of breast cancer (as well as thyroid and renal cancers) in PTEN-negative Cowden or Cowden-like disease (Ni et al. 2008). This may suggest that PGL patients could be at an increased susceptibility for breast cancer, dependent on their overall genetic background.

**Conclusions**

In multiple neuroendocrine tumor syndromes, reproductive function is affected by various mechanisms. Pituitary surgery may lead to partial or complete pituitary insufficiency. In addition, apart from the frequent menstrual cycle abnormalities, tumors and/or cystic lesions may complicate reproductive organs (ovary, uterus, breast, epididymis, testis). Heart and
other nonreproductive organ involvement may further compromise fertility and/or pregnancy outcome. Prior GH excess (MEN, CNC, MAS) may have affected heart architecture and compromise function, while heart myxomas in CNC may pose a problem requiring surgical therapy.

A pregnancy in a patient with a multiple tumor syndrome is a complex challenge. The presence of a pituitary adenoma or a pheochromocytoma poses a threat for a successful pregnancy and delivery. Mother and fetal/offspring safety concerns, genetic counseling issues, and doctor responsibility as well as social issues are in question.


Hyperthyroidism (MAS), hypercortisolism, hyperandrogenism or GH excess (MEN, CNC, MAS), and hyperparathyroidism (MEN) may cause maternal and fetal morbidity and mortality, including a higher rate of spontaneous abortions, preterm birth or stillbirth, metabolic imbalance (e.g. gestational diabetes or bone loss), maternal hypertension, maternal hypercalcemic crisis, or neonate hypocalcemia.

In addition, in NF1, a high rate of first trimester spontaneous abortions and cesarean sections is associated with maternal manifestations, including neurofibromas or bone abnormalities of the pelvis, skeletal deformities, pheochromocytoma, or spinal cord fibromas.

In CNC, abnormal sperm maturation appears directly associated with the PRKAR1A gene defect; thus, questions, such as, the chronic effects of hormonal excess and/or the significance of genomic defects for the structure and function of reproductive organs in the spectrum of multiple tumor syndromes remain to be answered.

Declaration of interest

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

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