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Case Report

Multiple Endocrine Neoplasia 1(MEN1) Guidelines and Surveillance: Advantages, Trials and tribulations

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ABSTRACT:

Multiple Endocrine Neoplasia 1 or MEN1 is a rare hereditary endocrine cancer syndrome characterized primarily by tumors of the parathyroid glands (95% of cases), endocrine gastroenteropancreatic tract (30-80% of cases), and anterior pituitary (15-90% of cases). Other endocrine and non-endocrine neoplasms including adrenocortical and thyroid tumors, visceral and cutaneous lipomas, meningiomas, facial angiofibromas and collagenomas, and thymic, gastric, and bronchial carcinoids also occur. MEN1 should be suspected in patients with an endocrinopathy of two of the three characteristic affected organs, or with an endocrinopathy of one of these organs plus a first-degree relative affected by MEN1 syndrome. We describe a case of a 34 year old man who was referred to the Endocrinology clinic for hypercalcemia with a family history of primary hyperparathyroidism requiring parathyroidectomy and intestinal perforation with peptic ulcer disease in his mother. Suspecting MEN1 syndrome, genetic testing was performed with Invitae that revealed a heterozygous pathogenic variant of MEN1, c.1546dup (p.Arg516Profs*15) on Exon 10. This finding led to improved surveillance for our patient and genetic counseling for his other family members. This case highlights the importance of performing genetic testing for MEN syndrome in patients presenting with hypercalcemia at young age with family history of multiple Endocrine disorders. We review current guidelines regarding work up, genetic counseling and surveillance for these patients for avoiding morbidity and mortality.

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INTRODUCTION

Multiple endocrine neoplasia (MEN) is a disorder that is comprised of tumors of two or more endocrine glands in a single individual. There are four major types of MEN: MEN type 1 (MEN1), because of mutations of menin; MEN2 (former MEN2A) because of mutations of tyrosine kinase receptor, (RET) protoncogene; MEN3 (former MEN2B) because of RET mutations; and MEN4 due to mutations of cyclin-dependent kinase inhibitor (CDNK1B).[1]

MEN1 follows Knudson's "two-hit" model for tumor suppressor gene carcinogenesis (30). The first hit is a heterozygous MEN1 germline mutation, inherited from one parent (familial cases) or developed in an early embryonic stage (sporadic cases) and present in all cells at birth. The second hit is a MEN1 somatic mutation, usually a large deletion, that occurs in the predisposed endocrine cell as loss of the remaining wild-type allele and gives cells the survival advantage needed for tumor development.

MEN1 is transmitted as an autosomal dominant disorder due to mutation in the MEN1 gene, located on chromosome 11q13 which is a tumor suppressor gene encoding menin protein comprising of 610-amino acid. Therefore, it is important to screen family members of the patients with MEN1 syndrome by mutational analysis. MEN1 comprises of the parathyroid, anterior pituitary and pancreatic islet tumors. Some patients may also have adrenocortical tumors, carcinoid tumors, facial angiofibromas, meningiomas, lipomas and collagenomas.[1] Signs and symptoms of MEN1 include fatigue, bone pain, broken bones, kidney stones, ulcers in the stomach. Although the disorder can affect all age groups, the first symptom is linked to the overactive parathyroid gland and often appears in people in their early 20s.

The average life expectancy noted in patients with MEN1 is decreased because tumors may be multiple, more aggressive, metastatic and resistant to treatment. Prognosis could be made better by detection of tumors early in the disease course i.e. before symptoms occur and by providing MEN1 specific treatment. Thus, a multidisciplinary team is required for the care of MEN1 patients and their families.[1]

CASE PRESENTATION

We present a case of a 34-year-old man who was referred to the Endocrinology service by his primary care physician for hypercalcemia. His past medical history was significant for hypertension requiring Lisinopril 10mg oral once daily. He had no known drug allergies. He was a former smoker who quit smoking about one and a half year. He drank alcohol two to three times per month.

His family history was positive for primary hyperparathyroidism requiring all four glands parathyroidectomy. He also stated that "his mother had too much acid in her stomach causing a hole in her intestine." No family members were known to have pituitary tumors.

