REVIEW PAPERS

Predictors of long-term remission in acromegaly – an updated review

Czynniki przepowiadające długotrwałą remisję akromegalii – przegląd piśmiennictwa

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KEYWORDS:

- acromegaly
- long-term remission
- predictors

ABSTRACT

Acromegaly is a rare chronic disorder due to growth hormone (GH) – secreting pituitary tumor. The first-line treatment of acromegaly is a transsphenoidal adenomectomy. Surgical remission rates range from 30-50% for macroadenomas to 70-90% for microadenomas. Thus in patients with active acromegaly after surgery, medical treatment is recommended. Treatment outcome on medical therapy differs a lot depending on medications.

The aim of this paper is to summarize the current knowledge of factors predicting acromegaly remission after surgery and biochemical control on medical treatment.

Factors affecting treatment outcome, not related to the patient and the tumor, are neurosurgeon's experience and visualisation tools used during surgery. Younger patients, as well as women tend to achieve acromegaly remission after surgery less often. Patients with lower GH and insulin-like growth factor-1 (IGF-1) concentrations at diagnosis, in oral glucose tolerance test (OGTT) and postoperatively have a greater chance of surgical remission. However, some publications do not confirm that. Patients presenting with larger and more invasive tumors achieve surgical remission less often. Hypointensive tumors on T2-weighted magnetic resonance imaging (MRI) scans are associated with better response to first-generation somatostatin receptor ligands (SRLs) and to pasireotide. Pathologic factors increasing the chance of acromegaly remission are densely granulated tumors, lower Ki-67 index, high expression of somatostatin receptors (SSTRs) and high expression of E-cadherin.

A thorough analysis of the above mentioned factors predicting the treatment outcome in acromegaly may be helpful for selecting the best treatment option for each patient.

SŁOWA KLUCZOWE:

- akromegalia
- długotrwała remisja
- czynniki przepowiadające

STRESZCZENIE

Akromegalia jest rzadką, przewlekłą chorobą powodowaną w większości przypadków przez guz przysadki wydzielający w nadmiarze hormon wzrostu (GH). Leczeniem pierwszego wyboru w akromegalii jest przezklinowa resekcja guza przysadki. Odsetek remisji pooperacyjnej waha się od 30-50% w przypadku makrogruczolaków do 70-90% w przypadku mikrogruczolaków. U pacjentów z czynną akromegalią po leczeniu operacyjnym zalecane jest leczenie farmakologiczne. Skuteczność leczenia farmakologicznego również jest zmienna w zależności od stosowanych leków.

Celem pracy jest podsumowanie aktualnej wiedzy na temat czynników przepowiadających remisję pooperacyjną oraz dobrą odpowiedź na leczenie farmakologiczne w akromegalii.

Czynniki wpływające na skuteczność leczenia operacyjnego, niezwiązane z guzem i pacjentem, to doświadczenie neurochirurga oraz stosowany przez niego sprzęt. Zarówno młodsi pacjenci jak i kobiety rzadziej osiągają remisję akromegalii po leczeniu operacyjnym. Pacjenci z niższymi stężeniami GH i insulinopodobnego czynnika wzrostu-1 (IGF-1) w momencie rozpoznania akromegalii, podczas doustnego testu obciążenia glukozą (OGTT) oraz po operacji mają

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większą szansę na uzyskanie remisji. Jednak niektóre prace nie potwierdzają takich związków. Pacjenci z większymi i bardziej inwazyjnymi guzami rzadziej osiągają remisję pooperacyjną. Obecność guzów hipointensywnych w T2 w obrazowaniu rezonansem magnetycznym wiąże się z lepszą odpowiedzią na analogi somatostatyny pierwszej generacji i na pasireotyd. Do czynników histopatologicznych zwiększających szanse na remisję akromegalii należą cechy guza bogato-ziarnistego, niższe wartości wskaźnika proliferacji komórkowej Ki-67, wysoka ekspresja receptorów dla somatostatyny (SSTRs) oraz wysoka ekspresja E-kadheryny.

