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REVIEW ARTICLE

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Multiple endocrine neoplasia type 1 (MEN 1) revisited

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Abstract Multiple endocrine neoplasia type 1 (MEN 1) is an inherited disease of the neuroendocrine cell system affecting primarily the parathyroids, pancreas, duodenum and the anterior pituitary. The pancreatic and duodenal tumours may metastasize, but generally have a low malignant potential. The diagnosis of MEN 1 is usually made in the second decade of life and based on the involvement of at least two organs and a family history. The recent discovery of the MEN 1 locus on the centromeric region of the long arm of chromosome 11 may become a further diagnostic criterion. The use of flanking DNA markers permits presymptomatic testing for MEN 1 in affected families.

Key words Multiple endocrine neoplasias · Hyperparathyroidism · Endocrine pancreatic tumours · Pituitary adenomas · Gastrinomas

Introduction

Multiple (neuro)endocrine neoplasia type 1 (MEN 1) is a rare and complex disease, which follows an autosomal dominant trait and is characterized by the multifocal synor metachronous development of cell proliferation primarily in the parathyroid glands, the neuroendocrine pancreas/duodenum and the anterior pituitary (Table 1). MEN 1 was first mentioned by Erdheim [19], linked to a familial setting by Rossier and Dressler [63] and recognized as a hereditary disease by Wermer [90]. During the last few years, several articles have presented new results concerning the prognosis, the tumour spectrum and development and the genetics of MEN 1. Here we focus on the morphological and clinical features of MEN 1-associated lesions in comparison with the sporadic (non-hereditary) occurrence of these entities. We review recent data on pathogenesis, prognosis and therapy.

Table 1 Clinical incidence of endocrine changes occurring in patients with multiple endocrine neoplasia type 1

	[%]
Primary hyperparathyroidism	90–97
Endocrine pancreatic tumours	30–82
Duodenal gastrinomas	25
Pituitary adenomas	>60
Neuroendocrine tumours (carcinoids)	5–9

Morphological and clinical features of MEN 1 lesions

The principal endocrine tissues involved in the MEN 1 syndrome are the anterior pituitary, parathyroids, endocrine pancreas and endocrine duodenum. Post mortem studies in MEN 1patients have revealed that neoplasms were invariably present in the pituitary, parathyroids and pancreas, regardless of any clinical manifestation [43]. Whether the neuroendocrine tumours of the duodenum also belong to the lesions which consistently develop in the MEN 1 syndrome is not known; duodenal microgastrinomas were only recently recognised as the cause of the Zollinger-Ellison syndrome (ZES) in most MEN 1 patients [56]. The incidence of MEN 1 associated non-duodenal and non-pancreatic neuroendocrine tumours (carcinoids) is 5%–9% [13, 17].

The clinical manifestations in MEN 1 patients depend on the number and combinations of endocrine tissues which are hyperfunctioning and proliferating. Most common is the metachronous or synchronous development of

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primary hyperparathyroidism (pHPT) and ZES, followed by symptomatic hypoglycaemia due to a pancreatic insulinoma [47]. Almost all (87%–97%) [9, 14, 60] MEN 1 patients develop pHPT, in about 60% as the first presenting manifestation (either alone or in combination with other lesions) between 12 and 28 (mean 19) years of age [79]. Conversely, 3%–20% [3, 14] of non-selected patients with pHPT are found to suffer from the MEN 1 syndrome. Diagnosis of MEN 1-related pHPT can be delayed by several years, due to the fact that in up to 80% of the MEN 1 patients biochemical changes (elevated total serum calcium and PTH) remain asymptomatic in the early stage of the disease [60]. In our patients pHPT was diagnosed between 7 years prior to, and 25 years after the development of other MEN 1-associated manifestations. Contrary to sporadic pHPT, which is expressed as single adenoma in the majority of cases, MEN 1-associated enlargement of the parathyroid is generally multiglandular with an asymmetric and metachronous evolution of disease [79], commonly with one or two glands of normal or minimally enlarged size [46]. In the Armed Forces Institute of Pathology fascicle [14] and the World Health Organisation classification [91] as well as in many case reports [23, 27, 33, 61, 66] MEN 1-associated parathyroid lesions are typed histopathologically as diffuse or nodular chief cell hyperplasia of all four glands. However, it has to be emphasized that it is difficult or even impossible to distinguish these proliferations of the parathyroid glands from adenomas, particularly if the parathyroid changes have a nodular appearance. Moreover, no clear differences have as yet been found, neither clinically [60] nor immunocytochemically [27] between hereditary and sporadic lesions or parathyroid hyperplasia and adenoma. This raises the question whether the parathyroid changes represent monoclonal neoplastic lesions rather than polyclonal hyperplasias.

