ORIGINAL PAPER

Submitted: 20.02.2024
Accepted: 13.04.2024
Early publication date: 06.05.2024

Endokrynologia Polska
DOI: 10.5603/ep.99452
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 75; Number/Numer 3/2024

Lymphocytic hypophysitis — various course of the disease and individualized therapeutic approach. An algorithm of the follow-up

***Łukasz Kluczyński*[1], *Edyta Tkacz*[2], *Anna Grochowska*[3], *Małgorzata Wójcik*[4], *Grzegorz Zieliński*[5], *Alicja Hubalewska-Dydejczyk*[1], *Aleksandra Gilis-Januszewska*[1]**

[1]*Chair and Department of Endocrinology, Jagiellonian University, Medical College, Krakow, Poland*
[2]*Department of Endocrinology, Oncological Endocrinology, Nuclear Medicine and Internal Medicine, University Hospital, Krakow, Poland*
[3]*Department of Radiology, University Hospital, Krakow, Poland*
[4]*Department of Paediatric and Adolescent Endocrinology, Paediatric Institute, Jagiellonian University, Medical College, Krakow, Poland*
[5]*Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland*

Abstract

Introduction: Lymphocytic hypophysitis (LH) is a rare inflammatory disorder of the pituitary or/and hypothalamus with variable disease course: from spontaneous remission to pituitary atrophy. The diagnosis, treatment and follow-up remain challenging. The aim of the study is to present long-term data and an individualized therapeutic approach and propose an algorithm for the follow-up of patients with probable LH.

Material and methods: A retrospective analysis of 18 consecutive adult patients (13 W/5 M, mean age 45.2 years) with LH diagnosed and treated in a tertiary referral center.

Results: The first manifestations were headaches (50.0%), polyuria/polydipsia (33.3%) and symptoms of hypopituitarism (16.7%). Somatotropic, adrenal, gonadal and thyroid axis insufficiencies were found in 44.4%, 33.3%, 33.3%, and 27.8% of patients, respectively. Arginine vasopressin deficiency was diagnosed in 8 patients (44.4%). Some of the dysfunctions were transient. Magnetic resonance imaging (MRI) revealed thickened pituitary stalk in all but 2 cases. In 2 patients an anterior pituitary lesion, most likely inflammatory was described. Four patients were given steroids (severe headaches) with clinical recovery and stable/improved MRI. One woman was operated on due to the progressive mass-related symptoms — histopathological examination confirmed LH. In the remaining 13/18 patients watchful waiting approach allowed to obtain hormonal and radiological stabilization/improvement.

Conclusions: LH is a disease with a complex clinical picture and challenging diagnosis. Treatment requires an individual approach: vigilant observation is the cornerstone of therapy, with steroid/surgical treatment reserved for cases with mass-related symptoms. Further multicenter research might help in better understanding of the LH and creating standards of care in this rare disease. **(Endokrynol Pol 2024; 75 (3): 300–309)**

Key words: *arginine vasopressin deficiency; hypophysitis; hypopituitarism; stalk enlargement*

Introduction

Various pathologies causing inflammation within the pituitary gland and its stalk are collectively referred to by the term hypophysitis. Primary forms of the disease affect only pituitary region, occurring without involvement of other organs. Histologically, lymphocytic, granulomatous, xanthomatous, IgG4-related and necrotizing variants of hypophysitis are distinguished [1]. Mixed types of the disorder were reported as well [2]. In this study we focused on and described patients with lymphocytic hypophysitis (LH). Inflammation limited to the anterior pituitary lobe (adenohypophysitis) is the most common and stands for 65% of cases, the involvement of the entire gland and posterior pituitary lobe/stalk occurs in 25% and 10%, respectively [1, 3]. In the secondary variant of hypophysitis, the pituitary gland is one of the organs affected by systemic process. A growing number of reports document the need to exclude a neoplastic background of hypophysitis in the first place [4]. The spectrum of clinical manifestations ranges from an almost asymptomatic course to a rapidly progressing disease. Observed symptoms may be related to the effects of tumor mass, arginine vasopressin deficiency (AVD), hormonal deficits as well as hyperprolactinemia [2]. Although pituitary biopsy remains the gold diagnostic standard, due to its invasiveness, the disease diagnosis is based on clinical, radiological and biochemical assessment. Magnetic resonance imaging (MRI) is the primary method of

Aleksandra Gilis-Januszewska, Assoc. Prof., Chair and Department of Endocrinology, Jagiellonian University Medical College, ul. Jakubowskiego 2, 30–688, Krakow, Poland, tel/fax: +48 12 400 23 00; e-mail: myjanusz@cyfronet.pl

visualizing the pituitary gland area [2]. In the majority of patients, hormonal testing reveals some degree of pituitary dysfunction [1]. Adrenal axis insufficiency is relatively common, may be the only abnormality and requires prompt detection and treatment [1]. Hormonal disorders can be transient, recurrences are also seen [5]. All patients stand in need of a holistic approach to establish an accurate diagnosis and identify possible underlying systemic disease.

Material and methods

The study is based on retrospective analysis of demographic, clinical and biochemical data of consecutive 18 adult patients (13 women and 5 men) with probable primary hypophysitis. All of them were diagnosed and monitored between 2015 and 2023 in the Department of Endocrinology, Jagiellonian University in Krakow. A part of the cohort are patients with childhood-onset diseases who were initially under the care of the Department of Pediatric and Adolescent Endocrinology, Pediatric Institute, Krakow. A diagnosis of hypophysitis was based on the clinical presentation, biochemical assessment (frequent transient hormonal deficits) and typical radiological abnormalities in MRI as well as the exclusion of other diseases that may affect the hypothalamic-pituitary area. One case was confirmed by histopathological examination — the patient was operated on because of the primary diagnosis of sellar tumor.

