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LONG-TERM NATURAL HISTORY OF GIANT NULL CELL PITUITARY ADENOMA

Pituitary adenomas that extend to the ventricular system are extremely rare. We present a 5-year natural history of a giant null cell pituitary adenoma with invasion into the cavernous sinus extending to the third ventricle. MRI series that were available could be useful for neurosurgeons, ophthalmologists, and endocrinologists as well as radiologists. Patients with the diagnosis of pituitary adenoma that are certain according to the radiological and clinical examination should be consulted by a neurosurgeon experienced in endoscopic endonasal surgery, a neuroendocrinologist, and an ophthalmologist. The surgery postponement in such cases results in disability and quality of life worsening. At that time, the surgery of giant pituitary adenomas demands high skills, and the risk of postoperative complications is high. The proper treatment modality including earlier surgery seems to be favorable for patient outcome.

Keywords: giant pituitary adenoma, null cell, third ventricle, endoscopic endonasal transsphenoidal surgery.

The overall understanding of pituitary adenoma (PA) biology has grown up for the last decades due to immunohistochemistry (IHC) and histopathology. It has been suggested to classify pituitary adenomas as PitNETs — pituitary neuroendocrine tumors [1, 2]. A null cell PA (NCPA) is defined as a lesion of the anterior lobe of the pituitary gland (adenohypophysis) with the obligatory absence of the clinical hormone expression, the negative IHC reactions for pituitary hormones, and the lack of the expression of any pituitary transcription factors [3, 4]. The aggressiveness and rapid growth with a positive Ki-67 reaction in 3% and more of tumor cells are the characteristic features of NCPA [5].

NCPA is a rare tumor. A comprehensive literature search with the use of the PubMed database covering the period from September 2003 to December 2018 with the search query "giant null cell pituitary adenoma" results only in eight studies.

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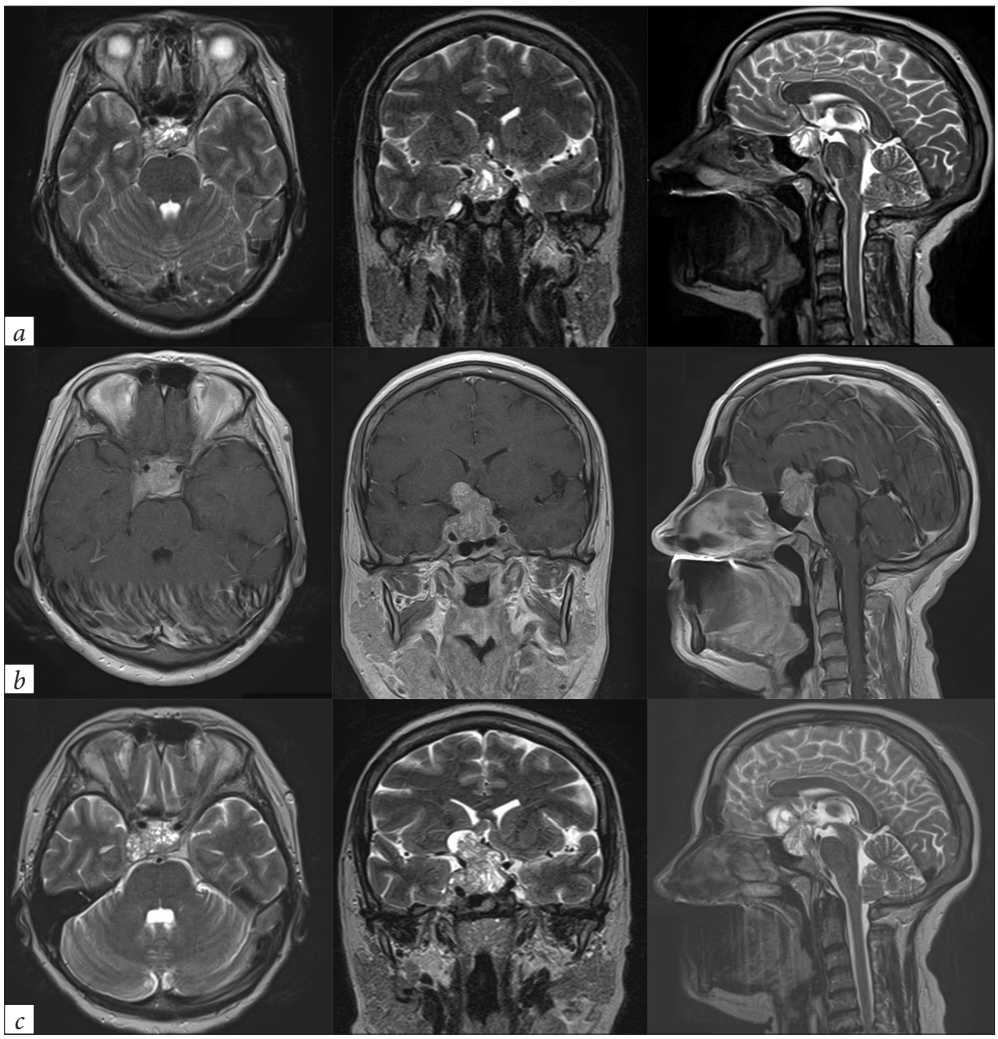

