University of Medicine and Pharmacy Tîrgu Mureș

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Abstract of PhD Thesis:

NEW PATHOLOGICAL MARKERS USEFUL IN MANAGEMENT OF PITUITARY TUMORS, ESPECIALLY GH TUMORS WITH OR WITHOUT ACROMEGALY

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Since medical treatment of pituitary tumors depends to a certain extent on the expression of somatostatin receptors (SSTR), a reproducible method able to detect the expression of distinct subtypes is required. In our **first study**, we have tested the immunohistochemical (IHC) detection of $SSTR_{2A}$ and $SSTR_5$ for all types of pituitary tumors using different procedures by two new monoclonal antibodies.

60 GH, 15 ACTH, 23 FSH/LH, 7 PRL, 3 TSH pituitary tumors were studied using two new specific monoclonal antibodies (UMB-1 and UMB-4), two fixatives (Bouin-Hollande and Zinc-Formalin) and two technical procedures (manual and automated IHC). Only membrane staining, considered as specific was taken into account and the SSTR expression was considered positive when >5% of the cells were immunoreactive (IR). GH pituitary tumors were classified as GH or GH/PRL, densely or sparsely granulated and into three groups taking into account the percentage of SSTR-IR cells (group 1: <25%; group 2: 25-75%; group 3: >75%). We found that $SSTR_{2A}$ and $SSTR_5$ were highly expressed only in GH and in TSH pituitary tumors. $SSTR_{2A}$ expression was significantly higher (P=0.005) in densely compared to sparsely granulated GH tumors. The expression of $SSTR_{2A}$ and $SSTR_5$ was found to be rare in the other tumors and the percentage of positive cells was very low.

The IHC detection of SSTR is a reproducible and specific method, which should now be considered for use in routine practice for pathological analysis of pituitary tumors. Also it may prove useful in the analysis of all endocrine tumors (including e.g. pancreas) with a view to adapting medical treatment to SSTR profile.

For GH tumors without acromegaly (silent), a first therapeutic option is surgery. If the surgical resection is not complete, further therapy is required, including medical treatment or radiotherapy. No data are available to choose the optimal treatment of these tumors. Therefore, the **second study** compared pituitary tumors with and without acromegaly highlighting some clinical and histological characteristics of these rare patients with silent GH tumors and suggesting several treatment options.

GH tumors without acromegaly were found predominantly in females and were generally identified due to headache, visual impairment or symptoms secondary to hyperprolactinemia. Most of GH pituitary tumors were macroadenoma, with no significant differences between two groups (with and without acromegaly) concerning tumor size, invasion, grade and age of the patients. So the absence of acromegaly seems not to be associated with an early diagnosis but more likely to tumor characteristics. Thus the percentage of $SSTR_{2A}$ immunoreactive cells was significantly lower in pituitary tumors without acromegaly than in those with acromegaly and GH tumors without acromegaly were predominantly sparsely granulated type, suggesting that silent GH tumors may be less differenciated than GH tumors with acromegaly.

The response of GH pituitary tumors to somatostatin analogues (SA) on GH secretion and tumor shrinkage seems to correlate with $SSTR_{2A}$ expression, but there is no data on the use of SA for the treatment of GH pituitary tumors without acromegaly. To our knowledge, this is the first study that compared the expression of $SSTR_{2A}$ and $SSTR_5$ in GH tumors with and without acromegaly. The study of SSTR expression may be useful to identify if the tumors without acromegaly will be susceptible to respond to SA treatment.

In conclusion, potentially aggressive character of the tumors without acromegaly may be due to the less differentiated morphologically aspect, therefore knowledge of somatostatin receptor expression may be useful in identifying those cases likely to respond to drug therapy.

Key words: pituitary tumors, somatostatin receptors, monoclonal antibodies, somatostatin analogues, silent tumors.