Dokładna analiza wspomnianych czynników przepowiadających skuteczność leczenia akromegalii może być pomocna przy doborze spersonalizowanego leczenia akromegalii.

Background

Acromegaly is a chronic disease caused in most cases by a growth hormone (GH) – producing pituitary tumor. Elevated GH levels lead to an overproduction of insulin like growth factor-1 (IGF-1) in the liver, which in turn results in disease symptoms such as coarsed facial features, enlargement of hands and feet, headaches and fatigue as well as comorbidities like hypertension, diabetes mellitus, nodular goiter, obstructive sleep apnea, chronic arthritis or osteoporosis (1). The first-line treatment of acromegaly is surgical adenomectomy of GH –producing tumor usually performed by a transsphenoidal approach. It is estimated that surgical treatment by an experienced neurosurgeon leads to disease remission in 70-90% of patients with a microadenoma and in 30-50% patients with a macroadenoma (2). In patients with persistent disease after surgery the medical treatment is recommended. First generation somatostatin receptor ligands (SRLs) are the first-line medical treatment with 25 to 40% of biochemical control of the disease (3, 4). Other medications used in acromegaly are dopamine agonists such as cabergoline with even lower efficacy compared to first generation SRLs. Biochemical control of acromegaly on cabergoline is estimated at 30% (5). In case of resistant acromegaly on first-generation SRLs, treatment with a second-generation SRL i.e. pasireotide or GH receptor antagonist – pegvisomant should be implemented leading to disease control in 39% (6) and 70-95% (7) for pasireotide and pegvisomant, respectively. It is still investigated which patients achieve acromegaly remission after surgery and on medical treatment. Such knowledge would be helpful by personalized treatment planning. Therefore, various groups of characteristics have been analyzed to indicate the best predictors of good treatment outcome. The aim of this paper is to summarize the current knowledge of factors predicting acromegaly remission after surgery and on medical treatment.

Demographic factors

The most commonly assessed demographic factors, which might affect the treatment outcome in acromegaly are age and sex. Guo et al. and Araujo-Castro et al. showed that younger patients face a greater risk of persistent disease after surgery (8, 9). This might be associated with the fact that younger patients usually present larger and more invasive tumors. Younger patients may also present a worse response to somatostain receptor ligands (SRLs) (10).

Gender differences in the course of acromegaly and treatment outcome were also often discussed. However, only a few studies confirmed gender disparities in terms of remission rates. Park et al. showed that premenopausal women have larger and more aggressive tumors with lower remission rates after surgery. However, among older patients no differences in surgical treatment outcome were found (11). Starke et al. presented lower remission rate in women, but the observation lost statistical significance in multivariate logistic regression analysis after considering biochemical and imaging characteristics (12). Lower immediate and long-term remission rate in women was also confirmed by Guo et al. (8).

Hormonal results

As far as hormonal predictors are concerned, many researchers have investigated GH and IGF-1 concentrations at diagnosis of acromegaly and at various stages of treatment. The interest in GH concentration concerned random GH, fasting GH and nadir GH in oral glucose tolerance test (OGTT) performed at various stages of the disease. It turned out, that GH concentration at diagnosis and shortly after surgery is one of the most commonly investigated hormonal result.

The majority of studies evaluating how hormonal results affect the treatment outcome in acromegaly analyze preoperative GH and IGF-1 concentrations. Higher random GH concentrations significantly decrease the remission rate (13-16). As far as IGF-1 is concerned some studies confirm its influence on long-term outcome (17, 18) and some do not (19, 20). In studies assessing both preoperative GH and IGF-1, the predictive value of GH concentration was higher that IGF-1 (12, 21). It might be attributed to the relationship between serum GH and IGF-1 which is linear below GH levels of approximately 20 ng/ml, but at higher levels of GH secretion IGF-I generation is maximally stimulated with no further increase in circulating IGF-1. However, when serum GH data are log10 transformed and plotted against serum IGF-I, a log-dose correlation is observed (22).

