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Review Article

How Often Should Infra Clinical Acromegaly be Sought During the Course of A Macroprolactinoma Resistant to Medical Treatment?

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Abstract

No consensus was proposed on routine screening for growth hormone (GH) co-secretion of a prolactin-secreting adenoma. Especially since cases of subclinical acromegaly have been published in the literature, Nevertheless, there are circumstances that suspect co-secretion, such as the persistence of clinical signs of hyper prolactinoma and the lack of normalization of prolactin level by dopamine agonists treatment and the absence of morphological control of the adenoma. An annual frequency of GH secretion screening seems reasonable considering that the evolution of this pathology is often progressive, nevertheless biological changes must challenge the clinician to detect co-secretion such as a drug resistance even partially of macroadenoma having already responded to treatment and the onset of glucose intolerance or secondary diabetes. A phospho-calcium balance and an oral glucose tolerance test (OGTT) initially seem more economical nevertheless this check-up will never replace the dosage of IGF1 as well as a GH braking test after OGTT.

Keywords: Prolactinoma; Subclinical Acromegaly; Drug Resistance

Introduction

The significant frequency of GH prolactin secreting pituitary adenomas as well as disconnection hyper-prolactinoma of a pituitary adenoma secreting GH of infra-clinical form are not uncommon [1] thus GH-prolactin co-secretion of pituitary macro adenoma should be routinely investigated at regular intervals which remains to be further clarified, even in the absence of therapeutic failure or partial response to dopaminergic agonist treatment. The infra-clinical acromegaly response to medical treatment seems better than the patent form.

Discussion

If prolactinomas are the most common pituitary tumors, the evolution of prolactinoma to active biological acromegaly, first and then clinically, is a rare phenomenon and even rarer than the co-secretion of GH is infra clinic. Often the search for acromegaly is made before the therapeutic failure of dopaminergic agonists (biological and morphological resistance respectively defined by the lack of normalization of prolactin levels and the absence of significant reduction in tumor volume after 3 months of medical treatment at adequate dose) [2].

The definition of infra-clinical acromegaly poses a real problematic and opens the door to several clinical and biological shapes. The clinical impact assessment finds all its interest as well as the dysmorphic syndrome which constitutes the typical picture of clinical acromegaly is only the reflection of the bone resonance of GH hypersecretion. Hypersecretion affects other organs than bone, such as liver (hepatomegaly), kidney (nephromegaly), spleen (splenomegaly)....

We can see in some patients: organomegaly without dysmorphic syndrome. This assumes, according to some authors, a clinical-biological continuum of this pathology traducing an embryo-histological continuum [3].

Biological features consist on moderately high level of insulin growth factor 1 (IGF1) and or Braking GH by unrestrained after Oral Hypoglycemia tolerance test (OGTT). Often only one of the two criteria is present. The diagnosis is usually based on the first criteria knowing that IGF1 level has been requested in the search of cause of dopamine agonist resistance or a somatotropic deficit which is a hormonal deficit secondary to the pituitary macro adenoma.

The question that must be asked is it an infra-clinical acromegaly with a progressive clinical-biological picture that will be completed over time. Or bone resistance to hypersecretion of GH.

Two cases must be distinguished: an acute resistance after years of stability of a macroprolactinoma having already well responded to observed medical treatment which supposes a dedifferentiation which suggests an asynchronous co-secretion [4] or the progressive appearance of symptoms and retrospectively the clinical picture will be complete.

In all cases, the therapeutic sanction is the same by somatostatin injections, the dose and frequency of which appear to be lower than that of the clinically active form in combination with dopaminergic agonists.

Some factors may help the clinician to establish a nosologically diagnosis such as the young age of patients as well as presence of kidney stones and other similar familial cases as well as in this setting secretion of GH and prolactin causes a suspicious form genetics that may be part of multiple endocrine neoplasia MEN1 (defined by a pituitary tumor often prolactinoma or acromegaly, pancreatic tumor, primary hyperparathyroidism manifested by kidney lithiasis) or MEN4 (great resemblance to MEN1 is distinguished by the frequency and delay of appearance of tumors).

The researchers have proposed two pathogenic hypotheses have been proposed to illustrate this co-secretion: either a Transdifferentiation of mammotropic cell to somatotropic cell following mutations occurring during the tumor progression. This phenomenon implies according to some authors, a reversible transformation that is a phenotypic Switch without cell division that can be observed in some physiological situations such as lactation [5].

Other authors propose that this is a transformation that affects the two kind of cells (mammotropic and somatotropic) that secrete their hormones separately, whose phenotypic translation varies according to the type of mutation [6].

The therapeutic management of this pathology seems necessary for two reasons: avoid aggravation and progression to a patent form and improve the therapeutic response of hyper prolactinoma to dopaminergic agonists. Therapeutic weapons are the same as for the patent form. Subclinical form prognosis seems better than the patent form for two reasons: the early diagnosis and the sensitivity in part to dopaminergic agonists, which means that surgery is second-line treatment, contrary to the patent form.in all forms of acromegaly, a review of complications and comorbidities should be requested [7].

Conclusion

Infra-clinical acromegaly is a particular form often characterized by a greater delay in diagnosis than the patent form already known to be diagnosed late by clinicians. His discovery may be fortuitous during the exploration of a non-secreting pituitary-like macro-adenoma or a macro prolactinoma.

The frequency of subclinical acromegaly screening may be biannual by a phospholipid check-up and OGTT (screening of deglycation) as well as an annual IGF1 determination and GH braking test by OGTT.

The therapeutic response, which is certainly influenced by prolactin secretion, seems to be better for the Borderline form than for the dysmorphic patent form. Despite good sensitivity under cocktail dopamine agonist and somatostatin which seems first line treatment and surgery second line; nevertheless, surgery remains the first therapeutic option in cases of a significant visual loss or when there is neither infiltration of the cavernous sinus nor surgical refusal by the patient, especially as it will remain the best way of diagnosis (histopathological evidence). Finally, a surgical debulking followed by a synergic medical treatment (dopaminergic agonist and somatostatin) seem the best complete management of this condition.

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