Evaluation of prognostic utility of MIB-1 and p53 expression in pituitary adenomas: correlations with clinical behaviour and follow-up results

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Pituitary adenomas (PAs) show a broad clinicomorphological spectrum. The proliferation activity, evaluated by MIB-1 labelling index (LI), and p53 expression have been pointed as predictive markers for invasiveness and progression. The aim of this study was to evaluate the proliferation rate and p53 expression and to look for any relationships with the clinical behaviour and follow-up results in a series of Bulgarian patients with PAs. A total of 93 patients with PAs (81 hormone-secreting, 12 non-functioning), who were operated on and followed up for a period of five years, were included. The MIB-1 LI and p53 expressions were determined by immunohistochemistry and correlated with various clinical and tumour variables. The whole group of PAs showed a low proliferation rate with evident variations in a small number of cases (MIB-1 LI = 0.50 ± 0.56, from 0.1 to 3.30). MIB-1 LI correlated with tumour size (p = 0.012) and was positively related with male gender (p = 0.23) and partial surgical resection (p = 0.036). We found no significant differences regarding the age, functional activity, invasion (n = 33), expansion (n = 37) and tumour recurrences (seven cases). Only 10 cases (10.8%) showed a focal, nuclear p53 immunoreactivity. The p53 positive tumours had higher proliferation rate (p = 0.0001) but no relationship with the other clinical and tumour variables. Among all cases, there was only one case with higher MIB-1 LI (3.3%), positive p53 expression and tumour recurrence after surgery. Our results show that most PAs have a low proliferation rate and lack of p53 expression, as well as no relationship with tumour invasion or postsurgical progression.

Keywords: pituitary adenoma; immunohistochemistry; proliferation rate; p53 expression

Introduction

Pituitary adenomas (PAs) are common neurosurgical lesions and have been reported to account for 10%—15% of all brain tumours.[1] They are most commonly encountered in patients between the third and fourth decade of life and can be present in both genders. Their clinical presentation is connected to the abnormal secretion of hormones (functioning adenomas) and/or the mass effect they have on neighbouring neural structures. The lesions that are big enough to have a clinically significant mass effect are most commonly non-functioning. PAs are highly differentiated tumours and arise from a certain cell type of anterior pituitary. Depending on the originating cell, the PA can secrete growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL), thyroid-stimulating hormone (TSH) and gonadotropins – luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The signs and symptoms of the particular disease that a functioning PA causes are the result of the specific hormonal abnormalities. Surgical treatment is complex and multidisciplinary. It consists of a thorough preoperative workup (physical examination, hormone panels and standard preoperative laboratory panels), surgical resection and postoperative follow-up of physical condition and hormone levels. Appropriate treatment with medication is also considered.

PAs show a broad clinicomorphological spectrum – from microadenomas to tumours with local invasion and recurrence after surgery. Tumour size, invasion and the adequacy of resection have been considered as important risk factors for recurrence or progression.[2] The growth of the pituitary tumour depends on the balance between the proliferating cells and the loss of tumour cells by apoptosis and ischemic or haemorrhagic events. The determination of cell proliferation activity has been suggested to be useful in making prognosis in anterior PAs. Landolt et al. [3] were the first who determine the proliferation-associated antigen Ki 67 in fresh-frozen specimens in a series of PAs. Ki-67 is a nuclear antigen expressed in G1, G2 and synthesis phases of the cell cycle but not in the resting G0 phase.[4] Today, the MIB-1 monoclonal antibody is the most commonly used one for the purpose of...
Clinical characteristics and follow-up of incidentally found adrenal tumours - results from a single tertiary centre