Imaging

In all patients the hypothalamic-pituitary area was visualized by MRI with administration of gadolinium contrast, in most of them multiple times during follow up. The MRI records were reviewed and verified by the radiologists and neurosurgeon experienced in assessing pituitary pathology. Homogenous enhancement of pituitary gland and thickened, non-deviated infundibulum, lack of the posterior lobe signal and dural tail sign were considered as the most characteristic imaging determinants for LH [6]. The normal pituitary stalk tapers from the level of optic chiasm, where it measures 3.25 ± 0.56 mm to 1.91 ± 0.4 mm at the connection with the pituitary gland on 1.5 T MRI [7]. These values are 3.35 ± 0.44 mm and 2.16 ± 0.37 mm, respectively, on 3 T MRI scans [8]. Following Doknic et al. we considered an enlargement of more than 2-3 mm in the MRI as stalk thickening [7]. Additional techniques such as ultrasonography, x-rays, computed tomography (CT) and nuclear medicine imaging were used in the diagnosis/exclusion of systemic process.

Laboratory assessment

The hormonal function of both lobes of the pituitary gland was assessed. In order to confirm the correct function of adrenal axis, adrenocorticotropic hormone (ACTH) and morning cortisol measurements were performed, as well as stimulation tests with cosyntropin or corticotropin-releasing hormone (CRH), if necessary. Deficiencies of gonadal and thyroid axes were diagnosed based on low levels of peripheral hormones in combination with a lack of expected increase in concentration of trophic hormones [luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol in premenopausal women/testosterone in men as well as thyroid-stimulating hormone (TSH) and free thyroxine (fT4), respectively]. Decreased age and sex adjusted values of insulin-like growth factor 1 (IGF-1) were considered suggestive for somatotropic axis dysfunction. During primary evaluation in Pediatric Institute, some patients with suspected growth retardation were tested with insulin, arginine, glucagon and clonidine in different constellations to verify growth hormone deficiency. AVD diagnosis included biochemical assessment and the water deprivation test, if recommended. In suspicion of generalized disease additional measurements of organ-specific, inflammatory or neoplastic markers and the QuantiFERON test were performed.

The treatment and follow up

Decision regarding the treatment and follow up was discussed during the Pituitary Tumor Board consultations in the presence of endocrinologists, a radiologist, a neurosurgeon and a radiotherapy specialist experienced in the pituitary pathology. Patients were followed up according to the internal algorithm based on the literature and our own experience.

Statistics

The Microsoft Excel (Microsoft Office 365, Microsoft Corporation, Redmond, USA) was used for collection and analysis of patient data.

Results

Eighteen patients (13 W/5 M) with probable lymphocytic hypophysitis were identified. The clinical and imaging data, the treatment strategy and the follow up of all patients are presented in Table 1. Mean age at diagnosis was 45.2 years (48.6 for W, 36.4 years for M). Headaches and polyuria/polidypsia were the first manifestation in 9 and 6 cases, respectively, while 3 patients presented with clinical symptoms of adrenal insufficiency (nausea, vomiting, muscle pain, weakness). During hormonal assessment, hypocortisolism was detected in 6 patients, of which 4 were of a transient nature. Eight patients were diagnosed with AVD (one temporary) and probable GH deficit was suspected in 8 patients (in 2 — transient). Gonadal axis dysfunction was detected in 6 cases (in 2 — transient), while central hypothyroidism was found in 5 patients – in all cases permanent. Four patients presented with hyperprolactinemia. One woman had insufficiencies of all anterior pituitary axes (except for elevated prolactin values) and AVD. Two patients maintained normal hormonal pituitary function. MRI revealed thickened pituitary stalk (max. 12 mm) in all but two cases; in two — lack of the posterior lobe signal. In two patients a lesion in the anterior pituitary lobe was described, which may correspond to an area of inflammation. Partially empty sella was visualized in one women with temporary adrenal axis insufficiency (Fig. 1). The hormonal substitution was administered appropriately to the deficits; due to the severe headaches 4 patients were given steroids (2 in intravenous pulses, 2 — orally) with subsequent reduction in the frequency and severity of complaints and stable/improved image of pituitary area in the control MRI. One woman was operated due to the progression in the pituitary tumor size and mass effect-related symptoms — histopathological examination confirmed LH. In the remaining (data available for 13 patients) cases watchful waiting approach allowed to obtain hormonal and radiological stabilization/improvement (in 5 and 8

Table 1. *The clinical and imaging data, treatment strategy and the follow up in patients with suspected lymphocytic hypophysitis (n = 18)*

Patient	Sex	Age	Age at diagnosis	Clinical presentation	ACTH	GH/IGF-1	TSH	LH/FSH	PRL	ADH	MRI findings	Strategy	MRI follow-up	Autoimmune abnormalities
					[1 — normal, 0 — deficit, e — elevated, t — transient]									
EA	F	56	51	Headaches, polyuria/polydipsia	1	1	0	1	1	0	Stalk thickening 5.5 mm	Steroids *i.v.*	Regression	no
MK	F	43	35	Headaches	1	1	0	1	1	1	Stalk thickening 3.5 mm	WW	N/d	no
RK	M	27	23	Polyuria/polydipsia	1	t	1	t	e	0	Stalk thickening 5.0 mm	WW	Regression	ANA+
KP	F	73	67	Vomits, nausea, headaches	t	1	0	t	1	t	Stalk thickening 3.5 mm	WW	Regression	vitiligo, RF+
TW	M	79	71	Headaches	1	1	1	1	1	1	Stalk thickening 3.6 mm	Steroids *p.o.*	N/d	RF+, ANA+
BI	M	66	62	Polyuria/polydipsia	1	1	1	1	1	0	Stalk thickening 4.0 mm	WW	Stabilization	AITD
IS	F	73	60	Headaches	0	0	0	0	0	1	Tumor 18x15x12 mm, stalk involvement	Surgery	Empty sella	AITD
PC	F	41	40	Weakness, muscle pain, pre-syncope	t	1	1	1	1	1	Partially empty sella	WW	Empty sella	AITD
MP	F	39	38	Weakness, vertigo, hypotension	t	0	1	1	1	1	Anterior lobe lesion 5x6 mm, stalk 3.0 mm	WW	Regression	ANA+
KF	F	39	37	Headaches	1	0	1	1	1	1	Stalk thickening 12.0 mm; anterior Lobe lesion 4x2 mm	Steroids *i.v.*	Regression	ANA +
AK	F	40	37	Headaches	1	0	1	1	1	1	Stalk thickening 5.5 mm	WW	Stabilization	no
BZ	F	53	52	Headaches	1	1	1	1	1	1	Stalk thickening 4.0 mm	WW	Regression	AITD
JR	F	62	57	Polyuria/polydipsia	t	1	1	0	1	0	Stalk thickening 5.0 mm	WW	Stabilization	no
MU	F	46	46	Headaches	1	t	1	1	e	1	Stalk thickening 5.6 mm	WW	Stabilization	no
KB	M	25	10	Polyuria/polydipsia	1	1	1	1	1	0	Stalk thickening 4.1 mm	WW	Regression	no
KS	M	17	16	Polyuria/polydipsia	1	1	1	1	1	0	Stalk thickening 4.2 mm	WW	Planned	no
MB	F	70	69	Headaches	1	0	1	0	e	1	Stalk thickening	WW	Regression	no
ASM	F	44	43	Polyuria/polydipsia	0	0	0	0	e	0	Stalk thickening 18.0 mm	Steroids *p.o.*	Progression	no

