bioscientia

lab.bulletin

Nr. 3/2009

Calcitonin determination in nodular goitre – diagnostic investigations of medullary thyroid cancer

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The European Thyroid Association (ETA) [1] and the German Endocrinology Society (DGE) [2] have recommended calcitonin screening for patients with thyroid nodules. Acceptance of this recommendation in Germany is, however, only between 15% and 54%, depending on the professional group [3].

A recent US study shows the cost-effectiveness of calcitonin determination as regards additional years of life gained [4].

Aims and effectiveness of calcitonin screening

Calcitonin screening provides an opportunity to discover a medullary thyroid cancer (MTC) early, before lymphogenic metastasis occurs. Only then is there every chance of having postoperatively unmeasurable calcitonin levels and very good 10-year survival rates of up to 97.7% [5].

If, on the other hand, lymphogenic metastasis of the MTC has already occurred, "biochemical healing" is achieved in only 10% of patients after systematic lymphadenectomy [6]. The patients identified through calcitonin screening had a 10-year survival rate of 87% [7], whereas before calcitonin screening was introduced, the 10-year survival rate at the same treatment centres had been 44% [7].

Data on the prevalence of medullary thyroid cancer

The mean prevalence of sporadic MTC in patients with thyroid nodules is given in the publications on calcitonin screening as 0.6%, with a range of 0.26-1.3% [10-19].

The feature common to all publications is that a selection of thyroid centres is involved.

Differential diagnostics of calcitonin elevation

Calcitonin is produced by the C cells that are clustered in between the thyroid follicles but do not form part of the thyroid follicular epithelium. The endocrinological importance of calcitonin for humans is unclear. An elevated calcitonin level (hypercalcitoninaemia) is a manifestation either of disease, reactive stimulation of the C cells or disturbed calcitonin breakdown. Hypercalcitoninaemia has a broad range of differential diagnoses (Table 1). In the event of hypercalcitoninaemia, an alcohol history, medication history and the exclusion of hypercalcaemia and renal failure are mandatory. Clinically, no bacterial infection and no severe disease must be present. Only under these conditions do C-cell hyperplasia (CCH) and MTC remain the two most common diagnoses.

Preanalysis of calcitonin determination

The blood sample should be taken with the patient fasting; alcohol and calcium are possible stimulators of calcitonin [20, 21]. The low stability of calcitonin at room temperature makes it necessary, after coagulation of the blood, to centrifuge the samples immediately and freeze the serum, then transport the samples to the laboratory frozen.

Differential diagnoses of hypercalcitoninaemia	Remarks
Medullary thyroid cancer (MTC)	In adult screening, predominantly sporadic MTC
C-cell hyperplasia (CCH)	Particularly in men or in combination with autoimmune thyroiditis, hyperparathyroidism or hypergastrinaemia
Renal failure	In patients with renal failure, only higher levels of stimulated calcitonin point to MTC
Hypercalcaemia	Applies to 2 hours after calcium intake, especially with absorptive hypercalciuria [8]
Medication with proton-pump inhibitors	Omeprazole, Pantozol, lansoprazole (bear in mind the broad range of trade names!) [10]
Medication with calcitonin or salmon calcitonin	Treatment to avoid accelerated loss of bone substance in postmenopausal women; bear in mind range of trade names and use as a nasal spray!
Paraneoplastic syndrome	In particular all neuroendocrine tumours, e.g. carcinoid, small-cell lung cancer

Differential diagnoses of hypercalcitoninaemia	Remarks
Chronic alcoholism	Even after 3 weeks' abstinence from alcohol [9]
Autoimmune thyroiditis, Hashimoto's thyroiditis	Calcitonin levels > 100 pg/ml rare after pentagastrin stimulation in Hashimoto's thyroiditis [28]
Bacterial inflammation	Procalcitonin as a marker for bacterial infection
Severe systemic disease	

Table 1: Differential diagnosis of calcitonin elevation

From what threshold is calcitonin regarded as elevated?

The thresholds differ according to the method used in each case. The basal calcitonin reference levels for men are, as a rule, higher than those for women [10, 21]; in our laboratory they are < 5 pg/ml for women and < 8.4 pg/ml for men. This gender-dependence must also be borne in mind when assessing a pentagastrin test or the stimulated calcitonin level. Hypercalcitoninaemia should be confirmed by a second analysis. There is no clear interpretation of an elevated calcitonin level between 10 and 100 pg/ml. This diagnostic uncertainty and possible serious consequences of treatment are the main problems with calcitonin screening. The positive predictive value for MTC in the study by Constante et al. [16] with a basal calcitonin level between 20 and 50 pg/ml was 8% and with a basal calcitonin level between 50 and 100 pg/ml it was 25%.

The study makes it clear that thyroidectomy purely on the basis of a basally elevated calcitonin level of up to about 5 times the upper reference level is not justified, and that a further pentagastrin test is required. Only a basal calcitonin level of > 100 pg/ml is almost always accompanied by MTC.

Pentagastrin test not conclusive

If hypercalcitoninaemia is due to a disease of the C cells (CCH, MTC), a clear rise in the calcitonin level is observed 2 minutes, 5 minutes and 10 minutes after the injection of pentagastrin. A stimulated calcitonin level after pentagastrin of > 100 pg/ml is proposed in the German endocrinology recommendations as the threshold for thyroidectomy [2]. On the other hand, however, a stimulated calcitonin level of 100 pg/ml may conceal MTC or CCH. In particular, Gibelin et al. [22] described a broad overlap between a small MTC of up to 5 mm and a CCH with calcitonin levels of between 100 and 200 pg/ml after pentagastrin stimulation.