In contrast to earlier assumptions [88] it seems that the typical picture of nesidioblastosis or islet hyperplasia of the *pancreas* is not feature of MEN 1 [29]. The latter change may only be seen in cases with additional severe obstructive pancreatitis due to duct stenoses by large endocrine tumours [29]. Typical for the pancreas in MEN 1 are multiple microadenomas (Fig. 1), usually in association with one or more larger tumours (diameter above 0.5 cm, so-called macrotumour) [29]. Histologically, most of the microadenomas show a trabecular, sometimes solid or pseudoglandular architecture and in many cases exhibit considerable interstitial hyaline sclerosis and/or a capsular-type confinement. The macrotumours do not differ histologically from sporadic endocrine pancreatic neoplasms. However, those tumours (irrespective of their size) associated with MEN 1 develop at a younger age. Immunocytochemical analysis of all tumours encountered in MEN 1 pancreas specimens has revealed that the neoplasms most commonly express pancreatic polypeptide (PP) and/or glucagon [29]. PP has been recommended as a screening hormone in affected patients [25]. Insulinomas are seen less often and, if found as microadenomas, are functionally silent [29]. Only in exceptional cases are MEN 1 associated gastrinomas located in the pancreas [56].

At least 25%–40% of patients with ZES develop their disease in the setting of MEN 1 [56]. The *gastrinomas* of these patients were thought to reside in the pancreas predominantly, but it is now clear that more than 90% of hereditary gastrinomas are located in the duodenum [56]. These neoplasms are commonly multiple measuring a few millimeters in diameter and thus, like the rare sporadic duodenal gastrinomas, they may easily be overlooked in the duodenal mucosa [86]. On resection of duodenal ulcers, small gastrinomas can be removed and lymph node metastases from such "occult" gastrinomas, detected during the further course of the disease or at postmortem examination, may be mistaken for primary tumours [15]. Histologically, duodenal gastrinomas consist of trabecular and pseudoglandular formations of well differentiated neuroendocrine cells, most of which stain strongly for gastrin [15]. Except for multicentricity regularly seen with MEN 1 associated neoplasms, no morphological differences exist between sporadic and hereditary duodenal gastrinomas [57].

The incidence of *pituitary adenomas* in MEN 1 patients (age at diagnosis: 13–40 years [71]) is probably higher than 60% [38, 43]. Almost 60% of these patients show pituitary enlargement accompanied by ophthalmological symptoms and/or pituitary hyperfunction [71]. Thirty percent of patients exhibit acromegaly [5], while Cushing's disease [59] as well as gonado- or thyreotropic pituitary adenomas [34, 87] are rare. There are no morphological differences between hereditary and sporadic neoplasms. Although functionally inactive chromophobe adenomas were thought to prevail among MEN 1- associated pituitary tumours [5, 6], in some more recent studies somatotropic hormone (STH)- and prolactin (PRL)-producing neoplasms predominate [39, 58, 66, 89]. Immunohistologically, in almost 50% of the tumours positivity for STH is found, which in the majority of cases is accompanied by positivity also for PRL and one or several more glycoprotein hormones [71]. The rate of multihormonality is comparable to that of sporadic pituitary adenomas [28, 70]. In 40% of the tumours PRL is the single detectable hormone; the remaining 15% are either adrenocorticotropic hormone (ACTH)-cell adenomas or so-called null-cell adenomas, that is to say tumours lacking immunoreactivity for all the tested pituitary hormones or hormone fragments [71]. The considerably lower rate of null-cell adenomas among hereditary patients as compared to sporadic series (7% [71] versus 16% [32] and nearly 30% [50]) can probably be explained by the far lower average age of MEN 1 patients (of patients with sporadic null-cell adenomas: 52 years [32]).