F — female; M — male; ACTH — adrenocorticotropic hormone; GH — growth hormone; IGF-1 — insulin-like growth factor 1; TSH — thyroid-stimulating hormone; LH — luteinizing hormone; FSH — follicle-stimulating hormone; PRL — prolactin; ADH — antidiuretic hormone; MRI — magnetic resonance imaging; WW — watchful waiting; *i.v.* — intreavenously; *p.o.* — per os; N/d — no data; ANA — anti-nuclear antibodies; RF — rheumatoid factor; AITD — autoimmune thyroid disorder

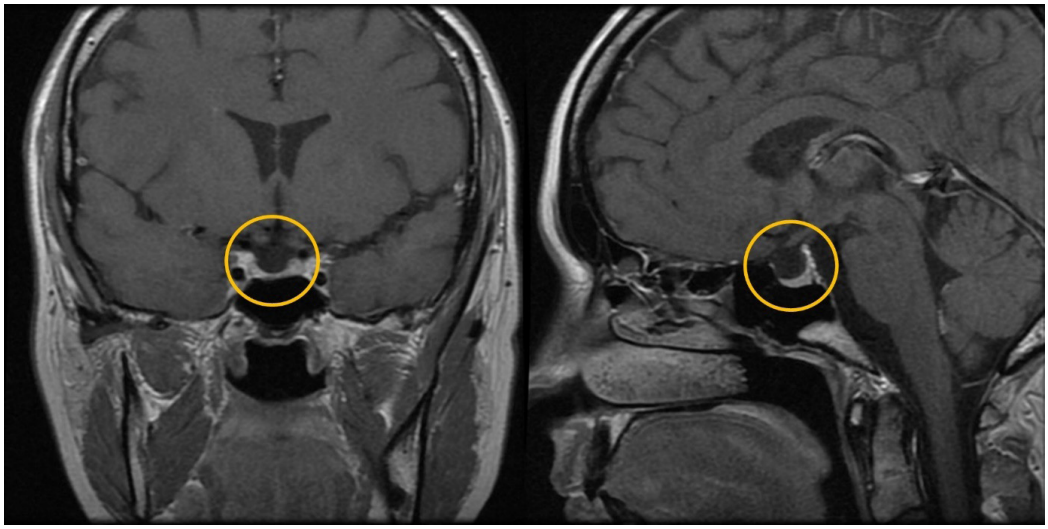

Figure 1. *Pituitary magnetic resonance imaging (MRI) T1 with contrast media. Partially empty sella in women with hypophysitis*

patients, respectively). The return to normal pituitary function in the case of transient hormonal abnormalities lasted from several months to 3 years.

Various course of the disease and individualized therapeutic approach

In this section, we present three cases with different course of the LH, reflecting the need for an individualized therapeutic approach to each patient.

1. A 37-year-old woman without chronic conditions reported daily headaches beginning in September 2021. Persistent pain, mainly located in the frontal area, radiating to the right orbit, was refractory to treatment with non-steroidal anti-inflammatory drugs. Additionally, the patient complained of irregular prolonged periods since the pregnancy in 2007, with menstruation stopping 3 years ago. The brain MRI revealed a homogenous lesion within the infundibulum (8 × 9 × 11 mm with intense enhancement after contrast administration) — radiological suspicion of LH was raised. In the hormonal evaluation decreased level of IGF-1 was detected as well as inappropriately low values of TSH, LH and FSH in relation to free thyroid hormones and estradiol were found. Adequate increase of gonadotropins and TSH was confirmed with gonadoliberin and thyrotropin-releasing hormone (TRH) stimulation tests, respectively — it suggests hypothalamus involvement or/and impaired function of pituitary stalk. Adrenal axis and prolactin were normal; no symptoms of AVD were found. MRI of the pituitary gland showed thickening of the pituitary stalk 8 × 7 × 12 mm and additionally area of 4x2 mm within the anterior lobe — suspicion of microadenoma (Fig. 2). Due to the severe headaches systemic steroid therapy was introduced. Between January and December 2022, the patient received a total of 4625 mg of methylprednisolone in intravenous pulses. Additional treatment with azathioprine was attempted, but the drug was discontinued due to bad tolerance. Recent MRI showed a slight reduction in the stalk size (current dimensions 7 × 7 × 11 mm), the lesion in the anterior lobe was not visualized (possible regression of inflammatory changes). The patient reported less intense headaches. Hormonal status remained unchanged — l-thyroxin substitution was started, the patient is waiting for the gynecological consultation and probable introduction of hormonal replacement therapy.
2. A 59-year-old woman with Hashimoto thyroiditis and suspicion of autoimmune liver inflammation was admitted to the Endocrinology Department in December 2008 in order to diagnose incidentally detected adrenal tumor. During hospitalization, based on hormonal tests the insufficiency of adrenal, thyroid and gonadal axis was detected. Prolactin was normal and no biochemical or clinical determinants of AVD were found. Data about function of somatotropic axis is missing. MRI showed intra- and suprasellar tumor of 18 × 15 × 12 mm that infiltrated the infundibulum along its entire length. Due to the radiological image suggesting pituitary macroadenoma, the patient was sent for transsphenoidal surgery. Postoperative histopathological examination revealed a typical microscopic and ultrastructural image of lymphocytic hypophysitis and biochemical assessment confirmed multihormonal anterior pituitary lobe insufficiency. AVD was excluded. The follow-up MRI visualized residual lesion in the sella turcica, which regressed

