Introduction

Today, most patients with hyperprolactinemia are taken care of by endocrinologists, general internists and gynecologists. With the development of reliable and sensitive hormone assays, the introduction of high definition imaging techniques, and studies of prolactin (PRL) physiology and gene regulation, our understanding of the pathogenesis of prolactinoma in humans has progressed at an astonishing pace over the past 20 years. Clinicians are now relating their clinical findings and therapeutic decisions to this new knowledge of the pathogenesis and biological behavior of human prolactinomas.

Pathogenesis

The prevalence of occult pituitary adenomas in unselected autopsies ranges from 11 to 23% (Burrow et al. 1981, Molitch & Russell 1990). Judged by staining characteristics, 45 to 50% of these adenomas are prolactinomas. PRL hormone excess results in the well recognized clinical syndromes of amenorrhea-galactorrhea and/or infertility in young women and decreased libido and/or impotence in men (Schlechte 1995). Prolactinoma accounts for up to 30% of patients with secondary gonadotropin suppression. In a review of 2230 patients who underwent surgery for pituitary adenoma, prolactinoma was the most common pituitary tumor, with a marked peak occurrence in women from the second to fifth decade of life and with a female to male ratio peaking to 14.5:1 in the third decade of life. After the fifth decade, prolactinomas are more common in men (Mindermann & Wilson 1994). A striking difference in prolactinoma size according to gender has been reported, with a predominance of small prolactinomas in women (<1 cm diameter) and large tumors in men (Schlechte 1995). Epidemiological data indicate that the prevalence of clinically relevant PRL-secreting adenomas remains, however, far below their prevalence found at autopsy (Faglia 1993). These epidemiological data also suggest that initiating factors leading to PRL-secreting tumors are quite common, while those factors necessary for clinical expression are present in a limited number of patients.

The cell of origin of a prolactinoma is a PRL-producing cell of the pituitary. Lactotrophs comprise 20-50% of total anterior pituitary cells. Pit-1, a functional transcription factor of the POU (Pit-1, Oct-1, Oct-2 and Unc-86) class, is required for the differentiation and proliferation of somatotrophs, lactotrophs and thyrotrophs (Rhodes et al. 1994). This is supported by the demonstration that humans with mutations in the Pit-1 gene have a syndrome of congenital hypothyroidism, dwarfism and PRL deficiency (Tatsumi et al. 1992). The factor that finally limits PRL expression to distinct lactotroph populations remains unknown.

On morphological and functional criteria two main PRL cell types have been identified. The densely granulated large polyhedral cells are thought to be in a resting, storing stage and the small cells correspond to a sparsely granulated cell that is actively secreting PRL (Horvath & Kovacs 1980). In a small proportion of cases, PRL is secreted by mammosomatotrophs that are also capable of secreting growth hormone (GH).

The synthesis and secretion of PRL by lactotrophs are subject to multiple endocrine, paracrine and autocrine regulators that originate from the hypothalamus and gonads, and the pituitary itself (Ben-Jonathan & Liu 1992). In physiological conditions, hypothalamic dopamine (DA) produced by tuberoinfundibular DA neurons exerts its predominant tonic inhibitory effect on pituitary PRL secretion (MacLeod & Lehmeyer 1974) through specific DA D2 receptors (Cronin 1982, Burris et al. 1991). In addition to DA, gamma-aminobutyric acid
may play a role as an inhibitor (Lamberts & MacLeod 1978, Enjalbert et al. 1979, Grandison & Guidotti 1979). Other potential PRL inhibiting factors have also been described, but their structure has not yet been completely elucidated (Molitch 1995). Superimposed on the tonic inhibition of DA are several factors that increase PRL secretion (Hazlerigg et al. 1996), including thyrotropin-releasing hormone (TRH) from the hypothalamus (De Greef & Visser 1981, Plotsky & Neill 1982, Martinez de la Escalera et al. 1988, Mogg & Samson 1990), vasoactive intestinal peptide (VIP) (Kato et al. 1978, Abe et al. 1985, Carillo et al. 1985) and steroid hormones such as estrogens (Maurer & Gorski 1977). These factors may be considered as PRL-releasing factors.