Neuroendocrine tumours (carcinoids) of the lung, thymus and stomach (embryonic foregut tissue) are considered to be an integral part of MEN 1 [20, 72] with either low or high penetrance in affected families [20]. They are most frequent in the thymus and/or mediastinum [16, 21, 52, 62, 76], followed by the lung [4, 16, 17, 20, 52,

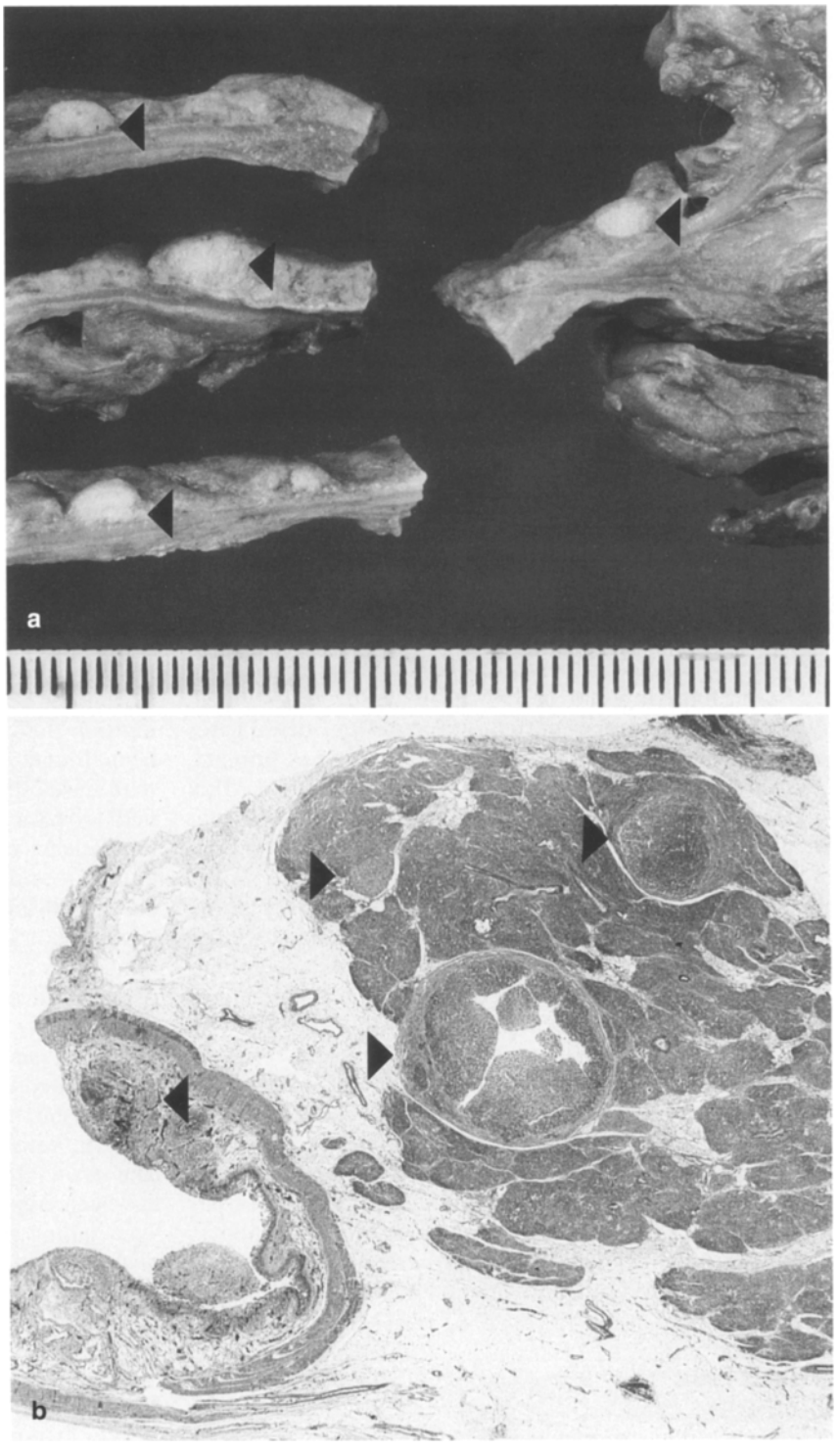

Fig. 1 **a** Macroscopy (top) and **b** histological low-power view (bottom; haematoxylin and eosin ×6) of duodenum and pancreatic head of a patient with multiple endocrine neoplasia type 1 (autopsy specimen). Note several gastrinomas (diameter up to 0.4 cm) in the duodenal mucosa (≥) and three endocrine tumours within the pancreatic parenchyma (measuring up to 0.6 cm) (≤)

67, 89] and stomach [16, 37, 52, 54, 80], whereas the jejunum and ileum are only occasionally affected [13, 73].

