Peer Review File

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Reviewer Comments

Comment 1:

There are some style/english issues (for example "...should be tested for the following items: serum gastrin, fasting blood glucose..." - is gastrin or glucose an item?) or examples of inconsistency ("Pancreatic neuroendocrine tumors occur in 30%-80% of patients with MEN1 and are mostly multifocal, usually on the pancreas and duodenum - so do authors refer to Pancreatic NET or Duodenal NET?" or "Family diagnosis: The patient meets the clinical diagnostic criteria, and the patient has a first-degree relative ....who has a tumor related to MEN1" - if patient meets the first criterium then why seek for other? This criterium needs only one of the typical tumor and first-degree relative with MEN1.

Reply 1:

Thanks for your comment. We have revised the English issues according to your comments (for example "Pancreatic neuroendocrine tumors suspected to be MEN1-related should be tested for the following items: serum gastrin, fasting blood glucose…" has been revised as "Gastro-entero-pancreatic endocrine tumors suspected to be MEN1-related should be tested according to the following biochemical screening program: serum gastrin, fasting blood glucose…")(see Page 12, line 227-229).

The inconsistency that "Pancreatic neuroendocrine tumors occur in 30%-80% of patients with MEN1 and are mostly multifocal, usually on the pancreas and duodenum" has been revised as "Gastro-entero-pancreatic endocrine tumors occur in 30–80% of patients with MEN1 and are mostly multifocal, usually on the pancreas and duodenum" (see Page 11, line 206-207).

The definition of "Family diagnosis" refers to previous literature (Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97:2990-3011). The diagnosis of MEN1 can be divided into three types: clinical diagnosis, family diagnosis and genetic diagnosis. Patients who meet any of the following three diagnostic criteria can be

diagnosed with MEN1. Clinical diagnosis: The patient has two or more of the three main tumors (parathyroid tumor, pituitary tumor, gastro-entero-pancreatic endocrine tumor). Family diagnosis: The patient meets the clinical diagnostic criteria, and the patient has a first-degree relative who has one of those three tumors. Both clinical diagnosis and family diagnosis belong to MEN1. Genetic diagnosis: Genetic testing of the patient found a mutation in the MEN1 gene.

Changes in the text: see Page 5/line 86, Page 9/line 173, Page 10/line 196, Page 11/line 206-207, Page 12/line 227-229, Page 12/line 242, Page 13/line 246, Page 14/line 268, Page 19/line 365, Page 19/line 371, Page 19/line 379-380, Page 23/line 453

Comment 2:

Authors stated in the abstract that early diagnosis is important and have impact on management. Therefore it would be interesting to write more about genetic diagnostics in MEN2 (essential impact of codons on management) or phenocopies and difficulties with regard to ambigous cases (typical phenotype and no mutation).

Reply 2:

We thank you for the comment. We have added more about hierarchical gene management of MEN2 in the revised genetics section of our article(see Page 8-9, line 148-157). Hierarchical gene management of MEN2-related MTC is of great help to improve the prognosis. According to the RET mutation site, the American thyroid Association divided the disease risk into four levels, from the lowest A to the highest D. The codons involved are as follows: A:768,790,791,804,649,891;B:609,611,618,620,630,631;C:634;D:918,883. Patients with grade A risk are recommended for total thyroidectomy after age 5 or when CT results are positive. Patients with grade B or C risk should have total thyroidectomy before age 5. Patients with grade D risk should have surgery as early as the first year of life.

For patients with typical phenotypes of MEN2 but no RET gene mutation, we make a discussion in the article(see Page 23, line 437-445). For patients with typical phenotypes of MEN2 but no RET gene mutation, we can make the clinical diagnosis of MNE2 when the patients meet the clinical diagnostic criteria of MEN2, which we have described in the diagnosis section of the article(see Page 20, line 385-399). As for these patients, their high-risk relatives should be screened regularly. Screening for MTC includes neck ultrasound graphy, basal and / or irritant calcitonin determination.

Pheochromocytoma is screened by measuring plasma or 24-hour urine concentrations of catecholamines and their metabolites. In addition, periodic tumor tests should be performed in patients who are suspected of MEN2 but do not meet clinical or genetic diagnostic criteria.

Changes in the text: see Page 8-9/line 148-157, see Page 23/line 437-445, see Page 20/line 385-399

Comment 3: Moreover, it needs to be emphasised that MEN need to be differentiated with sporadic tumors, not VHL of NF1 which are very rare and pancreatic NET are even rarer within these syndromes.

Reply 3: Thanks for your comment. We have emphasised that MEN need to be differentiated with sporadic tumors in the revised disscussion section, and we have pointed that some features of suspicious cases should arouse the vigilance of clinicians(see Page 22-23, line 413-435). For MEN1, it often has the following characteristics. Parathyroid hyperplasia or adenoma associated with MEN1 occurs earlier than sporadic case and often occurs in multiple glands. The onset age of gastro-entero-pancreatic neuroendocrine tumors related to MEN1 is earlier compared to sporadic cases. Gastro-entero-pancreatic neuroendocrine tumors usually manifest as multifocal and small lesions. For MEN2, it often has the following characteristics. 25% of MTC patients are associated with MEN2, so all MTC and C cell hyperplasia patients should be tested for RET gene. Bilateral adrenal pheochromocytoma is often associated with familial hereditary diseases and requires vigilance. Lichen amyloidosis on the back skin is a characteristic manifestation of MEN2A. The special manifestations (Marfanoid habitus, mucosal neuromas, protruding lips, gastrointestinal ganglion neuroma) of MEN2B is an important clue for early diagnosis of MEN2B.

Changes in the text: see Page 22-23/line 413-435

Comment 4: Both authors come from Gastrology and Radiology departments so I would expect to get more information about novel diagnostics and typical findings of MEN-related lesions.

Reply 4: Thanks for your comment. The novel diagnostics and typical findings related to MEN are a summary of key points, which can further deepen radiologists' and clinicians'

understanding and memory of the disease, identify suspicious patients quickly and sensitively in future work, make correct diagnosis quickly and improve patients' prognosis as much as possible. According to the characteristics of each type of MEN, some memory methods can be summarized, which we have highlighted in the conclusion section(see Page 23-24, line 450-459). MEN1 mainly involves parathyroid tumors, gastro-entero-pancreatic endocrine tumors, and pituitary tumors, which can be remembered as "2P1G". The clinical phenotype of MEN4 is similar to that of MEN1, but the genes involved are different. Thus far, there have been few studies on MEN4. MEN2A mainly involves MTC, pheochromocytoma, and parathyroid tumors, which can be simply remembered as "2P1M". MEN2B mainly manifests as MTC, pheochromocytoma, Marfanoid habitus, and mucosal neuroma, which can be remembered as "1P3M".

Changes in the text: see Page 23-24/line 450-459