Present evidence indicates that inappropriate production of stimulatory hormones and/or growth factors and genetic defects act in concert to induce prolactinoma formation. If the prolactinomas are analyzed for clonality (X chromosome inactivation), they are found to be monoclonal, whereas normal pituitary tissue is polyclonal (Herman et al. 1993). These data are strong evidence for sporadic mutation in the lactotroph cell as the primary event in prolactinoma formation. The intrinsic genetic defect responsible for mutation and leading to cell transformation has only been elucidated in a minority of pituitary adenomas.

Within tumor secretory subtypes (e.g. prolactinomas) there is considerable heterogeneity (Hofland et al. 1992) making a single genetic abnormality unlikely as the only basis for the development of prolactinomas. Extracellular growth factors, cell surface receptors, intracellular pathways and nuclear transactors are all involved in the control of mitosis, and in recent years abnormalities have been demonstrated in pituitary tumors at each of these levels.

Neoplastic transformation can involve tumor-suppressor genes. The genetic susceptibility to multiple endocrine neoplasia type 1 (MEN-1), which includes prolactinomas, has been attributed to a deletion mapped to chromosome 11q13. The MEN-1 gene has recently been cloned (Chandrasekharappa et al. 1997) and behaves as a defective copy of a normally constitutive tumor-suppressor gene. Although individuals with MEN-1 have inherited dominant predisposition to endocrine neoplasia, phenotypic expression of endocrine tumors involves inactivating mutations of the remaining functional copy of the gene. Genetic study of such a prolactinoma in a female MEN-1 affected patient showed loss of heterozygosity of chromosome 11 to be related to tumor development (Beckers et al. 1994). Moreover, distribution of prolactinomas in certain branches of a large kindred with a mutated MEN-1 is consistent with a secondary genetic defect acting in concert with the underlying MEN-1 gene defect (Burgess et al. 1996). Chromosome 11 allelic losses have also been reported in sporadic prolactinomas, suggesting that somatic mutational inactivations in the MEN-1 gene may be important events in PRL-tumor formation (Boggild et al. 1994). Comparison of invasive and non-invasive pituitary adenomas demonstrated a significantly higher frequency of deletions affecting 11q13, 13q12-14 and 10q26 in invasive tumors (Bates et al. 1997). Allelic loss suggests more rapid growth and indicates the need for more aggressive treatment.

Mutations of regulatory regions of the G proteins, which normally couple membrane receptors to the regulation of cAMP, have been demonstrated in a subtype of GH-secreting adenomas, but not in prolactinomas. This mutation (gsp oncogene) results in elevated cAMP formation and permanent GH hypersecretion (Vallar et al. 1987). Mutations in the α-subunit of the inhibitory G protein (Gi) (the so-called gip2 oncogene) have not been reported in pituitary adenomas. However, patients with prolactinomas resistant to dopaminergic treatment have a decrease in D2 receptors, associated with a decrease in Gαα protein (Caccavelli et al. 1996). Other constitutively activated mitogenic pathways, resulting from mutations of protooncogenes (activated oncogenes) have been characterized in only a minority of prolactinomas; a mutation that activates the ras protooncogene H-ras has been reported in one invasive prolactinoma (Pet et al. 1994), but is rare in benign prolactinomas (Cai et al. 1994). Heparin-binding secretory transforming gene (hst) mutations have been demonstrated in a few prolactinomas and GH tumors. Hst-transfected cells grow more aggressively as assessed by histological invasiveness and proliferating cell nuclear antigen staining (Shimon et al. 1996).

Although the initiation of cellular transformation may be due to a pituitary cell genetic defect, subsequent promotion of pituitary adenoma growth probably requires the action of hypothalamic hormones and/or growth factors. Alternatively, a hyperplastic response to hypothalamic and/or growth factors dysregulation may predispose pituitary cells to mutational events. Also, by expanding the population of cells carrying the first genetic event required for tumor formation, the chance of a second mutation is higher.

Hypothalamic releasing hormones act on their respective anterior pituitary hormone-secreting cells by binding to specific receptors. The activated signal transduction systems mediate hormone gene expression and secretion, but they also control cell differentiation and cell proliferation. Paraneoplastic secretion of a hypothalamic hormone can lead to hyperplasia of pituitary cells and eventually to tumor formation (Molitch 1987).