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Abstract: Aim: To evaluate the clinical features, hormonal activity and natural evolution of adrenal incidentalomas (AI) in patients investigated in a single endocrinological centre and compare the prevalence of metabolic disorders and hypertension between subjects with AI and the general population. Patients and methods: 515 patients with AI evaluated between 1995 and 2010 were retrospectively included in the study. Their anthropometric, clinical, metabolic and hormonal parameters were analyzed. Follow-up data was available for 142 patients. Results: Mean age of all participants was 53.45 ± 13.4 years (range 13 – 84) with strong female predominance – 376 (73%) vs. 139 (27%) males. Median size of AI was 28 mm (range 10 – 190 mm). Hormonal investigations revealed that 82.9% of patients harboured non-functioning adenomas, subclinical hypercortisolism was detected in 5.94%, overt Cushing’s syndrome – in 2.7%, pheochromocytoma – in 1.9% and primary aldosteronism was diagnosed in 1% of patients. Adrenal carcinoma was identified in 1.7%. The prevalence of metabolic abnormalities and hypertension did not differ between patients with subclinical Cushing’s syndrome and non-functioning adrenal adenomas. When compared to the general population, however hypertension, type 2 diabetes and metabolic syndrome were significantly more common in patients with hormonally inactive tumours. During the course of follow-up progression to overt hormonal hypersecretion was not observed. Conclusion: These results confirm other contemporary studies reporting lower rates of hormonally active and malignant lesions among AI as well as increased prevalence of hypertension and metabolic abnormalities in patients with non-functioning adrenal adenomas.

Keywords: Adrenal incidentaloma • Cushing’s syndrome • Pheochromocytoma • Primary aldosteronism

1. Introduction

Adrenal tumours constitute a heterogeneous group of neoplasms with diverse functional characteristics and evolution whose growing recognition in recent years exerts an increasing pressure on medical specialists and health care systems. In the last 25 years a large number of them are discovered by chance as a by-product of modern imaging techniques and are termed “incidentalomas”. The definition of adrenal incidentaloma includes any adrenal mass over 1 cm in diameter that is unexpectedly revealed in the course of diagnostic or therapeutic procedures undertaken for reasons unrelated to any clinical suspicion of adrenal dysfunction. Analyses of published autopsy series indicate prevalence of adrenal incidentalomas from 2.3% to 6% in the general population with age being the most important determinant: they are found in less than 1% in subjects < 30 years compared to almost 7% in individuals older than 70 years [1,2]. Prevalence data from abdominal and chest CT studies started from 0.35% in the 1980s and increased up to 4.4% with the wide-spread introduction of modern high-resolution scanners in recent years, approximating the percentage from autopsy series [3-6]. A wide range of pathologies such as primary or metastatic malignancies, pheochromocytoma, cortisol- or aldosterone-secreting adenomas may present as adrenal incidentalomas but the majority are benign adrenocortical adenomas that show no signs of hormonal hypersecretion [7]. The challenge for physicians lies in identifying the tumours that confer a significant health risk for the patient either by their malignant po-
Asymmetric Dimethylarginine (ADMA) and Soluble Vascular Cell Adhesion Molecule 1 (sVCAM-1) as Circulating Markers for Endothelial Dysfunction in Patients with Pheochromocytoma

One Sentence Summary: Circulating markers of endothelial dysfunction in patients with pheochromocytoma.

Authors

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Abstract

Background: Endothelial dysfunction is a common feature of hypertension and is associated with reduced nitric oxide bioavailability. The endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine (ADMA), and soluble adhesion molecules such as vascular cell adhesion molecule 1 (sVCAM-1) have been established as markers of endothelial dysfunction in a number of pathologic conditions including essential hypertension. There is little information, however, about these markers in endocrine hypertension.

Objective: To investigate the levels of circulating ADMA and sVCAM-1 in patients with pheochromocytoma.

Patients and methods: Serum ADMA and sVCAM-1 concentrations were assayed by ELISA technique in 18 patients with pheochromocytoma, 18 patients with essential hypertension (EH) and 18 healthy subjects serving as a control group.

Results: ADMA and sVCAM-1 levels were significantly elevated in pheochromocytoma patients compared to normotensive healthy controls (0.479 ± 0.072 vs. 0.433 ± 0.054 μmol/l, p = 0.037 and 690 ± 181 vs. 577 ± 108 ng/ml, p = 0.03, respectively). Patients with EH also had higher ADMA concentrations than the control group, but the difference was not significant (0.476 ± 0.075 vs. 0.433 ± 0.054 μmol/l, p = 0.06). No associations were found between the levels of ADMA, sVCAM-1 and some potential risk factors for endothelial dysfunction.

Conclusion: Endothelial function is impaired in patients with pheochromocytoma as indicated by the elevated circulating levels of ADMA and sVCAM-1. The lack of association of these markers with catecholamines, glucose and lipid abnormalities together with their comparable levels in EH patients suggests that endothelial dysfunction is most likely related to hypertension itself.