Immediate postoperative hormonal results also matter. It has already been shown that low GH concentration 24 to 48 hours after surgery predicts surgical remission of acromegaly (21, 23, 24). The postoperative GH cut-off values predicting remission range from 1 to 2.5 ng/mL. Some authors have analyzed nadir GH concentration in postoperative oral glucose tolerance test (OGTT) performed within the first week after surgery concluding that its concentration below 1 ng/mL can predict long-term postsurgical remission (23). Other studies confirming, that nadir GH in early postoperative OGTT is associated with long-term remission, were published by Feelders et al. (25) and Rotermund et al. (26).

Moreover, in early twenties the topic of short acting octreotide test in predicting the response to long acting SRLs was commonly raised. Biermasz et al. (27) showed that GH reduction below 5 ng/mL by intravenous octreotide predicts a good response to octreotide LAR treatment. Similar observations were made by Halperin et al., Wang et al., Halah et al. and Karavitaki et al. (28-31) who confirmed the predictive value of subcutaneous short octreotide test in predicting the response to long-term treatment. However,

the short octreotide test is not used in everyday practice for predictive purposes.

The predictive value of IGF-1 concentrations after surgery was also analyzed. Hazer et al. showed that over 50% decrease of IGF-1 concentration after the first month postoperatively is predictive of cure (32). In Antunes's et al. cohort IGF-1 concentration below 231% of upper normal limit (ULN) for sex and age matched groups measured one week after surgery predicted remission (24).

Imaging factors

Tumor size seems to be the simplest imaging factor which influences the treatment outcome.

Microadenomas have a higher remission rate in terms of surgical treatment compared to macroadenomas (33). Some researchers have indicated the cut-off values for maximal tumor diameter, below which the chance of long-term remission significantly increases. The above mentioned thresholds range from 1.5 to 2.0 cm. (21, 34-36) and are usually calculated using the ROC curves.

One of the most significant imaging characteristics in somatotroph tumors affecting the treatment outcome are features of invasion. They include extrasellar expansion and cavernous sinuses invasion. The invasive potential is often expressed by using the Knosp grade, which describes the localization of the lateral tumor wall in relation to intracavernous internal carotid artery using grades 0 to 4. A vast majority of studies have shown that invasion of the cavernous sinuses is a negative predictor of surgical remission (37, 38). Many researchers focused on Knosp grade as an indicator of tumor's invasion and demonstrated that lower Knosp grades are associated with a higher remission rate after surgery (16, 39).

Another imaging factor associated with long-term remission is the intensity of signal in T2-weighted MRI scans. It is estimated, that over 50% of somatotroph tumors are hypointense in MRI scan at diagnosis (40). Hypointense in T2 tumors are often smaller than iso- or hyperintense tumors, less often invade cavernous sinuses and present higher IGF-1 concentration (40). Hypointensity of the tumor in T2-weighted scans was associated with better response to first-generation SRLs – greater decrease in GH and IGF-1 concentrations and greater tumor shrinkage (10, 41). A similar association between T2-weighted scans and the response to medical treatment was observed for pasireotide (42).

Pathologic factors

Somatotroph tumors may be divided according to granulation pattern into sparsely granulated (SG) and densely granulated (DG) tumors. Granulation pattern was commonly investigated as a predictive factor of postsurgical remission as well as biochemical remission on medical treatment with first- and second-generation SRLs. The available literature indicates lower remission rate for SG tumors after surgical procedure (43, 44) and on medical treatment with first-generation SRLs and with pasireotide (45, 46). However, some studies do not confirm that (24, 47). It is worth to mention that the above observations were made on relatively small cohorts, not exceeding 105 patients. Another pathologic predictor of acromegaly remission is proliferation marker Ki-67. It is a nuclear antigen, present in all active cells – i.e., cells in all stages of cell cycle except for G0. Higher values of Ki-67 index usually related to tumor's proliferation potential and invasiveness are associated with lower remission rate. It was confirmed for both surgical (48, 49) and medical treatment (46, 49). The influence of p53 expression on treatment outcome was not so widely discussed so far. Sarkar et al. (47) and Haliloglu et al. (37) did not find significant association between p53 expression and remission rate in acromegaly.