Since the tuberoinfundibular dopaminergic system exerts a tonic suppressive effect on PRL secretion in normal subjects, ‘loss’ of dopaminergic tone and/or
and overexpression of EGF and EGF-R was found in Scanlon 1991, Velkeniers significant in pituitary tumor formation (Webster & factors and their respective receptors may turn out to be abnormalities in the expression and production of growth factor synthesis and both normal and transformed hypothalamic peptides, the pituitary itself is a site of regulate anterior pituitary hormone secretion. As for hormones, polypeptide growth factors have been shown to fibroblast growth factor (bFGF) and interleukins. EGF factor- epidermal growth factor (EGF), transforming growth pathogenic significance in PRL tumorigenesis are compared with normal pituitaries (Le Dafnier than somatostatin and DA in PRL-secreting adenomas, as replication; TRH and VIP are present in higher amounts VIP) able to elicit PRL secretion may further facilitate cell proliferation. As for these pituitary cells, resulting in development of hyperplasia and adenoma, but not carcinoma (McAndrew et al. 1995). The expression of bFGF, a potent mitogenic and angiogenic factor known to regulate PRL, was demonstrated by RT-PCR in prolactinomas (Ezzat et al. 1995). Patients with pituitary adenomas have detectable bFGF blood levels that decline following surgical adnectomy (Ezzat et al. 1995). Interleukin-6 and its receptor are overexpressed in pituitary adenomas and prolactinomas (Velkeniers et al. 1994b, Green et al. 1996). All these factors may, in addition to their paracrine and autocrine effects on PRL release, modulate pituitary cell growth.

Estrogens stimulate lactotroph proliferation (Lloyd 1983) and PRL biosynthesis (Lloyd & Landefeld 1986). These effects are partly mediated through a direct effect at the level of the pituitary. Such regulation is accomplished by binding of the estrogen-receptor complex to the specific estrogen-responsive element of the PRL gene (Sona et al. 1980). In addition to the primary stimulation of gene transcription induced by estrogen receptor binding, in vivo treatment with estrogen activates secondary responses (reduction in DA levels, upregulation of TRH receptors), which in turn influence PRL gene transcription. Moreover, estrogens can amplify tumor growth factor expression in pituitary cell lines. In rats, estrogens given for 30 days can cause reversible hyperplasia, but longer treatment (60 days) can cause true prolactinomas. Since estrogen-induced tumors occur only in certain strains of rats, additional mitogenic factors are probably required to lead to tumor formation. An abnormal arterial vascularization has been shown to occur in these PRL-secreting adenomas. Cellular receptors for sex steroids are widely distributed in pituitary adenomas, especially prolactinomas, with the highest density in hemorrhagic macroadenomas (Jaffrain-Rea et al. 1996). The possible impact of estrogens on growth promotion of prolactinomas has therapeutic implications.

Pituitary PRL gene expression is regulated by the coordinated expression and activation of multiple transcription (trans-acting) factors, including but not limited to Pit-1 and the estrogen receptor. Pit-1 is not only essential for the maintenance of the differentiated phenotype of the cell, but also for its proliferation. In prolactinomas, the level of expression of Pit-1 is enhanced compared with normal pituitaries. Since the basic
mechanisms initiating pituitary neoplasia are not uniform, a ‘gain of function’ abnormality in the Pit-1 gene has been postulated; alternatively the increased expression may be related to the underlying activated hormone secretion (Delhase et al. 1993).

In conclusion, the process leading to prolactinoma formation takes place in two fundamental stages: initiation and promotion. Spontaneous or acquired specific cell mutations in a number of regulatory pathways in the lactotroph are the initial events. Subsequent (or prior) clonal expansion of the genetically altered cell probably relates to its ‘microenvironment’. A lack of inhibitory control or an excess of hormones and/or growth factors stimulating cell proliferation are but a few examples of factors able to increase the number of target cells for mutational events or sustain ‘tumor development’.

