

Case Report

A rare case of invasive pituitary macroadenoma with hemorrhage in MEN 1 syndrome - A case report

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Abstract

Multiple Endocrine Neoplasia (MEN) disorders are very rare. These are hereditary diseases which develop into a number of endocrine glands and result in tumor formation. The MENs are run in families because they are the exact consequence of genetic mutations and their symptoms are completely dissimilar dependent on the involving glands. Multiple endocrine neoplasia (MEN) is characterized by the occurrence of tumors involving two or more endocrine glands in a single patient. Four major forms of MEN, which are autosomal dominant disorders, are recognized and referred to as: MEN type 1 (MEN1), due to menin mutations; MEN2 (previously MEN2A) due to mutations of a tyrosine kinase receptor encoded by the rearranged during transfection (RET) protooncogene; MEN3 (previously MEN2B) due to RET mutations; and MEN4 due to cyclin-dependent kinase inhibitor (CDNK1B) mutations. Each MEN type is associated with the occurrence of specific tumors. MEN1 is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors. In this case report we present a patient who developed an Invasive Pituitary Macroadenoma with Hemorrhage in MEN 1 Syndrome.

Key words

MEN 1 Syndrome, Pituitary macroadenoma, Hemorrhage.

Introduction

Multiple Endocrine Neoplasia (MEN) is characterized by the presence of tumors involving two or more endocrine glands in a

single patient [1-4]. Four major forms of MEN, which are autosomal dominant disorders, are recognized and referred to as:

MEN type 1 (MEN1) due to menin mutations; MEN1 is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors.

MEN2 (previously MEN2A) due to mutations of a tyrosine kinase receptor encoded by the rearranged during transfection (RET) protooncogene; MEN2 is characterized by the occurrence of medullary thyroid carcinoma (MTC) in association with pheochromocytoma and parathyroid tumors.

MEN3 (previously MEN2B) due to RET mutations; MEN3 is characterized by the occurrence of MTC and pheochromocytoma in association with a marfanoid habitus, mucosal neuromas, medullated corneal fibers and intestinal autonomic ganglion dysfunction, leading to megacolon.

MEN4 due to cyclin-dependent kinase inhibitor (CDNK1B) mutations. Each MEN type is associated with the occurrence of specific tumors. MEN4, which is also referred to as MENX, is characterized by the occurrence of parathyroid and anterior pituitary tumors in possible association with tumors of the adrenals, kidneys, and reproductive organs [2].

The sellar region is a site of various types of tumors, pituitary adenoma are the most common, arise from epithelial pituitary cells and account for 10-15% of intra cranial tumors, tumor >10 mm are macro adenoma and those < 10 mm are micro adenomas, most pituitary adenomas are micro adenomas. Most of the pituitary adenomas are diagnosed accidentally, as they don't have any physical symptoms and signs [5].

MEN type 1 Epidemiology

The incidence of MEN1 as estimated from random postmortem studies is 0.25%, and is 1–18% in patients with primary hyperparathyroidism, 16-38% in patients with gastrinomas, and less than 3% in patients with pituitary tumors [3, 6, 7]. The disorder affects all age groups, with a reported age range of 5 to 81 yr [3, 6, 7]. MEN1 is inherited as an autosomal dominant disorder with a high degree of

penetrance such that clinical and biochemical manifestations of the disorder will have developed in 80% and greater than 98% of MEN1 patients, respectively, by the fifth decade [3, 6, 7].

Genetics

MEN1 is an autosomal dominant disorder that is due to mutations in the tumor suppressor gene MEN1, which encodes a 610-amino acid protein, menin. In this way, the finding of MEN1 in a patient has important implications for family members because first-degree relatives have a 50% risk of developing the disease and can often be identified by MEN1 mutational analysis. MEN1 is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors. Some patients may also develop carcinoid tumors, adrenocortical tumors, meningiomas, facial angiofibromas, collagenomas and lipomas. Patients with MEN1 have a decreased life expectancy, and the outcomes of current treatments, which are generally similar to those for the respective tumors occurring in non-MEN1 patients, are not as successful because of multiple tumors, which may be larger, more aggressive, and resistant to treatment, and the concurrence of metastases. The prognosis for MEN1 patients might be improved by presymptomatic tumor detection and undertaking treatment specific for MEN1 tumors. Thus, it is recommended that MEN1 patients and their families should be cared for by multidisciplinary teams comprising relevant specialists with experience in the diagnosis and treatment of patients with endocrine tumors [8].