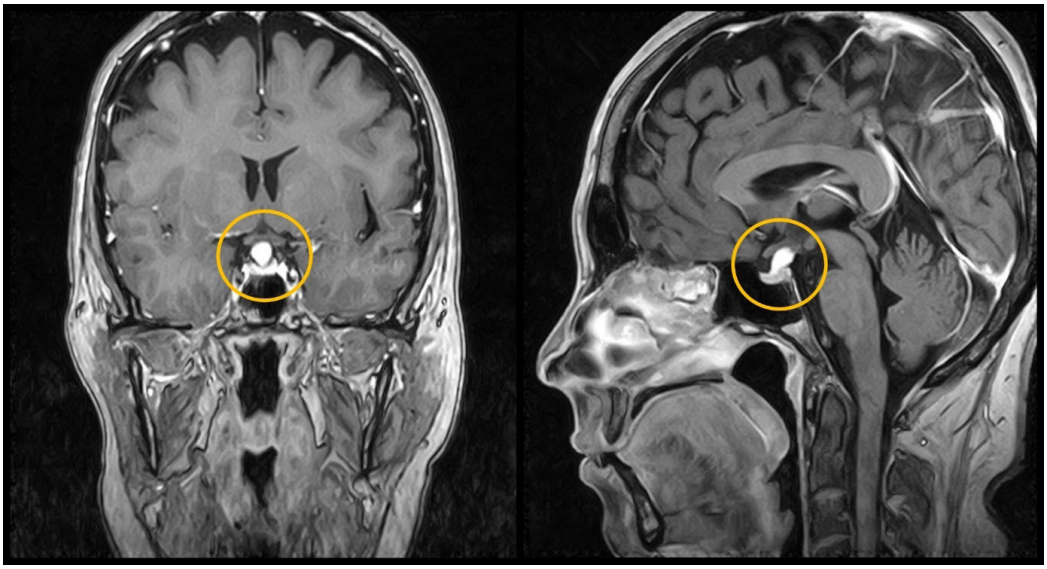

Figure 2. *Pituitary magnetic resonance imaging (MRI) T1 with contrast media. A significant stalk enlargement in 37-year-old woman with lymphocytic hypophysitis*

to dimensions of 3x5x6 mm in 2013 and remained stable in subsequent imaging studies. Patient is currently well controlled on hydrocortisone and levothyroxine substitution.

3. Polidypsia and polyuria were the first symptoms of the disease in a 22-year-old man with no known sickness burden. Although the patient was an amateur kickboxer, there was no history of significant head trauma. Water deprivation test performed in the regional hospital confirmed the diagnosis of AVD and the treatment with desmopressin was introduced with improvement. A thickened pituitary stalk (do 4.5 mm) as well as lack of the posterior pituitary lobe signal were detected in MRI. Mild hyperprolactinemia and dysfunction of both gonadal and somatotropic axes were diagnosed during hormonal assessment. The pituitary MRI showed enlargement of the infundibulum to 5 × 5 × 5 mm (Fig. 3A). Extensive testing were performed to rule out systemic background of observed abnormalities without relevant findings. Lymphocytic hypophysitis was diagnosed and due to the lack of significant symptoms the patient was under further monitoring. After several months stalk size normalization (2.5 × 3 × 3 mm) was observed in the control MRI (Fig. 3B). Biochemical evaluation confirmed reconstitution of the gonadal axis; prolactin level was normal. No new hormonal

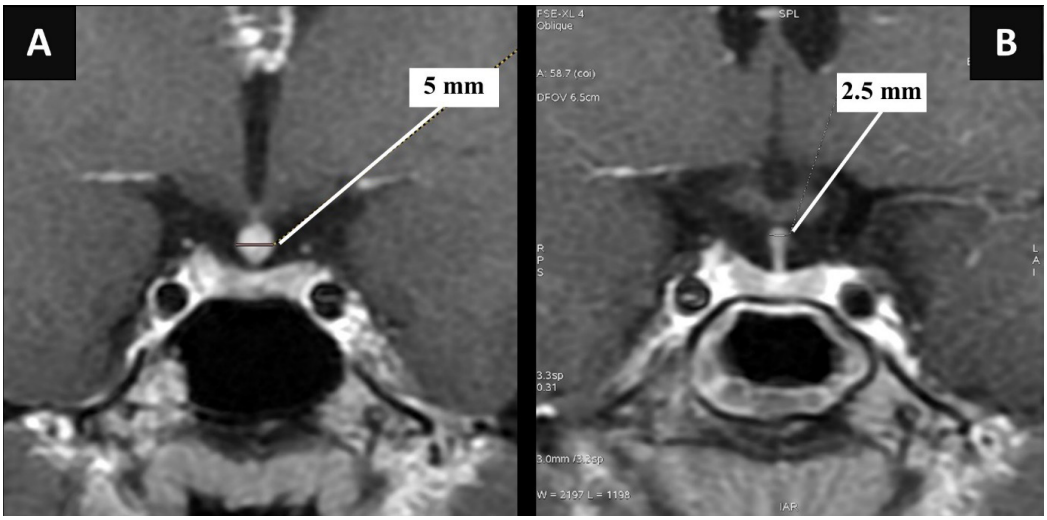

Figure 3. *Pituitary magnetic resonance imaging (MRI) T1 with contrast media — spontaneous normalization of stalk size in 22-year-old patient with lymphocytic hypophysitis.* **A.** *June 2018;* **B.** *January 2019*

abnormalities were found during follow-up, but AVD was persistent and only transient improvement in IGF-1 value was noticed.

