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scientifique

Commentaire

2007

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How to cite

TRIPONEZ, Frédéric, CADIOT, Guillaume. Non-functioning tumours of the pancreas in MEN1 patients. In: Journal of Gastrointestinal and Liver Diseases, 2007, vol. 16, n° 3, p. 295–296.

This publication URL: <https://archive-ouverte.unige.ch/unige:35300>

Non-Functioning Tumours of the Pancreas in MEN1 Patients

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Neuroendocrine tumours of the pancreas develop in about 80% of MEN1 patients, as demonstrated by autopsy series. Most of these tumours do not produce clinical symptoms and are therefore defined as non-functioning. They were previously suspected to be aggressive leading to a high death rate. They represented a major cause of death in all historical series of MEN1 patients, however, at that time, most of them were identified because of tumour-related complications such as gastrointestinal hemorrhage, biliary or gastric outlet obstruction, abdominal mass or metastases. They are increasingly recognized as a separate entity and are found more frequently as a result of earlier diagnosis after genetic testing, better standardized follow-up care, and more sensitive imaging studies currently able to detect tumours as small as a few millimetres, especially endoscopic ultrasonography (EUS).

Whether all small tumours will become large, malignant and kill the patients is still a matter of debate. Some authors have suggested that MEN1 patients should undergo pancreatic resection as soon as a tumour is identified by imaging techniques, or even before, when suspected on an increase in biological markers such as pancreatic polypeptide (1). By contrast, some other authors have suggested for a long time from data obtained in Zollinger-Ellison patients with MEN1 that small tumours can be safely managed non-surgically until they reach 2-2.5 cm in size (2, 3). Data is now accumulating, suggesting that not every small tumour will become aggressive and that, therefore, patients with small non-functioning tumours can safely be actively followed until one of the tumours begins to increase in size. Two prospective studies using systematic EUS in MEN1 patients have shown that: firstly, MEN1 patients have non-functioning tumours of the pancreas more often than

previously thought (55%); secondly, that most of the patients will have an increase in size and number of tumours over time; thirdly, that this increase is very slow for most of the tumours and patients, and finally that small tumours rarely lead to metastasis (4, 5).

The study by Botsios et al in this issue of the *Journal of Gastrointestinal and Liver Diseases* confirms that major pancreatectomies can be performed safely in experienced centres but also, as shown by numerous other studies, that the long term morbidity of pancreatectomy is also significant; two of their four patients are diabetic at follow-up, which is consistent with the rates of diabetes reported by other authors, ranging from 25% after pancreaticoduodenectomy (6) to 80% following an aggressive management of pancreatic tumours in MEN1 patients, including reoperations (7). This morbidity is of course acceptable in patients with large tumours who have a significant risk of metastases or of death due to their tumours, but has to be carefully weighed against the low risk of metastases in the case of small tumours.

Like in multinodular goitre, pancreas in MEN1 patients harbour multiple neuroendocrine tumours. In the absence of cytological or genetic markers of aggressiveness, the only clinically usable markers of aggressiveness are the size and the doubling time of the tumour. This is the reason the French Endocrine Tumour Study Group (Groupe des Tumeurs Endocrines, GTE) currently suggests to actively follow tumours below 2cm without metastases and to operate on tumours > 2cm and/or tumour that increase in size > 0.5 cm in one year (corresponding roughly to a doubling of the tumour volume for a 1.5 cm tumour) and/or tumour that have metastasised (Fig.1) (8).

Such an approach has been implemented by the NIH group for the management of other genetically related non-functioning tumours of the pancreas, in patients with von Hippel-Lindau (vHL) disease. In this study on 108 patients with non-functioning tumours of the pancreas among 633 vHL patients, the authors found that patients with small primary lesions (< 3cm), without a mutation of exon 3 and with a slow tumour doubling time (>500 days) could safely be managed non-operatively (9).

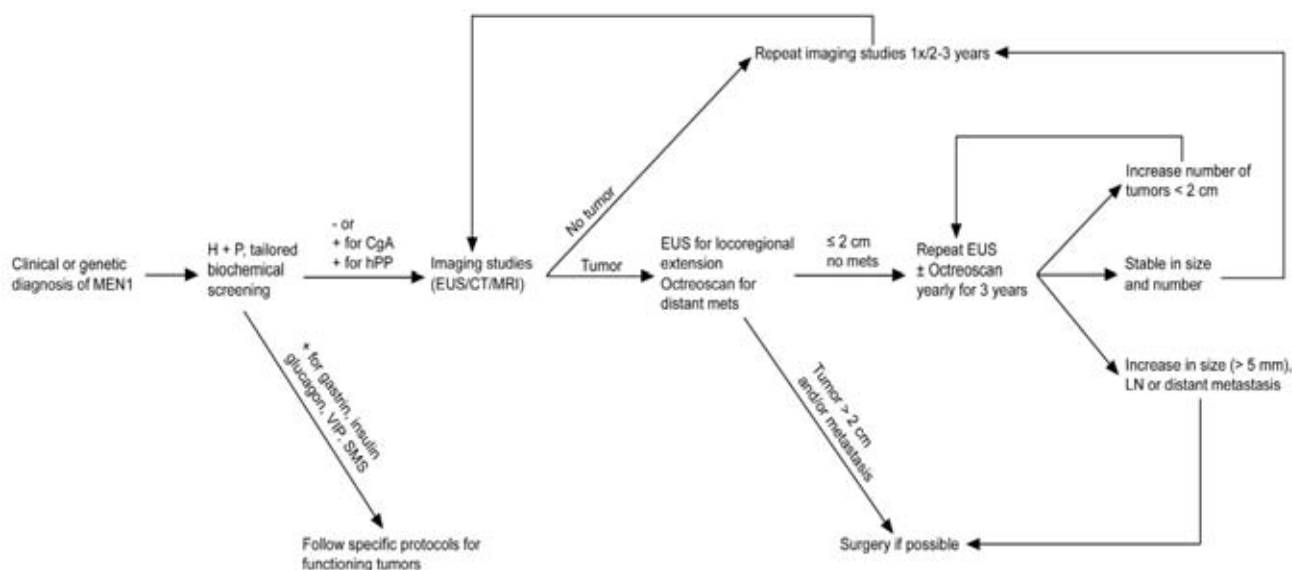


Fig.1 Proposed algorithm for the detection and management of NFPET in MEN1 patients. H+P: history and physical examination, tailored biochemical screening: according to signs and symptoms and following specific protocols, measurement of blood levels of Chromogranin A (CgA), human pancreatic polypeptide (hPP), gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP), somatostatin (SMS) - negative, + positive, EUS: endoscopic ultrasonography, CT: computer tomography, MRI: magnetic resonance imaging, LN: lymph node, mets: metastasis. 1: we do not recommend systematic dosage of hPP for NFPET diagnosis since its increase does not change the management of those patients. 2: because the risk of developing new tumors ≥ 2 cm seems low in patients without any tumors at the first pancreatic imaging studies, some authors recommend a EUS every 5 years for the follow-up of those patients. (From ref. 8, with kind permission of Springer Science and Business Media)

This non-operative approach of small non-functioning tumours of the pancreas in MEN1 patients still needs demonstration of its safety in the long term, but it should spare or delay pancreatectomy and its frequently associated complications in a significant number of MEN1 patients.

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