**Diagnosis and management**

**Diagnosis**

PRL secretion is pulsatile, and during the day occasional PRL levels may be above the accepted upper limit of normal. The finding of a minimally elevated PRL level in blood requires confirmation in other samples. A number of conditions may cause moderate elevations of PRL, although levels are generally below 200 µg/l. Among those, pregnancy, chronic renal or hepatic failure, primary hypothyroidism or the use of DA antagonists should be excluded before hypothalamic-pituitary disease is suspected. A PRL level above 200 µg/l is highly suggestive of a prolactinoma. There is a good correlation between prolactinoma size and PRL levels (Ross et al. 1985). A clinical distinction is to be made between PRL-secreting microadenomas and ‘other’ macroadenomas that cause a PRL elevation as a result of hypothalamic stalk dysfunction (also referred to in the literature as pseudohyperprolactinemia). Generally, PRL-secreting macroadenomas will have PRL levels above 250 µg/l, whereas stalk compression gives some levels between 25 and 250 µg/l. The various groups of hyperprolactinemia cannot be distinguished by dynamic tests (Bussen et al. 1996, Maraschini et al. 1996). Therefore, an evaluation of hyperprolactinemia, even mild (e.g. for suspicion of hypothalamic-pituitary disease), should include a high resolution imaging of the sella. T1-weighted magnetic resonance imaging (MRI) sequences, with early postcontrast study, represent the most sensitive imaging technique to detect microadenomas (Stadnik et al. 1994). However, about 10-20% of pituitary images contain lesions consistent with a pituitary incidentaloma, an adenoma without clinical significance (Hall et al. 1994). Interpretation should thus be made in the clinical context of the patient. MRI offers the advantage of a careful evaluation of the extension of a macroprolactinoma in the cavernous sinus.

**Treatment**

The therapeutic approach depends on the spontaneous evolution and progression of the tumor. Series of patients with microprolactinomas being observed for long periods without treatment have been published (Koppelman et al. 1984, Martin et al. 1985, Schlechte et al. 1989, Jeffcoate et al. 1996). In all series the risk of progression was low, and even spontaneous involution of microadenomas has been reported (Jeffcoate et al. 1996).

In order to evaluate the growth potential of a microprolactinoma, MRI (or computed tomography (CT)) at intervals of 1-2 years is advised in those patients who are not treated. Indications for therapy include decreased libido or impotence in men, galactorrhea, menstrual dysfunction and infertility with increased risk of premature osteoporosis in women.

Macroprolactinomas have already demonstrated their propensity to grow, and treatment is indicated. Macroadenomas may represent a separate disease entity, with a different natural history. DNA synthesis in vitro correlates with PRL plasma levels in cases of prolactinoma (Lloyd et al. 1995) and this suggests that macroprolactinomas have a greater tumor cell replication which is correlated with its higher growth potential.

In young patients, long-term hypogonadism due to hyperprolactinemia leads to premature osteoporosis in both sexes (Schlechte et al. 1987). Treatment reverses the increased rate of bone loss. For women with continued menses and no hypoestrogenemia the risk is not increased. Amenorrhea thus signals the need for correction of hyperprolactinemia. For the hyperprolactinemic women with microadenoma there are two possible choices if therapy is indicated: DA agonists alone, and transsphenoidal selective adenectomy. Eighty to ninety per cent of amenorrhic women will respond to medical treatment with restored normal ovulation. Medical treatment can be discontinued every 2 years in order to evaluate recurrence of hyperprolactinemia. Cure is infrequent and some patients have to be treated indefinitely (Ciccarelli & Camanni 1996). Therefore transsphenoidal surgery has been advocated as a primary therapeutic option. The rate of surgical cure for microadenomas appears to be between 45 and 80% (Thomson et al. 1994, Otten et al. 1996, Massoud et al. 1996, Molitch et al. 1997). The surgical approach seems sound in the case of microprolactinoma. If tumor removal is complete, late recurrences in these cases could result from persistent stimulatory events, leading ultimately to the emergence of a newly mutated cell clone. So far, no study has documented the origin of a relapsing tumor.
Reasons for secondary surgery are noncompliance, intolerance or resistance to DA agonists. However, prior bromocriptine treatment of microprolactinomas adversely affects the surgical outcome, probably through tumor fibrosis (Soule et al. 1996, Velkeniers et al. 1996). In our opinion, in view of the high frequency of relapses after medical treatment, surgical resection is the first choice as initial treatment whenever experienced surgeons are available.