Discussion

In our study we retrospectively analyzed long term follow up data of consecutive 18 adult patients with suspected primary hypophysitis examined and treated in specialized endocrinology tertiary clinical center. A clear diagnosis of the disease is only possible through histopathological examination, however pituitary biopsy as an invasive procedure with high risk of serious complications is very rarely performed [1]. In most cases, the diagnosis can be based on thorough clinical assessment, biochemical and imaging tests as well as exclusion of other possible pituitary pathologies [9]. A number of disorders should be included in differential diagnosis. Distinguishing sellar tumor from hypophysitis is particularly difficult, especially since both pathologies can coexist [10]. Many systemic conditions such as sarcoidosis, Langerhans histiocytosis or Erdheim-Chester disease may cause inflammation in the pituitary gland. Sporadically pituitary involvement is the only manifestation of these disorders, which is a particularly difficult diagnostic challenge. Hypohysitis is relatively often associated with other autoimmune diseases and may be a part of autoimmune polyglandular syndromes [1]. Abnormalities suggesting autoimmune disorders were found in half of our patients. Autoimmune thyroiditis was detected in 4 cases; in 4 patients, the titer of ANA antibodies was borderline positive (Tab. 1). Multiple infections such as tuberculosis or syphilis, may present with involvement of the pituitary gland as well [11]. Recent studies from Japan emphasize the need for search of neoplasms, as the lymphocytic hypophysitis may be the paraneoplastic syndrome [4]. Antibodies produced by malignant lesions can cause isolated hormonal deficits. Among others, thymomas, colon and lung cancers were identified as the source of such abnormalities [4]. Exclusion of the systemic process is particularly important in the elderly patient with concomitant hormonal insufficiencies and "red flag" symptoms. Significant attention should be paid to patient education due to the possibility of developing new/resolving existing hormonal disorders or revealing a systemic disease, as hypophysitis may precede it for years [12, 13]. Moreover, recurrences are occasionally observed, after surgical treatment as well [5, 10].

In a demographic context, most reports indicate a significant predominance of women among patients with LH. In various studies, the percentage share of women in the research group ranged from 59 to 91% [6, 11, 14]. Last meta-analysis showed 78% women among the total 355 patients evaluated [15]. Accordingly, in our cohort, women accounted for 72.2% of cases (female to male ratio of 2.6:1). Originally, it was postulated that LH often occurred during pregnancy or the postpartum period [16]; more recent reports did not confirm this association [6, 14, 15, 17]. Only one woman from our study showed temporal coincidence with miscarriage several months earlier. The mean age of patients in different studies varied quite significantly, from 31 to 47 years; our population is in the upper part of these values (mean age 45.2 years).

The clinical picture of hypophysitis depends on symptoms related to enlarged sellar structures or hormonal disturbances. It is worth emphasizing that the first phase of the disease may be asymptomatic [18]. In one of the largest studies including 79 patients with hypophysitis headaches and visual disturbances were present in 55% and 22%, respectively. AVD was diagnosed in 54% cases from this group [6]. A recent multicentric, retrospective study from Argentina among 22 patients headaches were reported in 68%, symptoms of AVD in 50%, and visual disturbances in 48% of patients [17]. Our observations remain similar — 9/18 (50.0%) patients complained of headaches, 6/18 (33.3%) were diagnosed with AVD. Symptoms of anterior hypopituitarism (weakness, nausea, vertigo, muscle pain) were initial manifestation in 3/18 (16.7%) of cases.

Hormonal assessment of pituitary gland is essential. Both anterior and posterior lobe function should be evaluated. What is very important, due to the dynamic nature of the disease, a test with cosyntropin may not be suitable for reliable verification of the functioning of the adrenal axis. Some authors postulate the use of insulin induced hypoglycemia in the early phase of the disorder [2]. There are reports about normal pituitary function in patients with lymphocytic hypophysitis [19]. In our group only one patient retained intact pituitary function, the rest showed at least temporary disturbances in its function. Somatotropic, adrenal, gonadal and thyroid axis insufficiencies were detected in 44.4% (8/18), 33.3% (6/18), 33.3% (6/18) and 27.8% (5/18), respectively. There are large discrepancies in the literature regarding the incidence of hormonal disorders. In study performed by Honegger et al LH/FSH deficit was the most common, followed by TSH and ACTH (62, 48 and 47%, respectively) [6]. In the recent Chinese meta-analysis insufficiency of gonadal axis predominated (54%); secondary hypoadrenalism was present in 49%, followed by central hypothyroidism and GH deficit in 42 and 22%, respectively [15]. Also in the Argentine study, hypogonadotrophic hypogonadism predominated [17]. Relatively frequent and early-onset secondary hypocortisolism as well as transient character of hormonal deficits are typical for hypophysitis [11].

The high frequency of somatotropic hypofunction in our study may result from an incomplete evaluation of this axis based only on the values of IGF-1. Long term follow-up documented recovery of adrenal axis function in 4 patients. Somatotropic axis insufficiency was transient in 2 patients, hypogonadism was temporal in 2 as well. Secondary hypothyroidism was persistent in all patients. Return to the correct hormonal function lasted from several months to 3 years. There is lack of data on predictive factors determining the probability and time of recovery of pituitary axes. Hyperprolactinemia may be caused by stalk compression, direct destruction of lactotrophs in the inflammatory process, or result from the presence of specific antibodies [1, 20] — elevated level of prolactin was found in 4 cases (22.2%). AVD was confirmed in 8 cases (1 transient), which constitutes 44.4% of cases. In available reports, the incidence of AVD ranged from 17 to 81.8% of cases [11, 21, 22], with the occurrence of 45% reported by Jia-Sheng in the meta-analysis consisting of 364 patients [15]. It is possible that some cases with isolated AVD symptoms and poorly expressed manifestation of anterior pituitary dysfunction may be not classified as hypophysitis [23, 24]. AVD may result from autoimmune reaction or be an effect of the stalk/posterior pituitary lobe compression. The presence of an enlarged pars tuberalis, disturbing the transport function of the infundibulum, explain the occurrence of AVD in cases of adenohypophysitis [25]. AVD in the course of hypophysitis in most often permanent [17], its occurrence may be a negative predictor of response to steroid treatment [26]. Coexistence of anterior hypopituitarism and AVD is very rare in pituitary adenomas and may be an important differentiating factor [11].