On physical examination, his temperature was 97.6 F, blood pressure was 128/72 mm Hg, heart rate was 84, and respiratory rate was 12 breaths per minute. His height was 71 inches with a weight of 244 pounds. His body mass index was 34.03.

He was awake, alert and oriented, in no acute distress, appropriate for age and co-operative with physical examination. Head was normocephalic and atraumatic with no scalp lesions. Extraocular movements were intact. Neck exam showed no thyromegaly or lymphadenopathy. Chest was clear to auscultation and cardiovascular exam showed normal rate and rhythm without murmurs. There was no edema in extremities. Neurological exam showed normal deep tendon reflexes. It was grossly non-focal.

Laboratory investigation: Comprehensive metabolic panel revealed normal electrolytes, blood urea nitrogen was 15 with creatinine level of 0.9. Liver function tests were in normal range. Serum calcium level was 11.6 mg/dl (8.6-10.0mg/dl). Total protein was mildly increased at 8.2mg/dl (6.1-8.1mg/dl). His ionized calcium was 6.1mg/dl (4.8-5.6). His thyroid stimulating hormone level was normal at 2.7. Intact parathyroid hormone level was high at 103pg/ml. 24 hour urine calcium level was 610mg.

Considering young age and positive family history, genetic testing was performed with Invitae for suspected multiple endocrine neoplasia syndrome type 1 and calcium sensing receptor mutation test which revealed a heterozygous pathogenic variant of MEN1, c.1546dup (p.Arg516Profs*15) on Exon 10.

The Endocrine society guidelines were followed for surveillance and genetic counseling was offered to our patients. The discovery of the genetic mutation in our patient helped in improved medical care for him and his family members.

DISCUSSION

Multiple endocrine neoplasia syndrome or MEN1 is diagnosed when at least one of the following three criteria is met: Two or more primary MEN1-associated endocrine tumors (*i.e.*, enteropancreatic tumor, pituitary adenoma and parathyroid adenoma), one of the MEN1-associated tumors in patient's first-degree relative with a clinical diagnosis of MEN, germline *MEN1* mutation discovery in an asymptomatic individual and has not yet developed serum radiological or biochemical abnormities indicating tumor development. Our patient fulfills two of the above criteria.[1]

People with high chances of MEN1 are advised to get DNA sequencing of the gene. Additionally, to evaluate associated tumors that occur with MEN1, the following steps should be considered:

- Ask patients if they are experiencing any related symptoms of diarrhea, stomach pain, postprandial bloating that could be reflective of peptic ulcer disease, flank pain, urinary symptoms that indicate nephrolithiasis or decrease libido, infertility, erectile dysfunction that will indicate hypopituitarism,
- Observing levels of PTH, calcium, prolactin, gastrin, check out for galactorrhea in women, visual field defects (particularly bitemporal hemianopia) that occur due to compression of optic chiasm by a pituitary tumor and look for features of acromegaly and lipomas.[4]
- Additional on positive Gene test , identify first degree relatives for genetic counselling and MEN1 mutation testing

Although extensive studies have been done in the diagnosis and management of MEN1-related tumors, life expectancy in patients with MEN-1 continues to decrease because of malignant neuroendocrine tumors. In 2012, the Clinical practice guidelines for MEN1 stressed upon the need for an intensive screening approach in both asymptomatic carriers and patients with this syndrome beginning at 5 years of age. The purpose of this intensive surveillance is to decrease morbidity and mortality in patients with MEN1- associated neoplasms by early detection and treatment. Of note, patients with this syndrome have no clear genotype-phenotype association. Moreover, surveillance specific to individual's mutation is also not possible presently.[1]