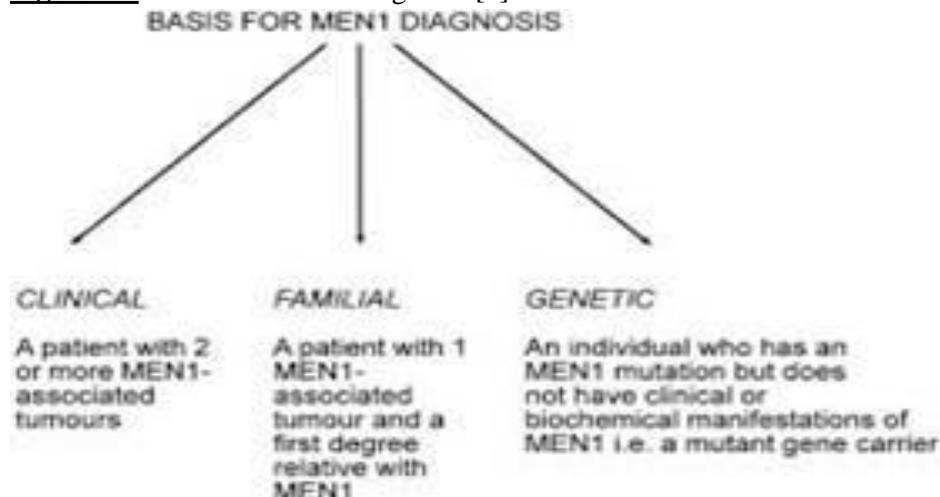
Criteria for diagnosis

There is a lack of evidence from the clinical trials to evaluate methods of diagnosis and screening for the tumors or treatment of MEN1 [8]. A diagnosis of MEN1 may be established in an individual by one of the three criteria (**Figure - 1**) [6]: on the basis of the occurrence of two or more primary MEN1-associated endocrine tumors (i.e. parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma) (**Figure - 1**) [6, 9, 10]. The occurrence of one

of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN; and identification of a germline MEN1 mutation in an individual, who may be

asymptomatic and has not yet developed serum biochemical or radiological abnormalities indicative of tumor development (**Figure - 1**).

Figure – 1: Basis for MEN1 diagnosis [6].



CLASSIFICATION

Hardy’s classification [20, 21]

Upper panel shows the classification of sphenoid bone invasion

- Grade 0:** intact with normal contour;
- Grade I:** intact with bulging floor;
- Grade II:** intact, with enlarged fossa;
- Grade III:** localized sellar destruction;
- Grade IV:** diffuse destruction.

Only grade III and IV tumors are considered invasive.

Lower panel depicts a classification of the suprasellar extension of an adenoma which may be symmetrical or asymmetrical

- Grade A:** suprasellar cistern only;
- Grade B:** recess of the third ventricle;
- Grade C:** whole anterior third ventricle;
- Grade D:** intracranial extradural;
- Grade E:** extracranial extradural (cavernous sinus) [20, 21].