Typical radiological characteristics of hypophysitis are thickened, non-deviated stalk, homogenous pituitary image before and after contrast enhancement, lack of posterior lobe signal as well as intact sellar bone structures [27, 28]. Dural involvement may present as dural tail sign, that is common also in meningiomas [2]. Despite all of these well-known features, up to 40-50% of lymphocytic hypophysitic cases are primarily mistaken for pituitary tumors [29]. Gutenberg et al suggested a score to help distinguish hypophysitis from pituitary adenoma [27]. Frequent imaging is essential to control the size of inflammatory lesions: in the majority of cases stabilization or regression of the infiltrates is observed (12/18 patients from our cohort). Rarely, the course of the disease lead to the need for surgical treatment. There are some reports describing the empty sella as a final stage of lymphocytic hypophysitis as well [29, 30] — we found similar changes in one case with probable recurrent disease. 2 patients were lost to follow-up and no result were obtained from repeat MRI, in one man control imaging was scheduled.

An individual approach is essential in the care of patients with hypophysitis. Our study proves that careful observation combined with hormonal replacement lead to stabilization or partial recovery in the vast majority of cases. Glucocorticoid therapy is connected with potential numerous side effects and should be reserved for patients with intense mass-related symptoms. Treatment with other agents such as azathioprine, rituximab and cyclosporin A was attempted with success [31–33]. Poor tolerance of azathioprine did not allow continuation of therapy in one patient from our group. Surgical treatment is necessary in rare cases of patients with persistent or rapidly progressing symptoms as well as resistance to pharmacological treatment. Among our patients, initially severe symptoms led to the surgery in one woman; the other is awaiting operation due to progression in control. A reduction in tumor mass was found in 43% of patients in the observation group, 62.5% of patients undergoing surgery and 50% patients taking immunosuppressive drugs [17]. In general, both medical and surgical treatment are more effective in achieving radiological improvement, but recovery of hormonal function was documented only in 17% (versus 27% in watchful waiting), resulting in the need for long term substitution [3]. The explanation may be based, at least in part, on the mechanism of the disease — hormonal disturbances are the effect of cell destruction resulting from inflammatory infiltrates rather than compression by an abnormal sellar mass [1].

The shortcomings of our study is the relatively small study and incompleteness of some date. The strength of the work is the analysis of data of all consecutive patients, diagnosed and treated in one tertiary clinical center with a multidisciplinary pituitary team consulting vast majority of cases. Another important issue is very long follow-up, in some cases lifelong.

There are no specific guidelines in the literature regarding the control of patients with lymphocytic hypophysitis. Based on the available data and our own experience we suggest an algorithm of follow-up (Fig. 4), including baseline biochemical and radiological assessment as well as proposed control points. Its purpose is to provide real help in everyday practice, with the individualized management depending on the clinical scenario.

The dynamic course of the disease makes the patient's vigilant attitude towards new abnormalities extremely important. Patients should be informed or given a written instruction on how to identify and react in case of symptoms of arginine vasopressin deficiency, adrenal insufficiency or mass effect.

