EUROPEAN THYROID ASSOCIATION (ETA) GUIDELINES FOR CENTRAL HYPOTHYROIDISM

D.A. Niculescu*

Department of Endocrinology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

European Thyroid Journal recently published on-line first the European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism (1). Prepared by leading personalities of the ETA in the field, the guidelines offer 34 clinically oriented recommendations to suspect, screen, diagnose or manage central hypothyroidism (CH).

The guidelines went through all necessary steps in order to provide the solid and unbiased opinion of ETA on CH. ETA selected the members of the task force on the basis of their clinical expertise in the field. It is important to note that these members declared no conflict of interest and worked without financial support from ETA. Moreover, before publication, the recommendations were first released in the “members only” section of ETA website for comments and corrections. The review of the literature was systematic. The recommendations were graded according to the well-known GRADE system. Interestingly, the recommendations are tagged as adult, pediatric or both. The guidelines start with a section on epidemiology and pathogenesis of CH with an exhaustive table on the candidate genes in inheritable forms of CH.

After the details of the guidelines methodology, the recommendations addresses the patients at risk for CH (recommendations 1-9), the diagnosis algorithm (recommendations 10-14), genetic analyses (recommendations 15-18), management (recommendations 19-34). In my opinion all the recommendations are clear, straight, clinically oriented and very easy to search and follow.

I would like to highlight two recommendations, 9 and 25. Recommendation 9 (“We recommend that the onset of CeH should be evaluated in patients on treatments with ligands of the retinoid X receptor (RXR), ipilimumab (or other checkpoint inhibitors), or mitotane”) points to the increasing number of endocrine, particularly pituitary, adverse effects of the new cancer therapies. With more and more checkpoint inhibitors on the market and prolonged survival of cancer patients CH

will become more prevalent. Recommendation 25 (“As in primary disease, we recommend to avoid treatment of milder forms of CeH (FT4 concentrations within the lower limit of normal range) in elderly patients > 75 years of age”) adds to the current debate of “to treat or not to treat” primary subclinical hypothyroidism with the guidelines favouring the “not to treat” side.

I believe that these ETA guidelines on CH will help clinicians in the management of this (still) infrequent and challenging disease.

Cardiovascular disease in thyroid cancer survivors

In the July issue of the Journal of Clinical Endocrinology and Metabolism Park J et al published a paper on Risk Factors for Cardiovascular Disease Among Thyroid Cancer Survivors: Findings From the Utah Cancer Survivors Study (2). In the light of the current ATA guidelines on the management of differentiated thyroid cancer indicating less aggressive treatments the study of Park shows that TSH suppression therapy increases cardiovascular (CVD) risk and probably mortality. Also, the modifiable and non-modifiable risk factors for CVD are detailed.

The study was a very large one, including almost 4000 thyroid cancer survivors. However, the main strength was the population-based strategy.

The authors showed that, as expected, older age, male sex and increased body weight are independent risk factors for CVD in thyroid cancer survivors. This is important when we indicate long-lasting TSH suppression therapy or frequent levothyroxine withdrawals for cancer staging.

Of note, cancer histology, regional disease (vs. localized) and treatment (surgery and radiation vs. surgery only) had no effect on CVD risk. Metastasized cancer (vs. localized) had a borderline effect on CVD risk, probably as an effect of more aggressive therapy. TSH suppression therapy induced a 25% increase in CVD risk after adjusting for age, race, sex, body weight,

*Correspondence to: Dan Alexandru Niculescu MD, “Carol Davila” University of Medicine and Pharmacy, Endocrinology, 34-36 Aviatorilor blvd, Bucharest, 011863, Romania, E-mail: d.niculescu@parhon.ro

cancer stage and comorbidities. The excess of risk was similar to that imposed by the increased body weight. An interesting sub-analysis of this study showed that patients diagnosed after 2005 had an increased CVD risk when compared with those diagnosed before 1999. The two groups were similar in all aspects except TSH suppression therapy and radiation therapy which were more prevalent in modern times.

This study shows us that in a disorder with long survival like thyroid cancer prevention of fatal associated conditions is as important as the treatment of the main disease.

TIRADS score for risk stratification of indeterminate cytological results

In the July issue of European Journal of Endocrinology a French group published a paper indicating that “TIRADS score is of limited clinical value for risk stratification of indeterminate cytological results” (3). An interesting study investigating the reverse way, from fine-needle aspiration biopsy (FNAB) to ultrasound, in risk stratification of thyroid nodules.

TIRADS score is mainly used as a risk stratification and FNAB indication tool in thyroid nodules. Of those nodules which are not benign on ultrasound (TIRADS greater than 2) FNAB is able to classify a proportion of them as benign (Bethesda 2) and to make surgery unnecessary. However, an important proportion still remains indeterminate (Bethesda 3, 4 or 5). The authors tried to find out if by coupling the TIRADS score with Bethesda 3, 4 or 5 categories is of any help in warranting benignity.

In the 602 nodules from their department for which they had the TIRADS score, FNAB with Bethesda classification and pathology reports the added value of TIRADS score was of no clinical use. For example, in the Bethesda 4 and 3 categories the malignancy rate for TIRADS 3 score was 10.26% and 15.79%. Authors also performed an interesting analysis by reclassification of encapsulated non-invasive follicular variant of papillary carcinomas (FVPTC) as non-invasive follicular thyroid neoplasm (NIFTP). Unfortunately, even after this change the TIRADS score remained of no clinical value.

At the end here are some of the authors' conclusions: “TIRADS NPV (negative predictive value) was insufficient in most cases to allow avoiding surgery and be used as a rule out test. On the contrary, the high PPV (positive predictive value) of malignancy for TIRADS 4B and 5 may suggest a surgical approach whatever the Bethesda category. Regarding Bethesda V nodules a surgical approach is recommended regardless of the TIRADS score”.

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