Stereotactic radiosurgery (gamma-knife surgery or LINAC (linear accelerator)-radiosurgery) has recently been proposed in the management of pituitary microadenoma. Although further follow-up is necessary to evaluate long-term tumor control and hormonal effects, initial results indicate a potential therapeutic role for radiosurgery (Voges et al. 1996).

In macroprolactinomas treatment with DA agonists gives excellent results, in contrast to surgery. DA agonists are therefore recommended as the initial therapy (Molitch et al. 1985, 1997, Colao et al. 1995). When DA agonist therapy is stopped, the prolactinoma may return to its initial size and recurrence of hyperprolactinemia is frequent. These data suggest that continuous life-long therapy with DA agonists is required. Often, however, the dose can be gradually tapered once maximal size reduction has occurred.

In all cases the anatomical response to therapy must be carefully monitored by CT or MRI (see also DA resistance).

External radiation therapy is not a primary therapeutic option. For patients whose tumor has shrunk within the confines of the pituitary fossa, some groups recommend radiotherapy (Plowman 1995), to avoid rebound tumor growth after interruption of therapy. The overall incidence of hypopituitarism following radiation (Feek et al. 1984) is a major drawback.

Estrogens and prolactinomas

In vitro and in vivo, estrogens have been shown to stimulate PRL synthesis and lactotroph mitotic activity. It may thus be reasonably asked whether oral contraceptives are implicated in the development and/or growth of prolactinomas. In early studies an increased frequency of prior oral contraceptive use was found in prolactinoma patients. Other studies have not confirmed this; in the long-term British prospective surveys of women using oral contraceptives, no increased rate of hyperprolactinemia was found (Wingrave et al. 1980).

The conclusions of the first studies were probably biased by the fact that amenorrheic women (among those patients with undiagnosed hyperprolactinemia) were often treated with oral contraceptives, before the diagnosis of a PRL-secreting adenoma was established (Molitch 1986).

Oral contraceptives have exceptionally been found to stimulate growth of microprolactinomas (Garcia & Kapcala 1995). Caution is thus recommended when prescribing contraceptives as a first-line medical management of amenorrhea. In these instances, PRL levels and growth of the prolactinoma should be monitored (CT or MRI). With DA agonist therapy, the stimulatory effects of estrogens on PRL biosynthesis are partially lost. We therefore prefer to treat medically with D2 agonists and use contraceptives, if necessary, after PRL levels have returned to normal.

Pregnancy causes PRL cell hyperplasia, with MRI scans showing a gradual increase in pituitary volume (Gonzalez et al. 1988). The special situation of pregnancy in women with prolactinomas requires a therapeutic decision that will mainly depend on the size of the adenoma. In a group of 246 women with previously untreated microprolactinoma, only 4 (1.6%) had symptomatic tumor enlargement during pregnancy and 11 (4.5%) had asymptomatic growth during pregnancy (Molitch 1985). Therefore, most specialists agree that DA agonists can be safely stopped in patients with microprolactinoma, once pregnancy has been achieved. Visual field testing and MRI is reserved for those patients who become symptomatic. In patients with macroprolactinoma, without prior treatment, 15.5% (7 of 45 patients) had symptomatic and 8.9% (4 of 45 patients) asymptomatic tumor enlargement during pregnancy. In the same study, 46 women with macroadenomas had been treated with irradiation or surgery prior to pregnancy, reducing significantly the risk of symptomatic tumor expansion to 4.3% (Molitch 1985). In another series visual loss during one or multiple pregnancies in patients with macroadenoma was estimated to be 80% (Kupersmith et al. 1994). As surgery is seldom curative and external radiotherapy in young patients may induce hypopituitarism, bromocriptine is used as primary therapy for women with macroprolactinomas who wish to become pregnant. It is recommended that the drug is used for at least 3 months, and reduction of tumor size is assessed before conception is attempted. If the tumor has shrunk within the confines of the sella, some authorities recommend withdrawal of the drug once pregnancy is confirmed. If neurological complications occur, bromocriptine treatment can be resumed later during pregnancy. If significant suprasellar extension persists before conception, the choice is between decompressive surgery or continuous bromocriptine treatment throughout pregnancy. There is no clearcut recommendation as to the best therapeutic approach. Prepregnancy transsphenoidal surgical decompression of the tumor greatly reduces the risk of tumor enlargement. Often after surgery, bromocriptine is still required to restore ovulation. Continuous bromocriptine is an alternative treatment. The follow-up studies of women...
taking bromocriptine throughout pregnancy are reassuring (Ciccarelli & Camanni 1996). An exceptional case of resistance to bromocriptine during pregnancy with return of sensitivity to the drug postdelivery has been reported (Shanis & Check 1996). For patients with macroadenomas careful follow-up with monthly visual field testing is warranted. MRI is reserved for patients with symptoms of tumor enlargement and should also be routinely performed after delivery (Molitch 1995).