Fig. 1. Series of axial, coronal, and sagittal MR images. (*a*) December 2015. Non-enhanced T2-weighted MRI showing a macroadenoma 25.8 × 17 × 21 mm with asymmetric suprasellar extension and obvious compression of the optic chiasm and right cavernous sinus invasion up to 6 mm (III-a type, by Knosp et al.). Tumor has a heterogeneous structure due to areas of cystic change. (*b*) December 2016. Contrast-enhanced T1-weighted MRI. Compared to the previous survey, tumor increased in size up to 32 × 21 × 28 mm. (*c*) December 2017. Non-enhanced T2-weighted MRI showing tumor progression up to 35 × 32 × 28 mm, mostly due to the ante-suprasellar part

We present a 5-year natural history of giant NCPA invading into the cavernous sinus and extending to the third ventricle.

A 57-year-old female referred to our clinic after an unsuccessful wait-and-see strategy and the treatment in a local hospital with the complaints of severe visual impairment in the right eye, left-sided visual field defect, headache, and weakness.

The previous case history was such as follows. The PA was diagnosed in 2015 after the first MRI (Fig. 1, *a*). With a serum prolactin level of 25.99 μg/mL, the patient was referred to an endocrinologist. Cabergoline (Dostinex) 0.25 mg/week was prescribed, and MRI control was recommended in one year. The patient strictly followed the recommendations and had annual MRI examinations and consultations with an endocrinologist, but no surgical treatment was performed. Since surgery was abandoned, there was an opportunity to follow the progression of adenoma within its natural history.

After two years of treatment, the dose of cabergoline was adjusted to 0.75 mg/week. However, cabergoline was canceled in three months and bro-