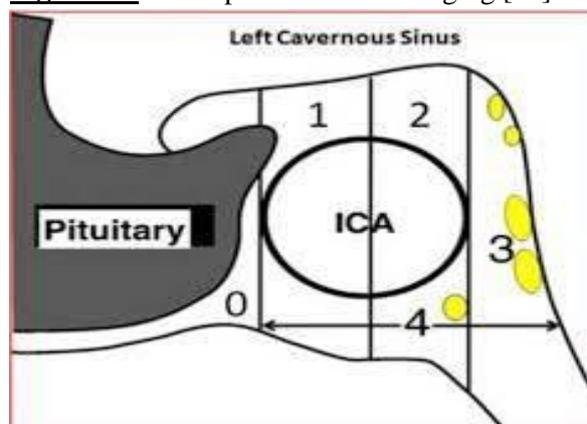
Knosp classification staging (Figure – 2) [22]

These lines are used to define 4 grades of tumor invasion:

- grade 0 = medial to medial tangent
- grade 1 = tumor extends to space between the medial tangent and the intercarotid line

- grade 2 = tumor extends to space between the intercarotid line and the lateral tangent
- grade 3 = tumor extends lateral to the lateral tangent
 - 3A = above the intracavernous ICA into the superior cavernous sinus compartment
 - 3B = below the intracavernous ICA into the inferior cavernous sinus compartment
- grade 4 = complete encasement of intracavernous ICA

Figure – 2: Knosp classification staging [22].



Treatment

The treatment for each type of MEN1-associated endocrine tumor is similar to the respective tumors occurring in non-MEN1 patients.

However, the treatment outcomes of MEN1-associated tumors are not as successful as those in non-MEN1 patients, for several reasons. First, MEN1-associated tumors, with the exception of pituitary NET, are usually multiple, thereby making it difficult to achieve a successful surgical cure. For example, MEN1 patients often develop multiple submucosal duodenal gastrinomas, thereby reducing surgical cure rates compared with similar sporadic solitary tumors, such that only approximately 15% of MEN1 patients, compared with 45% of non-MEN1 patients, are free of disease immediately after surgery, and at 5 yr this decreased to approximately 5% in MEN1 patients, compared with 40% in non-MEN1 patients [6, 11-14]. MEN1 patients also develop multiple parathyroid tumors, and subtotal parathyroidectomy has resulted in persistent or recurrent hypercalcemia within 10 yr in 20 – 60% of MEN1 patients, as opposed to 4% in non-MEN1 patients [6, 15, 16]. Secondly, occult metastatic disease is more prevalent in MEN1 patients with NET than in patients with sporadic endocrine tumors. For example, metastases are present in up to 50% of patients with MEN1-associated insulinomas, whereas less than 10% of non-MEN1 insulinomas metastasize. Thirdly, MEN1-associated tumors may be larger, aggressive, and resistant to treatment. For example, 85% of anterior pituitary tumors in MEN1 patients, as opposed to 64% in non-MEN1 patients, are macroadenomas at the time of diagnosis; 30% of anterior pituitary tumors in MEN1 patients have invaded surrounding tissue (Hardy classification grades III and IV), compared with 10% in non-MEN1 patients; and more than 45% of anterior pituitary NET in MEN1 patients had persistent hormonal oversecretion after appropriate medical, surgical, and radiotherapy treatment, compared with between 10 and 40% in non-MEN1 patients [17-19].

Case report

A 38 year old female came to the hospital, with complaints of sudden onset of right sided headache of one day duration, which was

pricking type and was associated with photophobia and phonophobia. She also had one episode of projectile vomiting, contained food particles and was blood tinged. She had associated symptoms like giddiness, sweating, generalized weakness and body pains, tingling sensation over both the upper and lower limbs were present. No history of fever, loss of consciousness, involuntary movements, loss of appetite, pain abdomen, loose stools. Patient developed blurring of vision and pain on eye movements the next day. Patient is a K/C/O Diabetes Mellitus since 2 years and on glyciophage.

Past history: Patient had a history of head injury 9 years ago, after which she had headache on and off. Underwent surgery for Renal Calculi 9 years ago. No history of HTN, thyroid disorders or epilepsy. No significant family history. Menstrual history: menorrhagia since 1 year.

