The Libyan International Medical University

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Multiple Endocrine Neoplasia and Hyperparathyroidism

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Abstract

Primary hyperparathyroidism is a common endocrinological disorder, it is associated with familial syndromes, such as multiple endocrine neoplasia type 1 (MEN1), this syndrome is caused by inactivating mutation of the tumor suppressor gene MEN1, which located on chromosome 11q13, consisting of 10 exons encoding a protein of 610 amino acids called menin, which is a nuclear protein with functions in transcriptional regulation, genome stabilization, cell division and proliferation, typically primary hyperparathyroidism is the initial clinical manifestation in MEN1 mutation occurring in more than 90% of patients and appearing at a young age, usually accompanied by multiglandular disease, clinically manifesting with hypercalcemia, it can remain asymptomatic for a long time and consequently not always be recognized early.

Introduction

Multiple endocrine neoplasia (MEN1), also known as warmer's syndrome , is defined by a MEN1 gene mutation, characterized by 1)primary hyperparathyroidism(PHPT) and hypercalcemia resulting from parathyroid adenomas, 2)hormone secreting or non-secreting pancreatic islet tumors (commonly gastrinomas, 3) anterior pituitary neuroendocrine tumors (pitNETs), ,although MEN1 may present with any of its major constituent manifestations, the Primary hyperparathyroidism (PHPT) is the most common and often earliest endocrine manifestation in MEN1[1], parathyroid tumors in MEN1 is usually benign and hyperactive in its function, leading to primary hyperparathyroidism (PHPT), the clinical manifestations of (MEN1) related (PHPT) are rather similar to those of sporadic PHPT cases, referring to bone loss and kidney stones, however PHPT/MEN1 usually starts four decades earlier, and its secondary bone and renal effects are often more sever than in sporadic cases[2] .

The aim was to search literature on indications for performing mutational analysis in young patients with PHPT and no family history of MEN1.

Case Presentation

A 31 year old woman with osteogenesis imperfecta was incidentally found also to have hypercalcemia and elevated PTH, exploratory neck surgery showed multiglandular parathyroid affection, she turned out to have MEN1, but she was diagnosed 7 years after her debut of PHPT.

Methods

A 31-year-old woman with osteogenesis imperfecta (OI) was referred to Rigshospitalet, Copenhagen, Denmark, due to an incidental finding of hypercalcemia and suspicion of primary hyperparathyroidism. She had no symptoms of hypercalcemia,. and the hyperparathyroidism was hypothesized to be due to abnormal

calcium metabolism from (OI), although not previously described [4], The patient was followed for years according to guidelines and remained normocalcemic until 7 years later, when recurrence was suspected due to a small rise in serum Ca^{2+} and PTH. She still had no symptoms of hypercalcemia.

Results

Routine biochemistry had revealed an increased Ca^{2+} level of 1.56 mmol/L (reference range, 1.12–1.32 mmol/L) as well as PTH of 116 ng/L (reference range, 10–65 ng/L). Parathyroid scintigraphy was normal, but by exploratory neck surgery, all parathyroid glands were found to be hyperplastic. Three and a half parathyroid glands and the thymus were removed

Mutational analysis for MEN-1 was done due to a research project in which all patients with verified PHPT were screened, and she was found positive for a mutation in the MEN1 gene .

Discussion

This patients had an inherited bone disease, which could potentially explain the PHPT, and the concomitant mutation in the MEN1 gene was only found incidentally 7 years later due to a screening project.

Table 1: indications for performing mutational analysis in patients with PHPT and no family history of MEN1 according to Brandi et al [3]

Multiple parathyroid tumors before the age of 30y
Two or more MEN1 related tumors
True recurrent hyperparathyroidism
Gastrinoma at any age
Familial isolated hyperparathyroidism

half of the relevant articles reviewed, considering age as an indication for performing genetic testing, agreed with international guidelines proposed in 2001 by Brandi et al, recommending screening in patients younger than 30 years [3].

Table 3: Indications for performing mutational analysis in patients with PHPT, according to Thakker et al [2].

a case with two or more MEN1 associated endocrine tumors

a symptomatic first degree relative of a known MEN1 mutation carrier
Individuals with parathyroid adenomas occurring before the age of 30 y
Multigland parathyroid disease, gastrinoma or multiple pancreatic neuroendocrine tumors at any age
Individuals who have two or more MEN1 associated tumors that are not part of the classical triad of parathyroid, pancreatic islets and anterior pituitary tumors(e.g parathyroid tumors plus adrenal tumor)

These guideline from 2012 of Thakker et al [2], it is suggested to perform genetic testing in patients with PHPT below the age of 30 years, but also in all patients presenting with multigland parathyroid tumor independent of age .

The typical age of onset of PHPT in MEN-1 is 20–25 years, but studies have shown that several patients presented with PHPT later in life, thus suggesting mutational analysis below the age of 40 years due to the possibility of delaying diagnosis in those patients.

Conclusion

In conclusion, According to international guidelines from 2001, genetic testing is indicated only in patients with PHPT below the age of 30 years. However, in updated guidelines from 2012, it is suggested to perform genetic testing in patients with PHPT below the age of 30 years, but also at any age in patients presenting with multigland parathyroid disease.

References

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