The penetrance of other tumours in patients with MEN 1 is similar to that in the control population except for adrenocortical and thyroid lesions and lipomas. The incidence of morphological changes of the *adrenal cortex* in MEN 1 patients has been reported in the literature as ranging between 25% and 40% [5, 13, 17]. First indications of MEN 1-associated adrenocortical disease were outlined by an analysis of the literature. In 85 autopsy protocols of MEN 1 patients over a 60-year period, 19 (22%) cases of diffuse or nodular hyperplasias, and 12 cases (14%) of multiple adenomas were described [5], whereby 4 of 16 members of one MEN 1 family showed the same adrenocortical finding. A similarly high incidence was found in more recent literature surveys (26% [17]) and series of MEN 1 patients (35% [64], 37% [78]) with more frequent bilateral than unilateral adrenal en-

largement [17, 78] and a predominance of hyperplasia over adenomas [13, 17]. All studies concur in that the vast majority of adrenocortical lesions in MEN 1 patients represent benign and endocrinologically silent processes; adrenal carcinomas [13, 78] and functionally active adenomas are rare exceptions. To our knowledge only five and ten adenomas with hyperaldosteronism or hypercortisolism, respectively, have been reported [7, 17, 26, 48]. Thus, primary adrenal Cushing's syndrome among MEN 1 patients appears to be even more rare than Cushing's syndrome as a result of ACTH-producing pituitary adenoma or of an ectopically ACTH-producing neuroendocrine tumour of the foregut region or the pancreas. In summary, it has been suggested but not demonstrated that the adrenocortical proliferations observed in MEN 1 patients are not primary manifestations of the syndrome but should, in most instances, be regarded as coincidental lesions or occasionally as secondary phenomena.

Thyroid diseases have been reported in 15% [5] –27% [13] of MEN 1 patients. Apart from euthyroid goitre [9, 17] follicular adenomas [13, 17, 85], papillary [52], follicular [67] and, more rarely, medullary carcinomas [17], chronic lymphocytic thyroiditis [13, 17] and both hypo- [17] and hyperthyroidosis [17, 85] have been described. As with the adrenal cortex the question here arises whether the thyroid changes can be regarded as primary, secondary or coincidental lesions. So far only one MEN 1 case report (pHPT and pituitary adenoma) would substantiate thyroid stimulating hormone (TSH)-induced hyperthyroidosis [34]. Because of the high incidence of various types of thyroid changes in the normal population, particularly in view of their frequent occurrence together with parathyroid disease outside established hereditary associations, it appears unlikely that the thyroid changes are causally related to the MEN 1 syndrome [13, 17, 82].

In approximately 10% of MEN 1 patients described in case reports or in larger series, partly multifocal, mostly subcutaneous and occasionally visceral or retroperitoneal *lipomas* [5, 9, 13, 17, 40, 82] and in one case a liposarcoma [13] have been reported. Since lipomas are the most frequent soft tissue neoplasm and because 5%–6% of patients afflicted by this condition exhibit multiple lipomas [18], these changes are most likely not a manifestation of MEN 1, but are merely coincidental.

Pathogenesis

Based on studies of somatic deletions in MEN 1-associated tumours and linkage analysis in affected families, the causative genetic defect has been mapped to the centromeric region of the long arm of chromosome 11 (band 11q13) [4, 35, 36, 53]. The MEN 1 gene still remains unidentified but is most likely considered a tumour suppressor gene [10, 11, 23, 36, 46, 83], the inactivation of which gives rise to cell proliferation. The assumption that some heritable tumours (retinoblastomas, familial polyposis coli) result from mutational events is known as the two-hit hypothesis of carcinogenesis first introduced by Knudson [30]. The theory proposes that a recessive mutation (first hit) is inherited via the germ cell line, which makes the individual a heterozygous carrier without effect on the phenotype, while a second recessive chromosomal event (second hit) within the somatic cell causes elimination of the remaining "normal" gene function, giving rise to (neoplastic) cell proliferation. A recent loss of heterozygosity study [8] has documented allelic losses in variable regions of chromosome 11 in different pathological tissues of an MEN 1-patient, suggesting that different somatic mutations are involved in the pathogenesis of MEN 1-associated tumours.