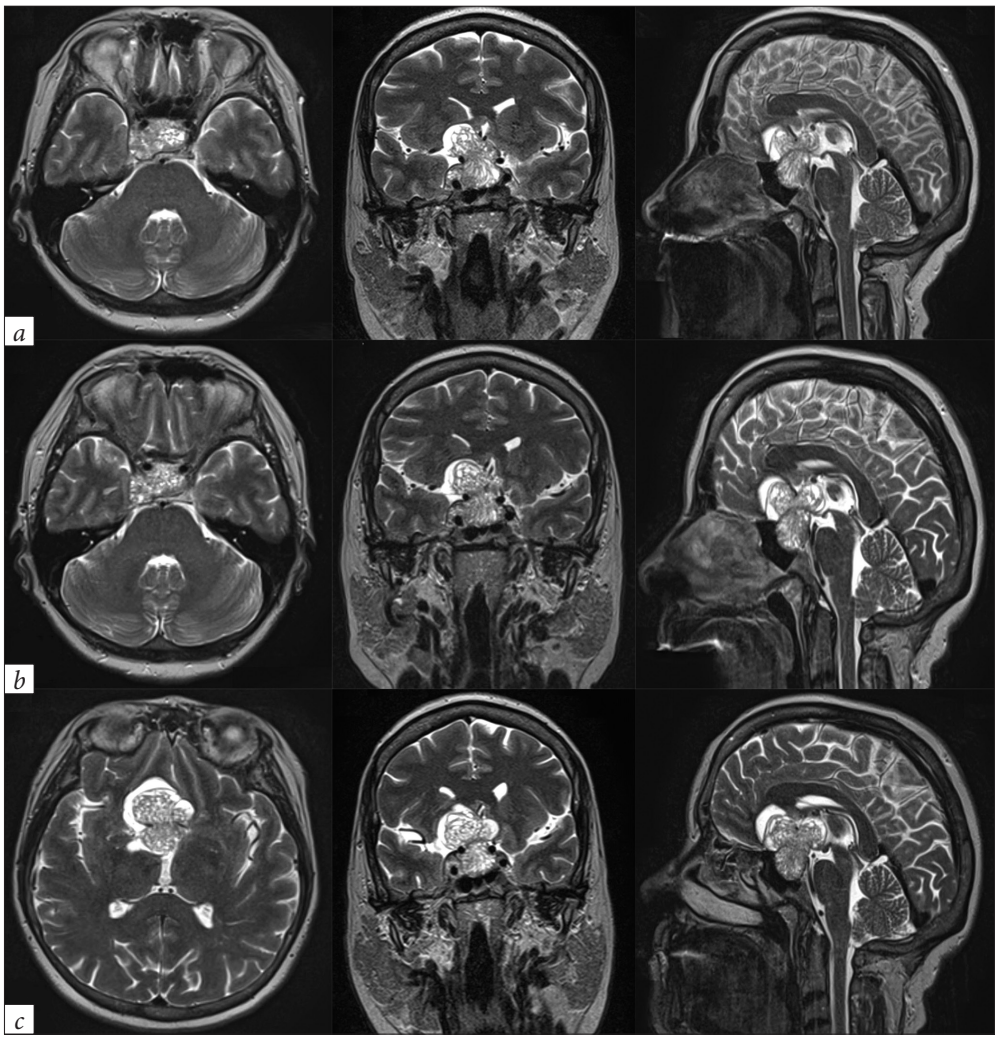

Fig. 2. Series of axial, coronal, and sagittal MR images. (*a*) December 2018. Non-enhanced T2-weighted MRI demonstrating almost unchanged size of adenoma compared to the previous survey (37 × 32 × 29 mm). (*b*) December 2019. Non-enhanced T2-weighted MRI. Compared to survey of December 2018, no significant dynamics were found (37.5 × × 32 × 29 mm). (*c*) December 2020. Non-enhanced T2-weighted MRI showing a giant pituitary adenoma (48 × 37 × 31 mm). Compared with the previous MRI data, the tumor's volume increased by 6.5%

mocriptine (Parlodel) was prescribed in a dosage of 7.5 mg/day instead. The next MRI data showed mild tumor progression (Fig. 1, *b, c*).

The MRI data (12/2018 & 12/2019) were considered by an endocrinologist as stable, and the medication was continued avoiding the multidisciplinary assessment (Fig. 2, *a, b*). According to the MRI data from 12/2020, the pituitary tumor had been growing up for the last two years. Furthermore, the final radiological report was: "Craniopharyngioma with signs of continuous growth" (Fig. 2, *c*).

The initial evaluation of the hormone panel showed the normal levels of LH, FSH, PRL, GH, TSH, and ACTH. For the neuroophthalmological evaluation, the standard methods were used. The physical examination revealed a decreased visual acuity (Vis OD = 0.01; OS = 1.0) and a loss of the visual field: the peripheral residual visual field in the right eye and temporal hemianopia in the left eye (Fig. 3, *a, b*). The fundoscopic examination revealed the primary atrophy of the optic nerves.

For this patient, the endonasal endoscopic transsphenoidal (EET) surgery was chosen and applied.