Introduction

Endothelium plays a crucial regulatory role in maintaining vascular homeostasis through the production and release of various vasodilator and vasoconstrictor substances [1]. Impairment of endothelial function by different cardiovascular risk factors is considered to be an early step in the pathophysiology of atherosclerosis and is characterized by decreased bioavailability of nitric oxide (NO). NO is one of the most important endothelium-derived vasoactive molecules. It is synthesized from L-arginine by the endothelial isoform of the enzyme nitric oxide synthase (NOS) [2] and causes vascular relaxation [3], prevents vascular inflammation by suppressing leukocyte adhesion [4] and preserves vascular structure through inhibiting smooth muscle cell proliferation [5]. The activity of NOS has been found to be competitively inhibited by the naturally occurring L-arginine analog asymmetric dimethylarginine (ADMA) [6] and since its discovery ADMA has been established as marker for endothelial dysfunction in a number of human disorders [7]. Furthermore, elevated ADMA is considered also to play a causative role in the atherosclerotic process [8]. Together with its inactive isomer – symmetric dimethylarginine (SDMA), ADMA is formed through proteolytic degradation of methylated arginine-containing nuclear proteins [9]. Both isomers are excreted through the kidneys but ADMA is also actively metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) which is expressed in various tissues and participates in the regulation of ADMA levels [10].
Treatment Outcome Results from the Bulgarian Acromegaly Database: Adjuvant Dopamine Agonist Therapy is Efficient in Less than One Fifth of Non-irradiated Patients

One Sentence Summary: We summarize the biochemical treatment outcome in acromegaly in Bulgaria during the last thirty years. We have emphasized on the treatment with dopamine agonists due to our significant experience before the recent introduction of somatostatin analogs in the routine clinical practice.

Abstract
Objective: We described biochemical outcome in regards to different treatment modalities in patients with acromegaly in Bulgaria.

Patients and methods: It was a retrospective analysis using data from the Bulgarian Acromegaly Database. Patients with eligible data on at least one treatment modality were included in the study. Disease control was assessed by both GH and IGF-1 values or by GH/IGF-1 alone in cases with one marker. Last follow-up was median 7.0 (range 0.5–51) years after diagnosis.

Results: We identified 534 patients with interpretable data, 65.4 % of whom were females. Overall surgical cure rate was 28.8 %. Adjuvant bromocriptine and cabergoline treatment was analyzed in 133 and 70 patients with disease control achieved in 18.8 % and 31.4 % respectively. Patients without prior radiotherapy had 16.3 % and 18.2 % control rates respectively. Predictors of response to dopamine agonist (DA) therapy were disease activity, radiotherapy and medication dose. Adjuvant somatostatin analog (SSA) treatment led to biochemical control in 38.6 % of 70 patients. Combination of SSA and cabergoline led to remission in 25 % of 20 patients. Growth hormone receptor antagonist (GHRA) alone or in combination resulted in remission in 61.5 % of 13 patients. Approximately one third of the patients were cured median 10 years after irradiation. Overall disease control was observed in 51.4 % of our patients increasing to 70.3 % in the last 5 years of the study period.

Conclusion: DAs are efficient in less than 20 % of non-irradiated patients. They are a good cost-effective alternative for carefully selected patients.

Introduction

Acromegaly is a rare chronic disorder characterized by increased mortality compared to the general population [1]. However, strict biochemical disease control proves to restore life expectancy close to normal rates [2]. Thus, appropriate treatment approach seems to be a cornerstone of this issue. Only analyses of big cohorts could give a realistic answer about the long-term efficacy of different treatment modalities and factors influencing disease outcome. Tools that could provide these answers are large databases or nationwide surveys on acromegaly, overcoming the bias created by small-numbered single-centre reports. In the last decade several national databases or surveys addressing treatment outcome have been described in the literature [3–14]. In 2008 a nationwide survey was initiated and an electronic acromegaly database was created with the collaboration of the endocrinology departments of all 5 medical universities in Bulgaria [15]. Individual patient data on demographics, diagnosis, morbidity and mortality, type of treatment and disease control was gathered from the medical records. Until recently the health-care system has been very restrictive, reimbursing only medical therapy with cabergoline. In this position we could assess the full potential of DAs, the overall control rates and compare them with other European registries.