Recommended screening for hyperparathyroidism with a yearly assessment of calcium and PTH is commenced as early as 8 years, the initial age at which the symptoms of PHPT have been reported (asymptomatic hyperparathyroidism was reported initially at age 4). Recommended screening for gastrinoma through yearly assessment of gastrin (± gastric pH) begins as early as 20 years, however, 2% of cases have been reported younger than 21 years. Screening for insulinoma through annual insulin and glucose measurement should commence as early as 5 years, the initial age at which the symptoms have been

reported. Recommended screening for other pNETs includes yearly measurement of pancreatic polypeptide, chromogranin-A, VIP and glucagon and annual imaging with CT, MRI, or EUS commenced before the age of 10, as larger pancreatic tumors may become apparent between 10 and 20 years of age.[1]

The current recommendation of MEN1 surveillance is by annual computed tomography (CT), endoscopic ultrasound (EUS), or magnetic resonance imaging (MRI). Moreover, screening of thymic or bronchial NETs from 15 years age is recommended through neck and thoracic CT or MRI every 1–2 years, while adrenal glands screening is through abdominal CT or MRI every three years and pituitary disease surveillance by MRI every 3–5 years. Recommended screening for non-functioning PNETS <2 cm is through CT or MRI every 6–9 months and patients with surgically resected tumors (grade 1–2) are monitored every 3–6 months with either modality.[2] In MEN1, radiological surveillance is associated with clinically significant exposure to ionizing radiation. In patients with MEN1, multi-modality imaging strategies designed to minimize this exposure should be considered.

In one retrospective study done on 43 patients diagnosed with MEN1 to determine the effects of Ionizing Radiation during radiological screening over an 8 year period. This study aimed to calculate the estimated risk of developing secondary malignancy in response to the magnitude of Ionizing Radiation associated with MRI and other radiologic studies. Results of the study showed that exposure to Ionizing Radiation for diagnostic purposes is responsible for 2 % of all cancer worldwide. Studies have shown that patients with a mutation in DNA repair genes and tumor suppressor genes are more susceptible to the effects of Ionizing Radiation and are more likely to develop a malignancy.[3]

According to one study done in a Swedish hospital, following MEN1 guidelines and maintaining a follow-up program plays a significant role in patients with MEN1. The vast majority of patients expressed the need to know the details about risk information and future screening plans about their diagnosis. The patients were more satisfied with being in a follow-up program. However, the inability to understand genetic and medical information related to MEN-1 caused frustration in the patients and thus such patients will not be able to reach their maximum health potential. Patients were of opinion that it is important to have regular follow-ups so that if suddenly tumors develop, treatment could be initiated and they could be cured.[4]

The MEN1 tumors most commonly secrete PTH or gastrin. After detecting their genes, management approaches of MEN1 are intensified. MEN1 has no clear syndromic variants. Tumor surveillance in MEN1 carriers includes annual biochemical tests but with less often imaging tests. Neck surgery includes total or subtotal parathyroidectomy with parathyroid cryopreservation, in addition to thymectomy. Somatostatin analogs or Proton pump inhibitors are the main treatment choices for hyper-secretion of entero-pancreatic hormones except for insulin.[5] Furthermore, MEN1 patients should be assessed for the progression of duodeno-pancreatic neuroendocrine tumors because of their possible malignancy. Apart from this, thymic neuroendocrine tumors should also be detected as early as possible as they are the most lethal tumors.

However, if there is a clinical diagnosis of MEN1, but no MEN1 mutation has been identified:

- One must consider occurrence of phenocopy and mutation analysis of other genes depending on clinical features e.g. CDC73, CASR, AIP and CDNK1B.
- Continued surveillance for additional MEN1 associated tumors as per MEN1 mutation positive individuals.
- Identify first degree relatives for clinical and biochemical evaluation.
- Asymptomatic first degree relatives should continue annual clinical and biochemical screening.
- First degree relatives with MEN1 associated tumors should undergo surveillance as per MEN1 mutation positive individuals.

CONCLUSION

Multiple Endocrine neoplasia syndromes are associated with increased risk for morbidity and mortality in patients. Improved surveillance has shown better outcomes. Genetic testing has become more affordable and accessible in recent years. We stress the importance of genetic testing for accurate diagnosis in patients suspected of having Multiple Endocrine neoplasia syndromes to improve healthcare outcomes in patients and their family members.

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