On investigation - Hb-10 g%, RBC count 7.2 mill/cumm, WBC count 8600 cells/cumm with Neutrophils - 72%, Lymphocytes - 24%, Eosinophils - 2%, Basophils - 0%, Monocytes - 2%, Platelet count – 2.4 lakhs/cu mm. ESR 1st hr - 20 mm, Blood Urea 19 mg%, Serum Creatinine - 0.7 mg, Complete Urine Examination (CUE) – normal, Random Blood Sugar of 384mg/dl, Serum Electrolytes: Na – 139 m mol/L, K – 4.3 m mol/L, CL – 105 m mol/L. LFT – Normal, Fasting Lipid Profile-WNL, ECG-Sinus Tachycardia, Thyroid profile - T₃-1.12 ng/ml, T₄-13.41 micro gm/dl, TSH-2.36 micro IU/ml, Anti TPO antibodies-0.44 IU/ml (N = < 4.11), Anti Tg Ab – 3.08 IU/ml(N = < 5.61), anti-ds DNA – 15.6 (negative). USG thyroid showed well defined echoic lesion with few cystic areas in right lobe of thyroid with minimal peripheral and internal vascularity, to rule out parathyroid lesion. FNAC of thyroid gland - Moderate cellularity comprised of monomorphous round and oval cells predominantly arranged in monolayered sheets with occasionally papillar fragments. There is no evidence of intranuclear inclusions or nuclear grooving. Very scant

colloid with occasional cyst macrophages noted. Impression - Parathyroid neoplasm.

Serum cortisol (between 7-9 AM) – 4.29 ug/dl (ref.4.30 – 22.4) , growth hormone 2.10ng/ml (up to 8 ng/ml), FSH – 3.75 mIU (follicular phase - 2.5 to 10.2 mIU /ml, mid cycle phase – 3.4 to 33.4 mIU /ml, luteal phase – 1.5 to 9.1 mIU /ml, post-menopausal – 23.0 to 116.3 mIU /ml), LH – 2.02 IU/L, Serum prolactin - 7.38 ng/ml (Ref. N = 2.8 to 29.2), Serum Calcium - 11.8 mg/dl (N = 8.6 to 10.2), Serum PTH levels - 377 pg/ml (N= 15 to 68 pg/ml). Ultrasound abdomen

revealed lt. ovarian cyst and hepatosplenomegaly with fatty changes in the liver. CT scan brain (**Figure - 3**) showed: bulky pituitary gland with heterogenous alteration and expansion of sella and extension into cavernous sinus. Pituitary Macroadenoma. Also showed sclerosis of Cranial vault with widening of diploic space. MRI brain (**Figure - 4**) revealed heterogeneously enhancing subtle T1 hyperintense mass lesion involving sellar and suprasellar region measuring 15x23x22mm (pituitary gland and infundibulum) which is suggestive of Pituitary Macroadenoma with hemorrhage.

Figure – 3: CT SCAN Axial Sections – showed bulky pituitary gland with heterogenous alteration and expansion of sella and extension into cavernous sinus. Pituitary Macroadenoma. Also showed sclerosis of Cranial vault with widening of diploic space.



Figure - 4A: T2 FLAIR AXIAL.

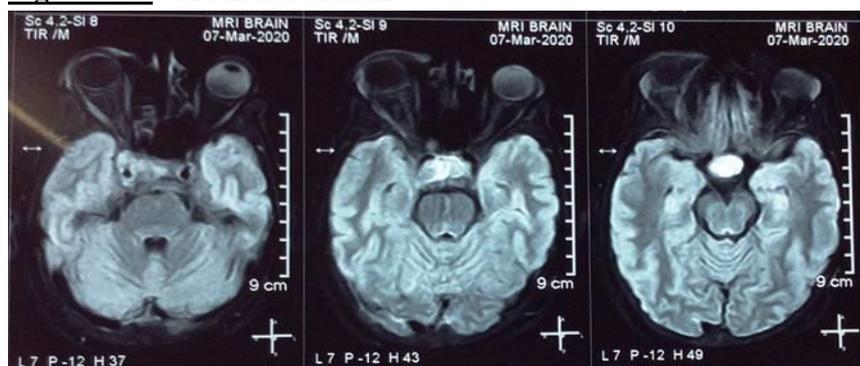


Figure – 4B: T2 SAGITTAL.