Patients and Methods

Patients
All patients were derived from the Bulgarian Acromegaly Database which is a part of the whole database for pituitary and adrenal tumors [16]. Diagnosis, follow-up and especially prescription of medical therapy are centralized in the university hospitals allowing inclusion of practically all adequately treated patients in the country. The study period was defined by follow-
CLINICAL STUDY

Transforming growth factor β1 is not a reliable biomarker for valvular fibrosis but could be a potential serum marker for invasiveness of prolactinomas (pilot study)

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Abstract

Background: Transforming growth factor β1 (TGFβ1) signaling pathway is crucial for both human fibrogenesis and tumorigenesis.

Objective: This study aimed to investigate the usefulness of TGFβ1 and matrix metalloproteinase 2 (MMP2) as potential circulating markers for fibrotic valvular heart disease (FVHD) and invasiveness as well as of Fetuin A as a marker for calcification in patients with prolactinomas.

Design: The study population consisted of 147 subjects divided into four groups: 30 dopamine agonist (DA)-treated prolactinoma patients with proven FVHD and three control groups with normal echocardiograms: 43 DA-treated patients, 26 naïve patients, and 48 healthy subjects.

Results: We observed significantly higher serum TGFβ1 levels in all three patient groups than in the healthy subjects (21.4 ± 8.86 vs 19.1 ± 9.03 vs 20.7 ± 11.5 vs 15.8 ± 7.2 ng/ml; P = 0.032). Moreover, TGFβ1 levels were significantly higher in patients with macroprolactinomas and invasive prolactinomas than in those with microprolactinomas and noninvasive tumors respectively. In addition, a strong positive linear relationship between TGFβ1 levels and invasiveness score (r = 0.924; P < 0.001) and a moderate correlation between TGFβ1 levels and tumor volume (r = 0.546; P < 0.002) were observed in patients with invasive prolactinomas. By contrast, prolactin (PRL) levels exhibited a better correlation with tumor volume (r = 0.721; P < 0.001) than with invasiveness score (r = 0.436; P < 0.020). No significant difference was observed in Fetuin A levels between patients with FVHD and healthy controls. Results concerning MMP2 were unclear.

Conclusions: TGFβ1, MMP2, and Fetuin A are not reliable biomarkers for valvular fibrosis and calcification in DA-treated patients with prolactinomas, but TGFβ1 may represent a useful serum marker for tumor invasiveness. The simultaneous determination of TGFβ1 and PRL levels could improve the noninvasive assessment of prolactinoma behavior.

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Introduction

Long-term treatment of Parkinson’s disease with the dopamine agonists (DAs) pergolide and cabergoline has been established to be associated with a significantly increased risk of developing fibrotic valvular heart disease (FVHD) (1, 2, 3, 4). The process is triggered by the activation of the serotonin receptors (5HT2b), which are highly expressed in cardiac valves (5, 6, 7). Cabergoline, which possesses a complete 5HT2b agonistic activity, is the drug of choice in the treatment of prolactinomas, but the results of observational studies investigating the risk of FVHD in these patients are still controversial. Some of them have reported no relevant findings (8, 9, 10, 11, 12), five trials have observed clinically insignificant valvular changes (13, 14, 15, 16, 17), and only one study has reported an increased prevalence of moderate tricuspid regurgitation with a cumulative dose-dependent risk (18). Published data on the potential profibrotic effect of bromocriptine, a partial 5HT2b agonist, are exclusively limited (19). Although there are numerous case reports in the literature, only a few studies have been dedicated to this topic (13, 17, 20, 21). As drug-induced valvulopathy in Parkinsonian patients has been shown to be a cumulative dose-dependent process, for potentially at-risk groups, not only patients receiving high daily doses, but also those on low-dose long-term treatment, such as patients with invasive macroprolactinomas who are often on lifelong therapy, should be considered. In this context, the discovery of reliable circulating invasive markers for fibrosis would help in the early identification of asymptomatic subjects at an increased risk of developing FVHD.

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Incidence and prevalence of Cushing’s Syndrome in Bulgaria


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Introduction: Epidemiological studies on Cushing’s syndrome (CS) are rare, based on a limited number of cases and most of them are out of date.

The aim of the present study was to analyze the incidence and the prevalence of CS in Bulgaria and to present the basic demographic characteristics of the patients with this disease.
Patients and methods: This was a retrospective study, including 633 patients with proven CS, treated in the main endocrinological clinics in the country (Sofia, Varna, Plovdiv, Stara Zagora and Pleven).