DA resistance

D2 receptors in normal and tumor lactotrophs are negatively coupled with adenylate cyclase, and DA and DA agonists inhibit hormone release through a reduction in intracellular cAMP levels. Lowering cAMP levels has the immediate effect of preventing PRL release and reducing PRL gene transcription and synthesis. This leads in bromocriptine-treated prolactinomas to involution of the rough endoplasmic reticulum and Golgi, with a decrease in cytoplasmic volume. In some patients, bromocriptine suppresses PRL levels, without tumor shrinkage. Others have persistent hyperprolactinemia (although suppressed as compared with basal values), with significant tumor shrinkage. In those patients in whom bromocriptine treatment does not lower PRL levels, tumor size will not reduce. Therefore, the response of tumors to DA agonist treatment must be monitored not only with PRL assays, but also with CT or MRI to observe the anatomical response of the tumor.

A prolactinoma patient fulfills the criteria for bromocriptine resistance if a daily dose between 15 and 60 mg for more than 3-6 months will not normalize plasma PRL levels and gonadal function. The percentage of bromocriptine-resistant prolactinoma patients reported in the literature varies between 5 and 17% depending upon the series (Bevan et al. 1992). Neither the initial tumor size nor the degree of PRL hypersecretion is predictive of such resistance (Kojima et al. 1995). Resistance has been shown to be associated with a relative or absolute deficiency of high affinity D2 receptor binding sites in tumor cells, or to a more complex impairment of the transduction mechanisms mediated via the G-proteins (Caccavelli et al. 1994, 1996, Soule et al. 1994). Postreceptor defects may only involve part of the response related to dopaminergic inhibition. This latter hypothesis could explain why some prolactinoma patients have normalized PRL levels, without significant changes in their tumor volume (effects on release and not on synthesis). New long-acting preparations of injectable bromocriptine (Colao et al. 1995, Tsagarakis et al. 1995, Jamrozik et al. 1996), together with new DA agonist drugs, have been developed, including quinagolide (CV 205-502), pergolide and cabergoline. The latter are related chemically to bromocriptine. Generally, the efficacy of these new drugs is similar to that of bromocriptine, but patients who cannot tolerate one DA agonist may tolerate another (Webster et al. 1994, Ciccarelli & Camanni 1996). Cabergoline has to be taken only twice a week and is better tolerated than bromocriptine (Delgrange et al. 1996, Webster et al. 1994). In some cases of bromocriptine resistance, better efficacy was observed with CV 205-502 and/or cabergoline (Merola et al. 1994, Morange et al. 1996, Colao et al. 1997). These new drugs thus represent considerable progress in the management of intolerance and/or resistance in patients.

Rapid progress in the understanding of PRL physiology and pathophysiology opens new perspectives in the diagnosis and management of prolactinoma patients. A unique pathophysiological model for prolactinoma does not exist. New knowledge on interaction of genetic events and environmental factors leading to phenotypic expression of prolactinoma has become possible by the close interaction between clinicians and molecular biologists. Clinician can use this information to guide their therapeutic decisions. Even so, definitive cure of prolactinoma remains difficult to achieve.

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