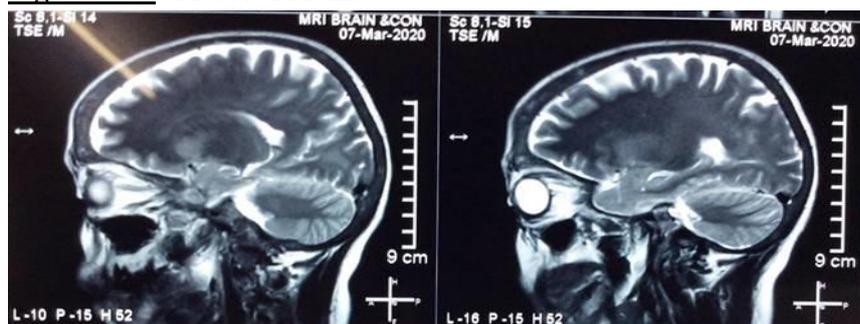


Figure – 4C: T2 AXIAL.



Figure – 4D: DWI.

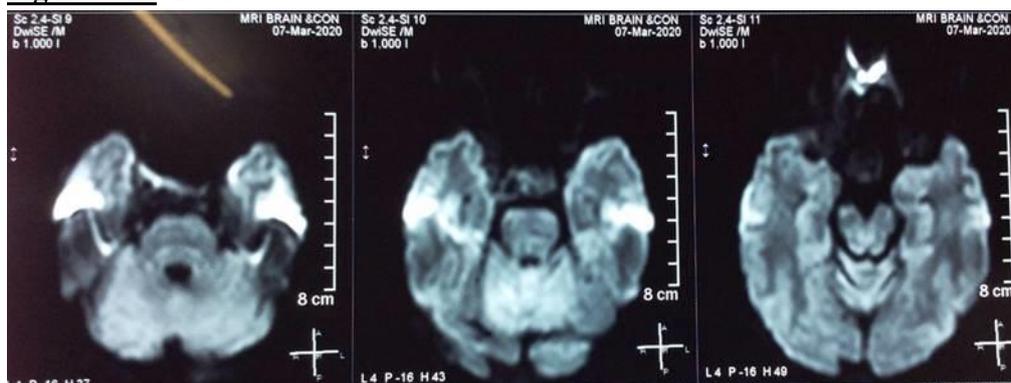


Figure – 4E: T1 POST CONTRAST AXIAL.

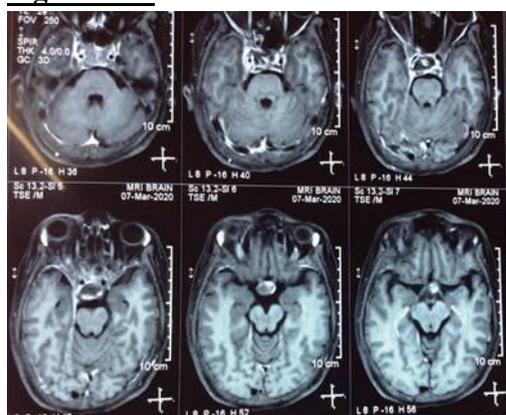


Figure – 4F: T1 POST CONTRAST SAGITTAL & CORONAL.

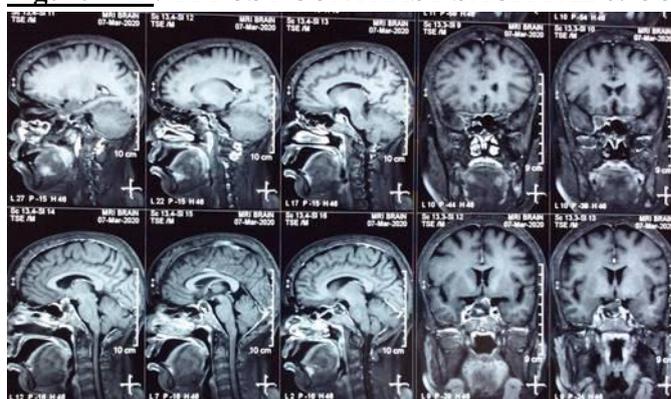


Figure – 4G: T2 SAGITTAL.