Loss of heterozygosity involving the chromosomal region of MEN 1 was originally observed in two syndrome-associated malignant *insulinomas* [36], a finding which was subsequently supported by other pancreatic tumour cases [4, 78, 81, 92]. Since allelic losses in the appropriate region of chromosome 11 have also been detected in sporadic pancreatic tumours [55, 69, 81] a conclusive answer whether hereditary or sporadic pancreatic lesions depend on closely related genetic mechanism may be given by further characterization of the MEN 1 gene.

In the most frequent MEN 1-involved organ, the *parathyroid*, loss of chromosome 11-specific regions has been found in 50%–60% of MEN 1 patients [23, 83], with virtually all gene carriers exhibiting evidence of pHPT by the age of 50 [45]. Whether either DNA rearrangements within the PTH or the recently characterized parathyroid disease related gene (PRAD1; cyclin D1) locus on chromosome 11 and/or a circulating parathyroid (mitogenic) growth factor in the plasma of MEN 1 patients play a relevant role in the pathogenesis of familial parathyroid cell proliferation is not yet clear [1]. While the majority of MEN 1-associated parathyroid lesions are typed has hyperplasia of all four glands some reports documented the occurrence of parathyroid double adenoma [12, 66] or solitary adenoma [5, 7, 22, 66], some of them in combination with parathyroid hyperplasia [66]. The association of parathyroid carcinoma with MEN 1 has been considered in rare single reports [44, 75]. However, taking into account the size heterogeneity and the histomorphological variance in individual parathyroid cases, it seems likely that at least some of the MEN 1 cases diagnosed as adenomas represent adenomatous hyperplasia with asymmetric gland involvement [41]. As alterations of chromosome 11 have also been detected in patients with sporadic parathyroid adenomas and hyperplasias [10, 24, 49], further investigations are necessary to clarify whether hereditary and sporadic parathyroid changes really depend on different molecular mechanisms [3]. Since the lesions in all other organs afflicted by MEN 1 are most certainly neoplasms, we assume that the parathyroid changes also represent multifocal neoplastic growth. It is of interest in this context that, according to a cytophotometric study of Komatsu et al. [31], only 8% of sporadic parathyroid hyperplasias, yet 33% of hereditary parathyroid lesions showed aneuploid (>4c) DNA-contents.

Among the studies on MEN 1-associated pulmonary, mediastinal and gastric *neuroendocrine tumours* (carcinoids) a recent investigation on a patient with fundic carcinoid tumour and ZES describes an allelic loss of chromosome 11, including the human muscle phosphorylase locus [11]. These authors thus favour the hypothesis of an MEN 1 genetic predisposition as already suggested earlier by others [80]. In another single published case of bronchial carcinoid [4] no chromosomal alterations of 11q markers could be demonstrated. Neuroendocrine tumours of the gastric corpus in MEN 1 patients with ZES most likely represent a hypergastrinaemia-promoted process. Under the condition of hypergastrinaemia, progressive multifocal proliferation of enterochromaffin-like (ECL) cells can be observed, which follows a hyperplasia – dysplasia – microcarcinoidosis – carcinoid sequence [80] up to the extreme picture of macrocarcinoidosis [54]. All 26 cases of ZES-associated neuroendocrine tumours of the stomach published so far could be categorized as belonging to the MEN 1 syndrome [11, 37, 52, 54, 64, 80]. With the exception of one (doubtful) case, no ECLomas have been reported in patients with sporadic ZES. It seems, therefore, that the MEN 1-associated tumours of the stomach represent another neoplastic manifestation of the syndrome. However, as almost all of the 26 above-mentioned MEN 1 patients with gastric tumours exhibited also pHPT, the neoplasms of the stomach might have a humoral as well as genetic pathogenesis [64, 76]. The hypothesis that the pHPT induced hypercalcaemia in association with hypergastrinaemia could play a promoter role [51] is supported by a study of more than 4,000 pHPT patients which revealed a 50% increased risk of developing malignant endocrine and non-endocrine diseases when compared to the normal population [42].

Pathogenetic studies on MEN 1-associated *pituitary tumours* are scanty, due to the facts that these lesions are operated on rarely nowadays or that the amount and quality of surgical specimens is hardly sufficient for DNA analysis. Allelic losses of chromosome 11q in pituitary tumours of MEN 1 patients have been shown only in rare single cases [7, 84, 93], indicating, however, the possible involvement of a tumour suppressor effect in the pituitary [7].