There are no literature data on genderspecific adaptation of the stimulated calcitonin threshold levels, but these must be demanded in future.

In the study by Vierhapper et al. [11], the "false positive" diagnosis of CCH involved mainly male patients: if thyroidectomy was performed with a pentagastrin-stimulated calcitonin of > 100 pg/ml, CCH was found in 37/45 (82%) of male patients, whereas suspected MTC was confirmed in 24/30 (80%) of the female patients.

In a study by Iacobone et al. [13], pentagastrin-stimulated calcitonin levels of > 200 pg/ml were always accompanied by MTC.

Thyroid ultrasonography

The study by Karanakis et al. [23] showed that elevated basal calcitonin levels of > 10 pg/ml are found in 1.7% of healthy subjects and in 6.8% of patients with thyroiditis without this concealing MTC. It may therefore be helpful to limit calcitonin screening to patients with defined morphological findings in ultrasound scans.

Ultrasonographic findings typical of MTC are:

- the echo-poor nodule,
- the absence of a halo sign (pseudocapsule of a thyroid nodule),
- intranodular calcifications (microcalcifications) and
- intranodular hypervascularization

Since MTCs amenable to curative treatment are often well under 1 cm in diameter, calcifications in a very small MTC will rarely be detected.

Calcitonin screening is not recommended if the focal finding can be clearly attributed to a cyst on the basis of ultrasound morphology or ultrasonography, or if scintigraphy shows it to be a focal autonomy.

Fine-needle aspiration

Since calcitonin screening detects mainly small MTCs, fine-needle aspiration and cytological workup achieved only limited sensitivity of about 60%, depending on tumour size [16, 17, 24]. If fine-needle aspiration is performed in a particular case, in addition to the air-dried smear preparations a liquid, buffered transport medium should if necessary also be used in agreement with the cytopathology establishment performing the analysis. Material in a liquid transport medium can be used for the detection of calcitonin.

When is a molecular genetic test required?

If an MTC is found, differentiation between sporadic and hereditary MTC is considered mandatory. The aim here is to check for a point mutation in chromosome 10 (RET proto-oncogene).

Mutations in at least 14 different codons are currently known. According to a European multicentre study [25], the mutation in codon 634 is the most common form of hereditary MTC; on average it manifests itself at about the age of 10 years, and at the latest by the age of 20. Mutations in codon 768, 790, 791, 804 or 891 are accompanied by the manifestation of hereditary MTC later in life, but are very rare. On the whole, calcitonin screening in middle-aged to elderly patients with thyroid nodules detects mainly the sporadic form of MTC [26].

However, if "low-risk" RET mutations with low penetrance for clinically manifest MTC are present (e.g. codon 791), first diagnoses of index patients with familial variants of MTC are found even after the age of 45. The mutation in codon 791 is comparatively common and has also been found in control groups with normal calcitonin levels [26].

Ultimately, the preoperative exclusion of a hereditary form of MTC cannot resolve the issue of tumour status in hypercalcitoninaemia. If it has been established that surgical treatment of hypercalcitoninaemia is indicated, however, there are two good arguments for performing the molecular genetic test preoperatively.

- Degree of resection:

If there is a mutation in the RET proto-oncogene, any C cell left in residual thyroid tissue can become the starting point for a later MTC and thyroidectomy, with removal of even minuscule remnants of dorsal and lateral capsule being mandatory. However, thyroidectomy with central lymphadenectomy is also the standard treatment for sporadic MTC.

- Assessment of histopathological findings in the event of CCH:

With a histological finding of CCH, only the molecular genetic test can show whether precancerous cells are present. Organizationally, a mutation analysis should not lead to a prolonged delay in an operation that is clearly indicated.

Calcitonin measurement well before the operation

If elevation of the calcitonin level basally and after pentagastrin stimulation is within a diagnostic grey area, the patient should be informed of the differential diagnoses and of the advantages and disadvantages of surgical treatment and watchful waiting. The complex data situation makes it necessary to leave enough time between briefing the patient and giving the treatment, for an expert second opinion to be obtained if necessary. Targeted calcitonin determination is considered necessary before every thyroid operation performed because of nodular goitre, cold nodule or cervical lymphadenopathy. It is, however, bad from an organizational point of view if the determination of basal calcitonin is not made until immediately before an operation on nodular goitre, since if hypercalcitoninaemia is found there is no time left to perform the pentagastrin test and the surgeon then has to take responsibility for a degree of resection that is based on a laboratory parameter with low predictive value.

Consequences for patient care

Targeted calcitonin determination is required if one of the following applies [27]:

- Presence of nodular goitre
- Combination of morphological findings in ultrasound scans of an echo-poor thyroid nodule with microcalcifications and no halo.
- The patient's past medical history contains diseases which could be indicative of multiple endocrine neoplasia (e.g. phaeochromocytoma either as sole finding or in combination with primary hyperparathyroidism).
- Positive family history for the hereditary form of MTC (plus gene analysis, diagnostic investigations regarding multiple endocrine neoplasia, counselling as regards prophylactic thyroidectomy, referral to an endocrinologist).

- Therapy-Refractory diarrhoea. 10-20% of patients with advanced medullary thyroid cancer have such diarrhoea [29].

- CEA elevation of unclear origin. Clinically manifest medullary thyroid cancers have elevated CEA as well as elevated calcitonin [29].

Summary

Determination of calcitonin should be advocated in patients with nodular goitre and if an echo-poor thyroid nodule is detected (no cyst, no focal autonomy), irrespective of nodule diameter, since treatment is effective and cure rates are greatly increased if an MTC is discovered early.

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29. L. Thomas. Labor und Diagnose. 7. Auflage 2008.

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