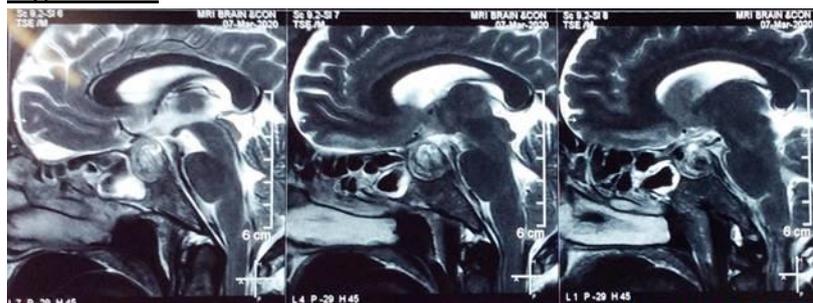


Figure – 4H: T2 FLAIR SAGITTAL.

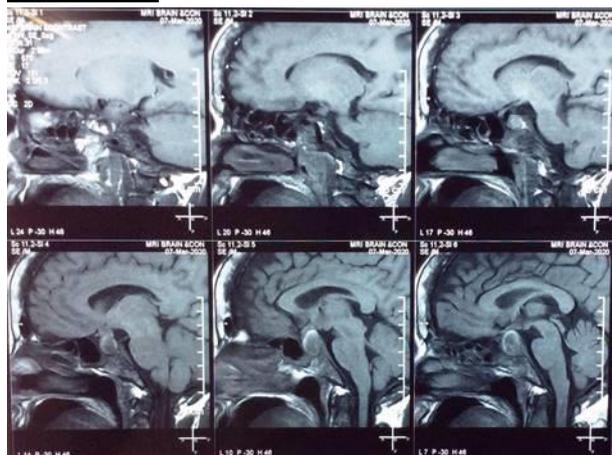


Figure – 4I: T2 CORONAL & T2 FLAIR CORONAL.

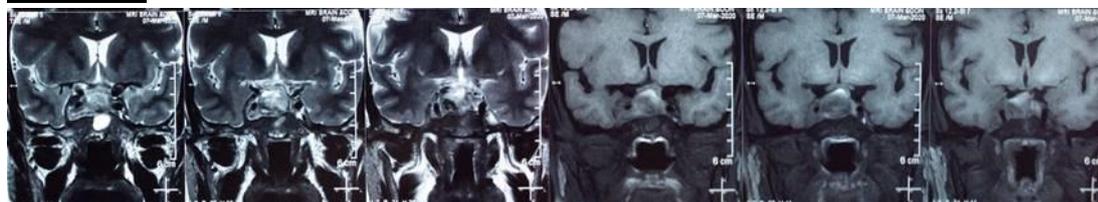


Figure - 4(A,B,C,D,E,F,G,H,I): MRI revealed heterogeneously enhancing subtle T1 hyperintense mass lesion involving sellar and suprasellar region measuring 15x23x22 mm (pituitary gland and infundibulum) which is suggestive of Pituitary Macroadenoma with hemorrhage.

A diagnosis of Invasive Pituitary Macroadenoma with Hemorrhage in MEN 1 Syndrome GRADE III - E (according to Hardy's Staging) and GRADE III (according to Knosp's Classification Staging) and Renal Calcular Disease P.O. Status, was made. Patient also had Parathyroid neoplasm apart from Pituitary macroadenoma.

