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Value of early postoperative random growth hormone levels and nadir growth hormone levels after oral glucose tolerance testing in acromegaly

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ABSTRACT

Objective: There is no ideal marker to identify residual tumor tissue after surgery in patients with acromegaly. The purpose was to elucidate if early postoperative hormone testing gives reliable information regarding complete resection of a GH-producing pituitary adenoma.
Design: Fourty-eight patients undergoing surgery for acromegaly from 04/2013-05/2014 were prospectively examined for random GH, IGF1, and GH levels after oral glucose tolerance testing (OGTT) in the early postoperative phase and on follow-up. Criterion for inclusion was a minimum follow-up of one year for each patient with respect to remission.
Results: Thirty-three patients showed GH suppression below 1 µg/l after OGTT in the early postoperative phase. Follow-up GH, IGF1 and OGTT tests confirmed the initial findings in 30 patients. The three remaining patients showed biochemical signs of persisting acromegaly. In the remaining 15 patients early postoperative GH suppression was above 1 µg/l. Of those, six patients went into remission during follow-up, nine patients without postoperative GH suppression < 1 µg/l remained acromegalic.
Conclusions: GH suppression to < 1 µg/l as well as random GH levels below 1 µg/l in the early postoperative phase seem to be of good positive predictive value for long-term remission. However, several patients without suppression of GH to < 1 µg/l in the early postoperative OGTT went into delayed remission. These results have to be taken into account prior to initiation of further therapy.

1. Introduction

Transsphenoidal surgery is the treatment of choice for acromegaly [1–3]. Completeness of tumor removal is crucial for avoiding or minimizing the use of adjuvant therapies including pharmacotherapy and radiotherapy. Persistent disease in the long run is associated with increased morbidity and the risk of premature mortality [3,4]. Therefore the aim was to evaluate if early postoperative endocrinological markers predict the extent of resection and may justify early reoperation as it is successfully performed in Cushing's disease [5–7]. The surgical concept of early reoperation is based on nearly no additional access morbidity since no scarring has happened.

2. Material and methods

Fifty-four consecutive patients undergoing surgery for acromegaly from April 2013 until June 2014 were included in the prospective analysis. Preoperative GH and IGF1 levels were collected. Preoperative tumor size was measured on a standard MRI (T1 with and without contrast enhancement, sagittal, coronal and transversal planes) and a possible invasive growth was estimated. The patients were classified into a primary surgery group and a group of patients who had previously undergone surgery. Somatostatin-analog pretreatment was noted. Intraoperatively the surgeon subjectively classified the operation as complete resection, questionable complete resection or partial resection. Postoperatively, GH and IGF-1 (Immulite® 2000 (GH) Siemens/ Liaison® (IGF1) DiaSorin) levels were measured on the morning of postoperative day one (07.00 a.m.). An early postoperative oral glucose tolerance test (epOGTT) with GH-sampling using 75 g glucose was performed within the postoperative days 2–4. The diagnosis of acromegaly was confirmed by standard neuropathological work-up whenever possible. Subsequently, the patients were followed for a minimum

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of one year. A postoperative MRI after 3 to 6 months was performed and visible residual tumor mass was documented. The patients were scheduled for routine follow-up every 6 months. Further follow-up data on GH and IGF1 were performed by the referring endocrinologists. In case of pathological IGF1 results, a follow-up OGTT was performed. For this study, the last follow-up is reported. Remission was defined by means of all collected values according to the current criteria (normalized IGF-1 plus either a random GH < 1 µg/l or a nadir GH < 0.4 µg/l after OGTT). Graphs were drawn using the Graph pad prism (GraphPad Software, Inc./USA).

3. Theory

In 2000, the Cortina Consensus Conference established general criteria for the diagnosis and biochemical control of acromegaly, which have been revised in recent years and adapted to emerging clinical evidence as well as evolving assay techniques. According to those recent consensus statements, postoperative cure in the long-term is defined by age-normalized Insulin-like growth factor 1 (IGF1) levels, a random growth hormone (GH) < 1 µg/l, and nadir GH after oral glucose tolerance testing (OGTT) < 0.4 µg/l [2,3,8–10]. We prospectively investigated whether the early postoperative random GH or the GH after OGTT gives reliable information regarding the resection grade of a tumor and performed a follow-up of at least one year.