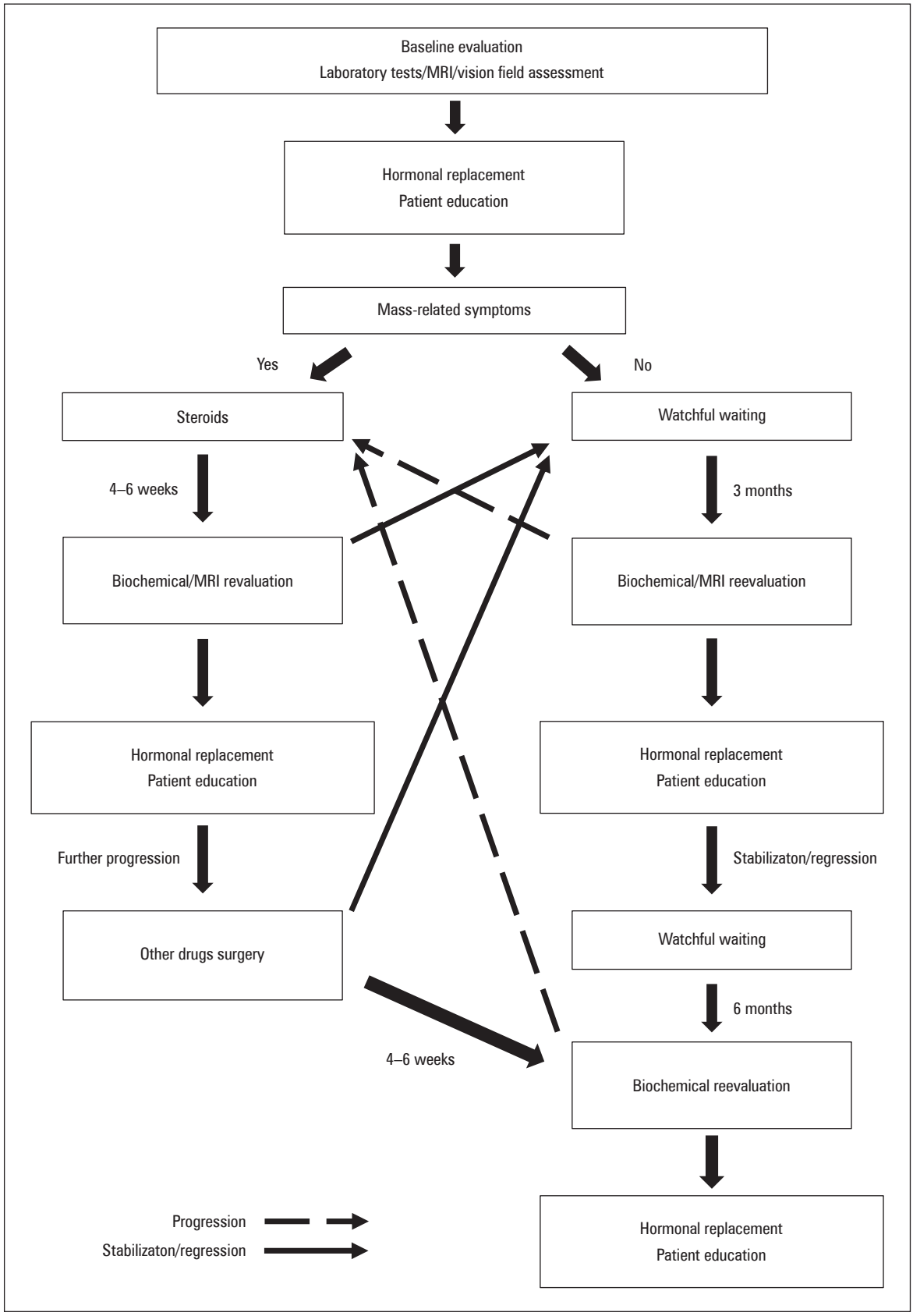

Figure 4. *A suggested algorithm of follow-up in patients with primary hypophysitis. MRI — magnetic resonance imaging*

Conclusions

Lymphocytic hypophysitis is a disease with a complex clinical picture. Non-specific, transient characteristic of the symptoms and hormonal deficits cause difficulties in establishing proper diagnosis.

A thorough clinical evaluation, biochemical assessment and MRI remain mainstays of management. The treatment may vary depending on the clinical and hormonal status. Individual approach is necessary. In patients without severe mass related symptoms, watchful surveillance along with hormonal substitution may be the optimal approach. Further multicenter research might help in better understanding of the lymphocytic hypophysitis, to create standards of care and follow up in this rare disease.

Data availability statement

Data available from the corresponding author on request.

Ethics statement

The study was approved by ethics committee (decision 1072.6120.110.2019 of 04/29/2019).

Author contributions

All authors listed have contributed sufficiently to the project to be included as authors. Ł.K. — data collection and analysis, writing the manuscript; E.T. — data collection and analysis; A.G. — data collection and analysis; M.W. — data collection and critical review; G.Z. — critical review; A.H.-D. — critical review; A.G.-J. — design, writing the manuscript and critical review

Funding

The study is a part of a project "Assessment of the health condition of patients with hypopituitarism in Poland" (grant N41/DBS/000408).

Conflict of interest

Authors declare no conflicts of interest.

