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Acromegaly and prostate cancer

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Acromegaly is an uncommon pituitary disease, characterized by progressive bone and organ overgrowth, and frequently accompanied by dysfunctional cardiovascular, cerebrovascular and respiratory systems, which contribute to the premature deaths observed in this condition[1–4]. In addition, evidence is growing to suggest that acromegaly might predispose to an increased risk of benign and malignant neoplasms, thus influencing the final outcome of the disease[1–5]. Such neoplastic lesions have been reported predominantly in the gastrointestinal tract, but sites such as the breast, thyroid, skin and lymphohaematological system have also been found to be involved[5–14].

The exact mechanism of neoplastic events in acromegaly has not been completely clarified. *In vitro* studies indicate an autocrine–paracrine role for growth hormone (GH) and insulin-like growth factor I (IGF-I) in the proliferation of cells. Such factors may stimulate the proliferation and transformation of cells by means of specific membrane, cytoplasmic and nuclear receptors[15–17], and may induce proto-oncogene transcription, thus demonstrating probable tumorigenic activity. *In vivo*, GH therapy has been associated with an increased risk of neoplasms of the lymphopoietic system, adrenal gland, ovaries and breast, both in animal models and in young humans who have received GH therapy[18,19], although such findings have not been confirmed by more recent reports[20–22].

A role for IGF-I in cancer development has also been suggested by the finding of higher IGF-I levels in patients suffering from prostate or breast cancer, although a precise explanation of the source of this IGF-I production is still awaited[23,24]. On the basis of these observations and the claim that IGF-I is a positive predictor of prostate cancer, the role of IGF-I in prostate development is currently under thorough investigation.

In a recent study[25], we assessed the effect of GH and IGF-I levels on prostate pathophysiology in 46 patients with acromegaly (30 with active disease, 10 cured and 6 with GH deficiency [GHD]) and 30 age-matched male controls (free from previous or concomitant prostate disorders), who were undergoing pituitary, androgen and prostate hormonal assessments and transrectal ultrasonography (TRUS). In patients with active disease, GH, IGF-I and IGF-binding protein-3 (IGFBP-3) levels were increased, and testosterone and dihydrotestosterone levels were reduced, compared with controls. Hypogonadism was present in 28 of the 46 patients with acromegaly (60.8%). The anteroposterior and transverse prostate diameters and the prostate transitional zone volume were increased in the patients with acromegaly compared with the controls. Prostate volume (PV) was significantly higher in untreated patients with acromegaly than in controls, cured and GH-deficient patients. In the patients with active disease, PV significantly correlated with disease duration ($r = 0.606$, $P < 0.0001$) and age ($r = 0.496$, $P < 0.0001$), whereas in controls it correlated with age ($r = 0.476$, $P < 0.01$) and IGF-I levels ($r = -0.448$, $P < 0.05$). Benign prostate hyperplasia (BPH; PV ≥ 30 ml) was found in 58% of the patients and 26.6% of the controls. When grouped by age (< 40 years, 40–60 years and > 60 years), PV was higher in elderly patients than in younger ones and controls. The prevalence of structural abnormalities, including calcifications, nodules, cysts and vesicle inflammation, was significantly higher in patients compared with controls (78.2 versus 23.3%; $\chi^2 = 5.856$, $P < 0.05$). No clinical, TRUS or cytological evidence of prostate cancer was detected in patients with acromegaly or controls. An increased prevalence of BPH and micro-/macro-calcifications was also found in young patients with acromegaly, despite the fact that all patients had secondary hypogonadism, as diagnosed by low testosterone levels[26]. After 1 year of treatment with octreotide (0.3–0.6 mg/day), normalization of circulating GH and IGF-I levels was achieved in seven of 10 patients. In these seven patients,

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TRUS significantly reduced the anteroposterior, transverse and craniocaudal diameters of the prostate. As a consequence, a significant decrease in PV was recorded. PV increased in two of the three patients who did not achieve normalization of GH and IGF-I after octreotide treatment[26].

In conclusion, although a number of reports suggest that longer exposure to elevated GH/IGF-I levels is associated with an increased risk of cancer, most epidemiological studies do not focus on strict biochemical criteria in evaluating this risk, and it is therefore not possible to exclude a direct cause–effect relationship as a result of the persistence of active disease. In particular, although a chronic excess of GH and IGF-I caused prostate overgrowth and other structural abnormalities, no case of prostate cancer was observed in our series. In fact, there appeared to be an overall reduction in the incidence of cancer events in those patients with acromegaly who achieved long-term biochemical remission with surgery, radiotherapy or pharmacotherapy, although long-term prospective studies are needed to confirm this finding.

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