Treatment given

1. Tab. Nimodipine 30 mg 2 tid
2. Tab. Glyciphage 500 mg 1 tid

After which patient was referred to neurosurgery centre

Discussion

A diagnosis of Invasive Pituitary Macroadenoma with Hemorrhage in MEN 1 Syndrome GRADE III - E (according to Hardy's Staging) and GRADE III (according to Knosp's Classification Staging) and Renal Calcular Disease P.O. Status, was made. Patient also had Parathyroid neoplasm apart from Pituitary macroadenoma. MEN 1 Syndrome itself is very rare, and hemorrhage in

the Pituitary Macroadenoma is still much more rarer.

The treatment for each type of MEN1-associated endocrine tumor is generally similar to that for the respective tumors occurring in non-MEN1 patients. However, the treatment outcomes of MEN1-associated tumors are not as successful as those in non-MEN1 patients, for several reasons. First, MEN1-associated tumors, with the exception of pituitary NET, are usually multiple, thereby making it difficult to achieve a successful surgical cure.

Pituitary tumors

Clinical manifestations and diagnosis

The incidence of pituitary tumors in patients with MEN1 varies from 15 to 50% in different series [17, 18, 23, 24]. These occur from 5 yr of age to the ninth decade. MEN1 pituitary adenomas occur frequently in women, and significantly more of these were macroadenomas, i.e. diameter greater than 1 cm [18]. About one third of these pituitary tumors showed invasive features such as infiltration of tumor cells through surrounding normal juxtatumoral pituitary tissue on histology. Despite the apparent larger size, more aggressive behavior and reduced response to therapy, no increased prevalence of pituitary carcinoma is observed in MEN1. Approximately 60% of MEN1-associated pituitary tumors secrete prolactin, 25% secrete GH, 5% secrete ACTH, and the remainder appear to be non-functioning, with some secreting glycoprotein subunits [17, 24], although the occurrence of non-functioning adenomas has been reported [25]. However, pituitary tumors derived from MEN1 patients may exhibit immunoreactivity to several hormones, and particularly in the higher occurrence of somatolactotrophinomas [17]. Infact, plurihormonal expression is more frequently observed in MEN1-associated pituitary tumors compared with non-MEN1 pituitary tumors [17, 18]. Pituitary tumors, which are usually prolactinomas, may be the first manifestation of MEN1 in 15% of patients, and somatotrophinomas occur more often in patients older than 40 yr [3, 18, 23], although there may

not be any clear genotype-phenotype correlation [17]. Fewer than 3% of patients with anterior pituitary tumors will have MEN1 [26]. Clinical manifestations of these tumors in patients with MEN1 are similar to those in patients with sporadic pituitary tumors without MEN1 and depend on the hormone secreted and the size of the pituitary tumor. Thus, patients may have symptoms of hyperprolactinemia (e.g. amenorrhea, infertility, and galactorrhea in women, and impotence and infertility in men) or have acromegaly or Cushing's disease. In addition, enlarging pituitary tumors may compress adjacent structures such as the optic chiasma or normal pituitary tissue and may cause visual disturbances, and/or hypopituitarism. In a MEN1 mutation carrier, who would be considered to be at high risk of developing tumors, periodic biochemical monitoring should include measurement of serum prolactin and IGF-I levels, as well as MRI of the pituitary. In patients with abnormal results, hypothalamic-pituitary testing should characterize further the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones.

Treatment

Treatment of pituitary tumors in patients with MEN1 consists of the use of therapies similar to those in patients without MEN1 and consists of appropriate medical therapy (e.g. bromocriptine or cabergoline for prolactinoma; or octreotide or lanreotide for somatotrophinoma) or selective transsphenoidal adenomectomy if feasible, with radiotherapy reserved for residual unresectable tumor tissue. However, pituitary tumors in MEN1 patients are more aggressive and less responsive to medical or surgical treatments [17, 18, 25, 27]. Thus, treatment in MEN1 patients with hormonally secreting pituitary adenomas was significantly less effective in restoring the hypersecretion of hormones to normal (MEN1 vs. non-MEN1 patients) [18]. Furthermore, a separate analysis of the 85 prolactinomas in MEN1 patients revealed that treatment was successful in normalizing plasma prolactin concentrations in only 37 (44%) patients. It is likely that surgery will be required more

frequently in the treatment of MEN1-associated than in non-MEN1 pituitary adenomas.