References

1. Caturegli P, Newschaffer C, Olivi A, et al. Autoimmune hypophysitis. Endocr Rev. 2005; 26(5): 599–614, doi: 10.1210/er.2004-0011, indexed in Pubmed: 15634713.
2. Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in Endocrinology: Hypophysitis: diagnosis and treatment. Eur J Endocrinol. 2018; 179(3): R151–R163, doi: 10.1530/EJE-17-0009, indexed in Pubmed: 29880706.
3. Prete A., Salvatori R. Hypophysitis. Endotext. NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK519842/ (13 May 2020).
4. Takahashi Y. Paraneoplastic autoimmune hypophysitis: a novel form of paraneoplastic endocrine syndrome. Endocr J. 2023; 70(6): 559–565, doi: 10.1507/endocrj.EJ23-0050, indexed in Pubmed: 37045779.
5. Yang GQ, Lu ZH, Gu WJ, et al. Recurrent autoimmune hypophysitis successfully treated with glucocorticoids plus azathioprine: a report of three cases. Endocr J. 2011; 58(8): 675–683, doi: 10.1507/endocrj.k10e-334, indexed in Pubmed: 21666339.
6. Honegger J, Schlaffer S, Menzel C, et al. Pituitary Working Group of the German Society of Endocrinology. Diagnosis of Primary Hypophysitis in Germany. J Clin Endocrinol Metab. 2015; 100(10): 3841–3849, doi: 10.1210/jc.2015-2152, indexed in Pubmed: 26262437.
7. Doknic M, Miljic D, Pekic S, et al. Single center study of 53 consecutive patients with pituitary stalk lesions. Pituitary. 2018; 21(6): 605–614, doi: 10.1007/s11102-018-0914-2, indexed in Pubmed: 30276501.
8. Satogami N, Miki Y, Koyama T, et al. Normal pituitary stalk: high-resolution MR imaging at 3T. AJNR Am J Neuroradiol. 2010; 31(2): 355–359, doi: 10.3174/ajnr.A1836, indexed in Pubmed: 19797792.
9. Caturegli P, Dalmazi GDi, Lombardi M, et al. Hypophysitis Secondary to Cytotoxic T-Lymphocyte–Associated Protein 4 Blockade. Am J Pathol. 2016; 186(12): 3225–3235, doi: 10.1016/j.ajpath.2016.08.020, indexed in Pubmed: 27750046.
10. Leung GKK, Lopes MBS, Thorner MO, et al. Primary hypophysitis: a single-center experience in 16 cases. J Neurosurg. 2004; 101(2): 262–271, doi: 10.3171/jns.2004.101.2.0262, indexed in Pubmed: 15309917.
11. Langlois F, Varlamov EV, Fleseriu M. Hypophysitis, the Growing Spectrum of a Rare Pituitary Disease. J Clin Endocrinol Metab. 2022; 107(1): 10–28, doi: 10.1210/clinem/dgab672, indexed in Pubmed: 34528683.
12. Yamamoto M, Iguchi G, Bando H, et al. Autoimmune Pituitary Disease: New Concepts With Clinical Implications. Endocr Rev. 2020; 41(2), doi: 10.1210/endrev/bnz003, indexed in Pubmed: 31513261.
13. Bando H, Iguchi G, Kanie K, et al. Isolated adrenocorticotropic hormone deficiency as a form of paraneoplastic syndrome. Pituitary. 2018; 21(5): 480–489, doi: 10.1007/s11102-018-0901-7, indexed in Pubmed: 30008158.
14. Chiloiro S, Tartaglione T, Angelini F, et al. An Overview of Diagnosis of Primary Autoimmune Hypophysitis in a Prospective Single-Center Experience. Neuroendocrinology. 2017; 104(3): 280–290, doi: 10.1159/000446544, indexed in Pubmed: 27165294.
15. Ju JS, Cui T, Zhao J, et al. Clinical presentation and magnetic resonance imaging characteristics of lymphocytic hypophysitis: a systematic review with meta-analysis. Arch Med Sci. 2023; 19(4): 976–986, doi: 10.5114/aoms/144628, indexed in Pubmed: 37560735.
16. Gutenberg A, Hans V, Puchner MJA, et al. Primary hypophysitis: clinical-pathological correlations. Eur J Endocrinol. 2006; 155(1): 101–107, doi: 10.1530/eje.1.02183, indexed in Pubmed: 16793955.
17. Tkatch J, Szuman G, Agüero M, et al. [Primary hypophysitis: diagnosis and treatment multicenter study]. Medicina (B Aires). 2023; 83(5): 744–752, indexed in Pubmed: 37870332.
18. Caturegli P, Iwama S. From Japan with love: another tessera in the hypophysitis mosaic. J Clin Endocrinol Metab. 2013; 98(5): 1865–1868, doi: 10.1210/jc.2013-1912, indexed in Pubmed: 23650339.
19. Rumana M, Kirmani A, Khursheed N, et al. Lymphocytic hypophysitis with normal pituitary function mimicking a pituitary adenoma: a case report and review of literature. Clin Neuropathol. 2010; 29(1): 26–31, doi: 10.5414/npp29026, indexed in Pubmed: 20040330.
20. Bellastella A, Bizzarro A, Coronella C, et al. Lymphocytic hypophysitis: a rare or underestimated disease? Eur J Endocrinol. 2003; 149(5): 363–376, doi: 10.1530/eje.0.1490363, indexed in Pubmed: 14585081.
21. Wang S, Wang L, Yao Y, et al. Primary lymphocytic hypophysitis: Clinical characteristics and treatment of 50 cases in a single centre in China over 18 years. Clin Endocrinol (Oxf). 2017; 87(2): 177–184, doi: 10.1111/cen.13354, indexed in Pubmed: 28423475.
22. Park SMi, Bae JiC, Joung JiY, et al. Clinical characteristics, management, and outcome of 22 cases of primary hypophysitis. Endocrinol Metab (Seoul). 2014; 29(4): 470–478, doi: 10.3803/EnM.2014.29.4.470, indexed in Pubmed: 25325267.
23. Imura H, Nakao K, Shimatsu A, et al. Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. N Engl J Med. 1993; 329(10): 683–689, doi: 10.1056/NEJM199309023291002, indexed in Pubmed: 8345854.
24. Abe T. Lymphocytic infundibulo-neurohypophysitis and infundibulo-panhypophysitis regarded as lymphocytic hypophysitis variant. Brain Tumor Pathol. 2008; 25(2): 59–66, doi: 10.1007/s10014-008-0234-8, indexed in Pubmed: 18987830.
25. De Bellis A, Bizzarro A, Perrino S, et al. Characterization of antipituitary antibodies targeting pituitary hormone-secreting cells in idiopathic growth hormone deficiency and autoimmune endocrine diseases. Clin Endocrinol (Oxf). 2005; 63(1): 45–49, doi: 10.1111/j.1365-2265.2005.02296.x, indexed in Pubmed: 15963060.
26. Lupi I, Cosottini M, Caturegli P, et al. Diabetes insipidus is an unfavorable prognostic factor for response to glucocorticoids in patients with autoimmune hypophysitis. Eur J Endocrinol. 2017; 177(2): 127–135, doi: 10.1530/EJE-17-0123, indexed in Pubmed: 28626085.
27. Gutenberg A, Larsen J, Lupi I, et al. A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. AJNR Am J Neuroradiol. 2009; 30(9): 1766–1772, doi: 10.3174/ajnr.A1714, indexed in Pubmed: 19628625.
28. Caranci F, Leone G, Ponsiglione A, et al. Imaging findings in hypophysitis: a review. Radiol Med. 2020; 125(3): 319–328, doi: 10.1007/s11547-019-01120-x, indexed in Pubmed: 31863360.
29. Amereller F, Küppers AM, Schilbach K, et al. Clinical Characteristics of Primary Hypophysitis — A Single-Centre Series of 60 Cases. Exp Clin Endocrinol Diabetes. 2021; 129(3): 234–240, doi: 10.1055/a-1163-7304, indexed in Pubmed: 32770534.
30. Karaca Z, Tanriverdi F, Unluhizarci K, et al. Empty sella may be the final outcome in lymphocytic hypophysitis. Endocr Res. 2009; 34(1-2): 10–17, doi: 10.1080/07435800902841306, indexed in Pubmed: 19557587.
31. Angelousi A, Cohen C, Sosa S, et al. Clinical, Endocrine and Imaging Characteristics of Patients with Primary Hypophysitis. Horm Metab Res. 2018; 50(4): 296–302, doi: 10.1055/s-0044-101036, indexed in Pubmed: 29458219.

32. Bellastella G, Maiorino MI, Bizzarro A, et al. Revisitation of autoimmune hypophysitis: knowledge and uncertainties on pathophysiological and clinical aspects. Pituitary. 2016; 19(6): 625–642, doi: 10.1007/s11102-016-0736-z, indexed in Pubmed: 27503372.

33. Schreckinger M, Francis T, Rajah G, et al. Novel strategy to treat a case of recurrent lymphocytic hypophysitis using rituximab. J Neurosurg. 2012; 116(6): 1318–1323, doi: 10.3171/2012.2.JNS111456, indexed in Pubmed: 22443503.