4. Results

The fifty-four consecutive patients included 27 male and 27 female patients (Fig. 1). Due to the consecutive patient cohort this gender distribution happened by chance. Six patients were lost to follow-up (two of those patients were lost for complete follow-up due to missing epOGTT and additionally four patients did not provide their follow-up data). The remaining 48 patients with a minimum of one year follow-up (median: 16 months, range: 12–22 months) were evaluated (Table 1). There were no missing data. The patients' age ranged from 22 years to 80 years with a median age of 46 years (male: 43 years, female: 49 years). 42 patients had the primary diagnosis of acromegaly, six patients were previously surgically treated for acromegaly. 31 adenomas were macroadenomas, the remaining 17 were microadenomas. Fourteen tumors were classified as invasive according to MRI studies. Five patients received either cabergoline, octreotide/lanreotide or pegvisomant pretreatment. Four other patients had undergone both previous surgery and SSTR- analog pretreatment in the past. Any pretreatment had been discontinued more than eight weeks prior to the current admission. Thirty of the 48 patients (63%) were classified as complete resection by the surgeon, in fourteen of 48 patients (29%) the surgeon was unsure regarding completeness of resection, and four patients (8%) underwent intended debulking/partial resection of large invasive adenomas (Table 2). None of the patients had pituitary insufficiencies before or after surgery. Immunohistochemical markers assessed can be seen in Table 3. The intra-assay variability for GH was 4.97% and the intra-assay variability for IGF1 was 6.47%, both calculated in a quality control over the six months previous.

Of the 48 patients enrolled, 33 showed GH suppression below 1 µg/l after OGTT in the early postoperative phase. Follow-up by GH (Fig. 2), IGF1 (Fig. 3), OGTT and MRI confirmed the initial findings in thirty of 33 patients (91%). The three remaining of 33 patients had persisting biochemical signs of acromegaly (9%). In fifteen patients, GH suppression was above 1 µg/l in the early stage. Six of those 15 patients went into remission during follow-up (40%). The remaining nine of 15 patients without postoperative GH suppression showed persistent disease (60%). Based on the thesis that detection of residual tumor mass by epOGTT could be useful mainly in cases with surgically questionable complete resection, the collective was divided into groups according to surgeons' impression of resection grade (Table 4). However, these analyses also failed to show a significantly correct prediction. Correct

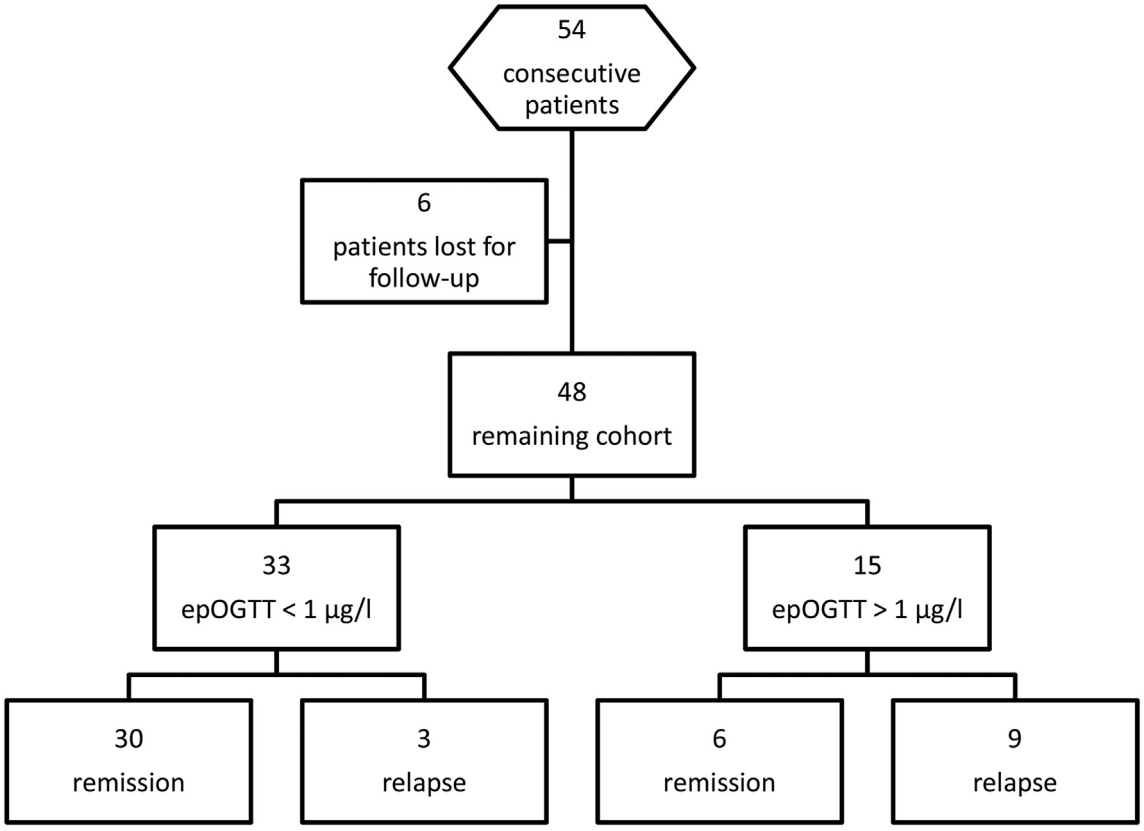

Fig. 1. Long-term remission in relation to epOGTT.