Parathyroid tumors

Clinical manifestations and diagnosis

Primary hyperparathyroidism is the most common feature of MEN1 and occurs in approximately 90% of all patients with MEN1 [3, 6]. Patients may have asymptomatic hypercalcemia, nephrolithiasis, osteitis fibrosa cystica, vague symptoms associated with hypercalcemia (e.g. polyuria, polydipsia, constipation, or malaise), or occasionally peptic ulcers. Biochemical investigations reveal hypercalcemia, in association with increased circulating PTH concentrations. The hypercalcemia is usually mild, and severe hypercalcemia resulting in crisis or parathyroid cancers is rare. Additional differences in the primary hyperparathyroidism associated with MEN1, compared with features of the disorder in those patients without MEN1, include earlier age at onset (20 to 25 yr vs. 55 yr), greater reduction in bone mineral density [28], and an equal male/female ratio (1:1 vs. 1:3) [3, 6, 29]. Preoperative imaging (e.g. neck ultrasound with Tc99m sestamibi parathyroid scintigraphy) is of limited benefit because all parathyroid glands may be affected, and neck exploration is required irrespective of preoperative localization studies.

Treatment

Surgical removal of the abnormally overactive parathyroid glands in patients with MEN1 is the definitive treatment, but it is controversial whether to perform subtotal (3.5 glands) or total parathyroidectomy and whether surgery should be performed at an early or late stage of the disease. Open bilateral neck exploration is recommended, as opposed to minimally invasive parathyroidectomy, because all four parathyroid glands are usually affected with multiple adenomas or hyperplasia, although this histological distinction may be difficult; parathyroid carcinoma is rarely found in patients with MEN1, and to date only three patients with germline MEN1 mutations have been reported to have parathyroid carcinoma [30, 31]. Subtotal

parathyroidectomy (i.e. removal of 3.5 glands) has resulted in persistent or recurrent hypercalcemia within 10 to 12 yr after surgery in 40 to 60% of patients, and in hypocalcemia requiring long-term therapy with vitamin D or its active metabolite calcitriol in 10 to 30% of patients with MEN1 [15, 16, 32, 33]. These recurrence rates are markedly higher than those observed after parathyroidectomy in patients who do not have MEN1, in whom recurrent hypercalcemia occurs in 4 to 16% and hypocalcemia in 1 to 8% of patients. For total parathyroidectomy with autotransplantation, both fresh and cryopreserved parathyroid tissue has been used. To improve the outcome of parathyroid autotransplantation, one study has reported that the use of less tissue (e.g. approximately 10 fresh parathyroid pieces 1 mm³ in size) helps to reduce both the recurrence of hypercalcemia and the hypoparathyroidism rates [34]. Subtotal parathyroidectomy is suggested as the initial treatment of primary hyperparathyroidism in MEN1, but total parathyroidectomy with autotransplantation may also be considered in some cases. Total parathyroidectomy may be reserved for those with extensive disease either at first or at repeat surgery. Persistent hypocalcemia is treated with oral calcitriol (1,25-dihydroxyvitamin D), although management of hypoparathyroidism can be challenging in some patients, even with the use of vitamin D and calcium replacement.

Conclusion

A diagnosis of Invasive Pituitary Macroadenoma with Hemorrhage in MEN 1 Syndrome GRADE III - E (according to Hardy's Staging) and GRADE III (according to Knosp's Classification Staging) and Renal Calculus Disease P.O. Status, was made. Patient also had Parathyroid neoplasm apart from Pituitary macroadenoma. MEN 1 Syndrome itself is very rare, and hemorrhage in the Pituitary Macroadenoma is still much more rarer.

There has been technological advances in the diagnosis of MEN1, which include radiological

modalities. The optimal treatment of MEN1-associated tumors is still not clear. As there are very few patients scattered around the world, there should be multicentric studies to monitor optimal modalities of treatment [8].

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