Results: From a total of 633 patients, 86% (544) have been treated in the CCEG - Sofia, 8.7% (55) - in the UH „St. Marina” - Varna, 4% (26) - in the UH „Aleksandrovskas” - Sofia, 1.3 % (8) - in the UH „Sv. Georghi” - Plovdiv, 6 patients with CS, 2 of them have been hospitalized in the CCEG and 1 – in Plovdiv, in the UH „Stara Zagora” have been treated 3 patients with CS, of them have been followed afterwards in the CCEG.

Etiology: ACTH-dependant CS: 69,2% (Cushing’s disease: 66,3%; ectopic ACTH secretion: 2,9%); ACTH-independent CS: 30,8% (adenomas: 21,5%; carcinomas: 7,2%; ACTH – independent micro and macronodular hyperplasia: 2,3%). Srednata vâzраст pri diagnostiцhane на заболеванието бе 38 ± 12 г. Cъотношението жени: мъже бе 5:1 (жени 84%, мъже 16%). Средната заболеваемост бе 1,6 млн/година или 14 нови случая на година. Болестността за 2010 год. бе оценена на 32,6/млн жители.

Conclusions: In this first of its kind large clinical study, involving all the university clinics in the country, was estimated the incidence (1,6 mln/year) and the prevalence (32,6/mln habitants) of CS.

KEY WORDS: Cushing’s syndrome, incidence, prevalence
Фертилитет, бременност и лактация при жени с хиперпролактинемия

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Хиперпролактинемията е чест проблем в ендокринологичната и гинекологичната практика и представлява една от най-честите коригируеми причини за инфертитет при жените. Честотата на клинично изявената хиперпролактинемия варира в зависимост от изследваната популация: 0,5% сред здравите лица; 9% сред жени с аменорея; 25% сред жените с галакторея и 70% сред жените с аменорея-галакторея синдром (1,2).

Екзистиращата физиологична хиперпролактинемия е тази при бременност, при която нивата на серумния пролактин се покачват пропорционално с напредване на бременността и достигат ниво до девет от първата половина на третото тримесечие. Патологичните хиперпролактинемии могат да бъдат органични и функционални. Органична хиперпролактинемия се наблюдава при агеноми на хипофизата, пролактином при пролактином и соматопролактином (пролактином и соматопролактином). Функционалната хиперпролактинемия е поликлетиологичен съдържим и може да бъде медикаментозно индуцирана (при прием на неберемници, антигептасептици, опиати, орани контрацептиви, някои противопротези и антихипертензивни медикаменти и гр.) или да бъде резултат на редица състояния и заболявания, нарушаващи физиологичния допаминергичен инхибиторен контрол (прекъсване на хипофизната дръжка; хормонескретираща макроаденома, представляваща се клинично като "псевдопролактином", лифоцитарен хипофизом; метастази в хипоталамо-хипофизарната област и гр.). В случаите с лекото и средно повишена пролактинова нива трябва да се изключат заболявания като поликистоза, правичен хипотиреоидизъм, пролактиномия, както и предана на гастролабораторна грешика, докато се е наложило условия при вземането на кръвната проба. Пролактинът е изключително стресов хормон и за да се избегнат фалшиво позитивни резултати е необходимо вземането на Веноznата кръв да се извърши след поне 20-30-минутен покой в лежало или седноло положение.

Ефектът на хиперпролактинемията върху половата система се реализира на 3 нива: на хипоталамично ниво пролактинът инхибира пулсативната секреция на гонадотропния рилинг хормон (GnRH), на хипофизарно ниво се нарушава пулсативната секреция на LH и FSH и се блокира позитивната обратна връзка на естраденето; на яйчниково ниво е налице директно потискане на фоликулгенезата посредством пролактиновите рецептори в гранулоцитите и андрогени, както и инхибиране на синтезата на естраден и прогестерон. Резултатът е хронична ановулация, лека хиперандрогения, хипоандрогенопедогеназис (3-5).

Установяването на хиперпролактинемия налага извършване на разнообразно изследване на хипоталамо-хипофизарна област (предпоръчителна е магнитно-резонансна томография с контрастно усилване на образа) за изключване на органична причина.