Another pathologic factor influencing medical treatment outcome is somatostatin receptors (SSTR) expression. It seems obvious that high expression of SSTR improves the response to medical treatment with SRLs. High expression of SSTR type 2 is associated with a good response to first-generation SRLs (50, 51), whereas high expression of SSTR type 5 improves the response to pasireotide (45).

As far as the influence of immunohistochemistry (IHC) result on treatment outcome is concerned, studies assessing its influence on medical treatment outcome seem to be scarce. Prolactin (PRL) staining remains controversial in predicting surgical remission. There are some studies confirming predictive value of PRL staining. They show that positive PRL staining is associated with lower (52-54), higher (47) or similar remission rate (55) compared to pure GH-positive tumors. What is more, pure GH-positive tumors present better outcome than plurihormonal tumors (56). α-SU-staining also matters as far as surgical remission is concerned. Patients with α-SU-positive tumors have a greater chance of surgical remission (36).

E-cadherin is a transmembrane protein involved in cellular adhesion. Loss of E-cadherin expression is associated with gain of tumor cell motility and invasiveness. It was identified in human malignancies and was associated with invasion in prolactinomas. Nuclear staining of E-cadherin was also identified in malignancies as well as in pituitary adenomas. It is common in non-functioning pituitary adenomas and in GH-secreting pituitary adenomas, in which it correlates with tumor size and invasiveness. In acromegaly a high E-cadherin expression in tumor cells was associated with better response to SRLs (57, 58), but it was not confirmed by some authors e.g. Soukup et al. (59).

Other factors

There are also some factors affecting the treatment outcome and not related to patients or type of a tumor. First of all, a specialized, experienced neurosurgeon is one of the most important determinant of surgical remission. It has been shown, that increasing surgeon's experience improves postsurgical remission rate (32). The researchers have also studied the influence of visualization tools used during operation i.e. endoscope or microscope. A systematic review and meta-analysis from 2017 showed similar remission rates in patients operated via microscopic and via endoscopic approach. The only exception according to this publication was a group of patients with non-invasive macroadenomas, who achieved higher remission rates by endocsopic approach (60).

Predictive models of treatment outcome

Many authors raising the subject of predictors of treatment outcome in acromegaly use univariate and multivariate logistic regression analysis to indicate independent predictors

and to create predictive models. Factors in predictive models that often repeat in various publications are age, GH concentration, tumor diameter, Knosp grade and cavernous sinuses invasion (61). Older age, lower GH concentration, smaller tumor, lower Knosp grade and lack of cavernous sinus invasion are associated with a greater chance of surgical remission. One of such predictive models published recently showed that fasting GH concentration <8.63 µg/L, maximal tumor diameter <15.5 mm, normoprolactinemia and DG tumor were independent predictors of surgical remission. Independent predictors of good response to first-generation SRLs in this cohort were fasting GH concentration <36.6 µg/L and DG tumor (36).

Conclusions

To sum up, prediction possibilities in acromegaly seem to be relatively wide. They include a thorough analysis of the patient in different fields as well as combined analysis of several predictive factors. Older age, male sex, lower GH and IGF-1 concentrations, smaller tumor, lack of tumor invasion in MRI scan, densely granulated tumor, lower Ki-67 index and high expression of SSTR increase remission rate in acromegaly patients. Clinicians should always bear this in mind as it may be helpful by treatment planning and let select the best treatment option for each patient.

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