Adrenocortical lesions have shown retained genotypes as far as the common benign hyperplastic lesions are concerned [78], whereas allelic losses within the MEN 1 locus have been demonstrated in at least two syndrome-associated tumours; an aldosterone-secreting adenoma [7] and an adrenocortical carcinoma [78].

Prognosis

Family screening by genetic linkage analysis and early biochemical detection of serum changes are of vital importance since an affected individual has a 50% chance of passing the disease to her or his offspring, with family-specific differences in the potential for the development of malignancy [79]. Recent prospective screening studies of MEN 1 kindreds have permitted identification of involvement of at least one of the three classic target organs for MEN 1 at an average age of 14–18 years, with identification of all affected individuals by the age of 25 years [76, 77, 79].

The incidence of postoperative persistent *pHPT* in MEN 1 patients is much higher (25%–60%) than in patients with sporadic lesions (3%) and the most benefical factors for successful surgery are the involvement of an experienced parathyroid surgeon and the biopsy confirmation of all identified glands [61].

Prognostically, *endocrine tumours of the pancreas* in MEN 1 differ from their sporadic counterparts by their considerably lower malignant potential: patients with hereditary pancreatic neoplasms show statistically significant longer median survival (15 years) when compared with those with sporadic tumours (6 years) [53]. If hyperinsulinaemic hypoglycaemia in MEN 1 patients occurs, it is commonly due to an insulin producing macrotumour, the surgical enucleation of which cures the symptoms clinically and biochemically [29]. As in the parathyroid gland, MEN 1-related pancreatic lesions require a multidisciplinary approach and experienced practitioners to minimize mortality while maximizing cure rate, especially in younger asymptomatic patients.

The malignancy rate of *duodenal gastrinomas*, as documented by the detection of metastases, is comparable for both hereditary and sporadic cases at approximately 60%. However, only few MEN 1-associated tumours cause liver metastases in addition to regional lymph node metastases. The lower malignant potential of hereditary duodenal gastrinomas as compared to sporadic pancreatic gastrinomas is also documented by the considerably higher 10-year survival rate (87% versus 52%) [15, 86]. Correspondingly, the therapy of hereditary (and also of sporadic) duodenal gastrinomas, successfully performed and recommended by Thompson [86] since 1986, only consists of duodenotomy and selective tumour excision accompanied by exploration of the regional lymph nodes. Since gastrointestinal bleeding secondary to peptic ulcer disease is considered to be the most common cause of death in MEN 1 patients, improved treatment, especially of symptomatic ZES, will almost certainly increase their life expectancy.

The successful management of a *pituitary tumour* in a patient with MEN 1 requires the selective use of surgical, medical and radiotherapeutic strategies. Invasive growth or apoplexy caused by haemorhage into a pituitary tumour constitute potential, but rather uncommon, causes of tumour-related death among MEN 1 patients [79]. It is important to distinguish primary MEN 1-associated STH-cell adenomas from secondary growth hormone (GH)-cell hyperplasias caused by ectopically secreted GH releasing hormone (GHRH). The list of neoplasms responsible for ectopic GHRH production includes pancreatic endocrine tumours, phaeochromocytomas and medullary thyroid carcinomas [65, 68, 74]. Some tumours have been found to be associated with

MEN 1 and cause both acromegaly and pituitary enlargement [2].

For MEN 1-associated *neuroendocrine tumours (carcinoids)* of the thymus and lung, correlations appear to exist between their localisation and different clinical parameters. The majority of neuroendocrine thymic tumours occur in males in combination with pHPT, are associated with ACTH-production and Cushing's syndrome and follow an aggressive course [16, 62]. Neuroendocrine lung tumours, however, are more frequently observed in females are associated with pituitary adenomas, and in most cases show benign behaviour [16]. A carcinoid syndrome due to a serotonin-producing tumour of the ileum has not yet been described in MEN 1.

Conclusions

Although recent investigations have elucidated many of the genetic changes underlying MEN 1, it is still not possible to identify MEN 1 patients solely on the basis of genetic abnormality. Thus, family history, clinical presentation and histopathological examination are necessary to establish this diagnosis. The combined use of flanking DNA markers enables carriers of the mutant gene to be detected within a certain MEN 1 family. Only the characterization and cloning of the thus far unidentified MEN 1 gene would result in earlier detection and therapeutic intervention, with consequent improvement in both the quality and longevity of life in these patients.

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