Медикаментозното лечение с допаминови antagonisti (DA) е персистирано средство при всички случаи на хиперпролактинемия, включително пролактин-секретиращ агеном и особено при инвазивните макроаденоми, при които очакваният успех от хирургична интер-
Венция е малък (7-9). Индикациите за оперативно лечение са твърде ограничени. На трансфенозална агеномектомия посъществува консенсус за пролактинома, извънредно немелан реакции или резистентност в хода на лечението с ДА. Спешна индикация за неброкурична намеса е част от случаите на хипофизарна аполексия, а допълнителна индикация се явява изреченото желание на пациента да се лекува по хирургичен път (7,9,10). От друга страна, меканитозната терапия е превъзхождана, особено в случаите с пролактинома, защото цели не само трайно нормализиране на пролактиновите нива, но и намаляване на туморния обем. Консервативната терапия е базирана на физиологичния механизъм на регуляция на пролактината: синтезираните в хипоталамуса допамина, събързащи се с допамиnergичните рецептори клас 2 (D2-рецептори) в лактотрофите осъществява тоничен инхибаторен контрол върху пролактиновата синтеза и секреция. Допамиnergичните агонисти са синтетични аналоги на допамина с висок аfinity към D2-рецепторите. Над-широко използваните препарати в клиничната практика са Каберголин, Бромокриптин и по-рядко Явинагонол.

С оглед на слабото нежелано стървенство на пролактиновите риска от кислни условии (хипопитутиаризм, съдоби инсулин и втро- рични неопласти) радиотерапията се явява "средство на отчаяние", към което се пристъпва при изчерпване на възможностите на хирургичната и меканитозната терапия при агресивно инвазивни тумори и при изключително редки случаи на малгант пролактинома. От литературни данни стабилна нормопролактинемия се постига при една една трета от лекуваните само с радиотерапия пациенти (11-13).

Установяването на хиперпролактинемия при жена в репродуктивна възраст поставя при основни въпроса: как да бъде възстановени фертилитетът; необходимо ли е лечение по време на образност; към кояли или поставява- ване на терапията с допаминови агонисти.

I. Възстановяване на фертилитета при жени с хиперпролактинемия

Постизането на нормална пролактинова нива при част от функционалните хиперпролак-тинемии е лесно. При меканитозното инсулинизиране хиперпролактинемия нормопролактинемия се постига в кратък срок след преустановяване на приема на медикамента, което е преизкушено (14,15). Акжеи Видмата субститу- рация терапия на първичния хипопитутиаризъм се последва от нормализиране на нивата на ТСХ и пролактина. Реален проблем представлява органичната хиперпролактинемия при пролак-тином, която налага прецизна преценка на те- ражевтичния подход, особено в случаите с макроидномем. След започване на лечение с ДА възстановяването на обусловите настъпва бързо, понеже кори стресс нормализирате на на мениструалния цикъл. От друга страна, трябва да се вземе под внимание факта, че по време на образност хипофизата може да увличи дълго обема със 2 до 3 пъти за сметка на хипертрофия на лактотрофите. Нелекуваните прегрупи временната, препоръчителна планови образност, след тази нормализиране на пролактиновите нива и редукция на туморния обем. Пациентките могат да се привлекат с голям мотив и при прием на образността намалява рискът на пълн. В тези случаи е превъзхождението на пролактиновите нива и тема на образността. По време на образността намалява тониче- ната, но трябва да се има предвид, че на фона на образността ендовенозноят за 15-30% от дените в началото на образността, което намалява възможността на пролактиновата агонист. Пациентките с инфантиталната на базата на макроиднометъм и непосредствен резистентност което ДА са показани за хирургич- на интервенция - трансфенозална агеномекто- мия (7,9).

II. Хиперпролактинемия и образност

Функционалните хиперпролактинемия не налагат лечението с ДА по време на образността. След постигане на образността лечение трябва да се преустанови. Наклона рандомизирани плезио-контролирани проучвания години след прекъсване на образността. Бъдееше по време на образност. Няма данни за повишен риск от съмнен образност, екстремна образност или вродени аномалии при деца, родени от майки, забременели на фона на образността (16-19). Каберголин е въ- веден в клиничната практика 20 години след прекъсване на образността. На базата на индикациите за хайфенозална агеномектомия (7,9).
II. Prolactinomas and Lactation

III. Prolactinomas and Lactation