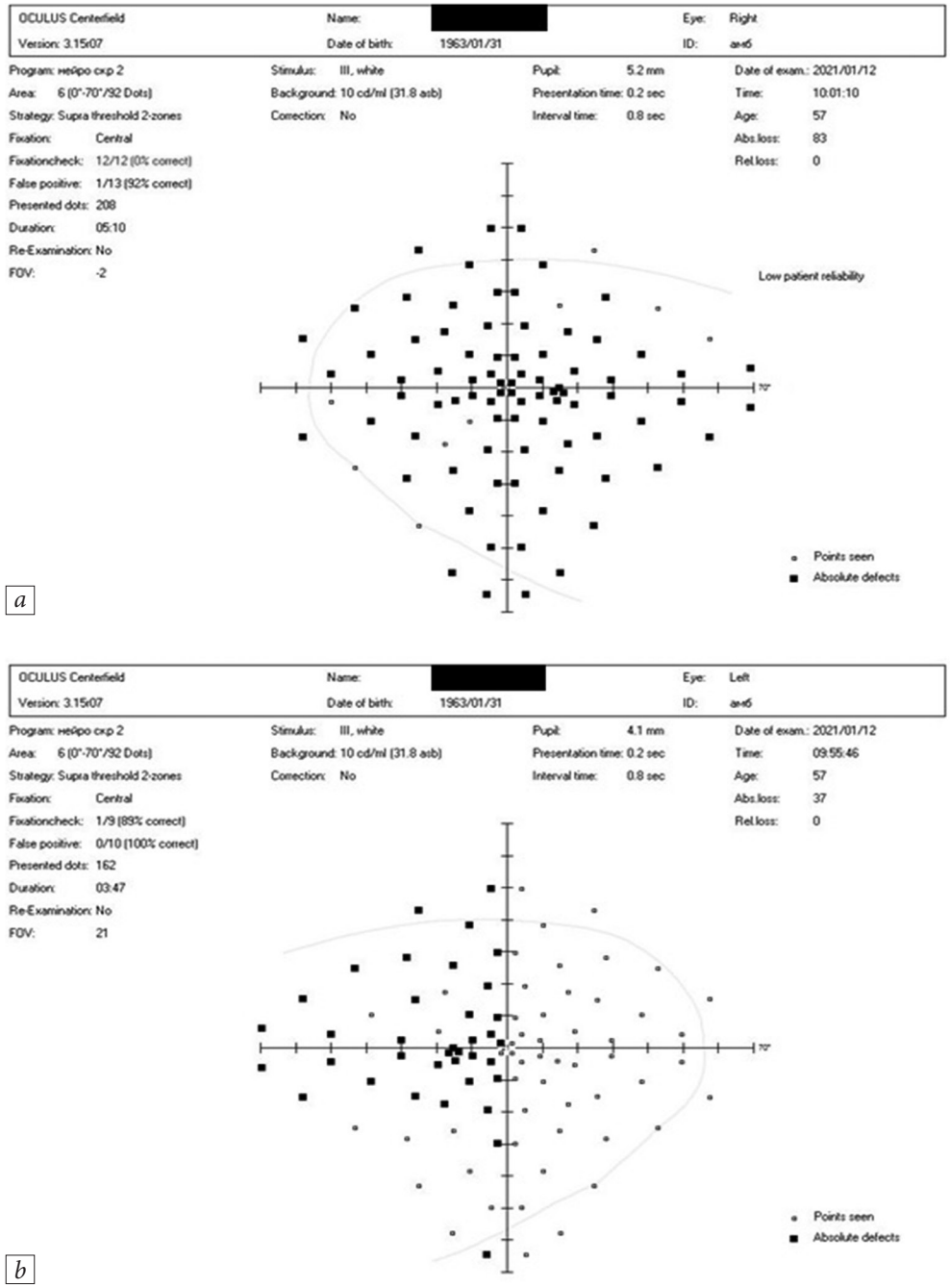

Fig. 3. Automated perimetry showing a peripheral residual visual field in the right eye (*a*) and temporal hemianopia in the left eye (*b*)

We used a transsphenoidal transtubercular transplanum endonasal approach. The consistency of adenoma was ranged as Grade 3 according to the "5-point scale for pituitary adenoma consistency" [6]. The mechanical debulking was performed with plain cup forceps, and the rest part of the tumor was removed with the double suction technique and curettage of the suprasellar part of the tumor. Intraoperatively, after the removal of the superior part of the tumor, high flow CSF leakage from the third ventricle occurred. The parasellar part of the tumor was partially removed. The multilayer closure with in-layer artificial dura mater, fat graft, and fascia lata graft harvested from the thigh covered with nasoseptal flap was performed (Fig. 4). The operation lasted 5 h 30 min. CSF was drained over 5 days through the lumbar drainage to decrease the intracranial pressure and to avoid a CSF

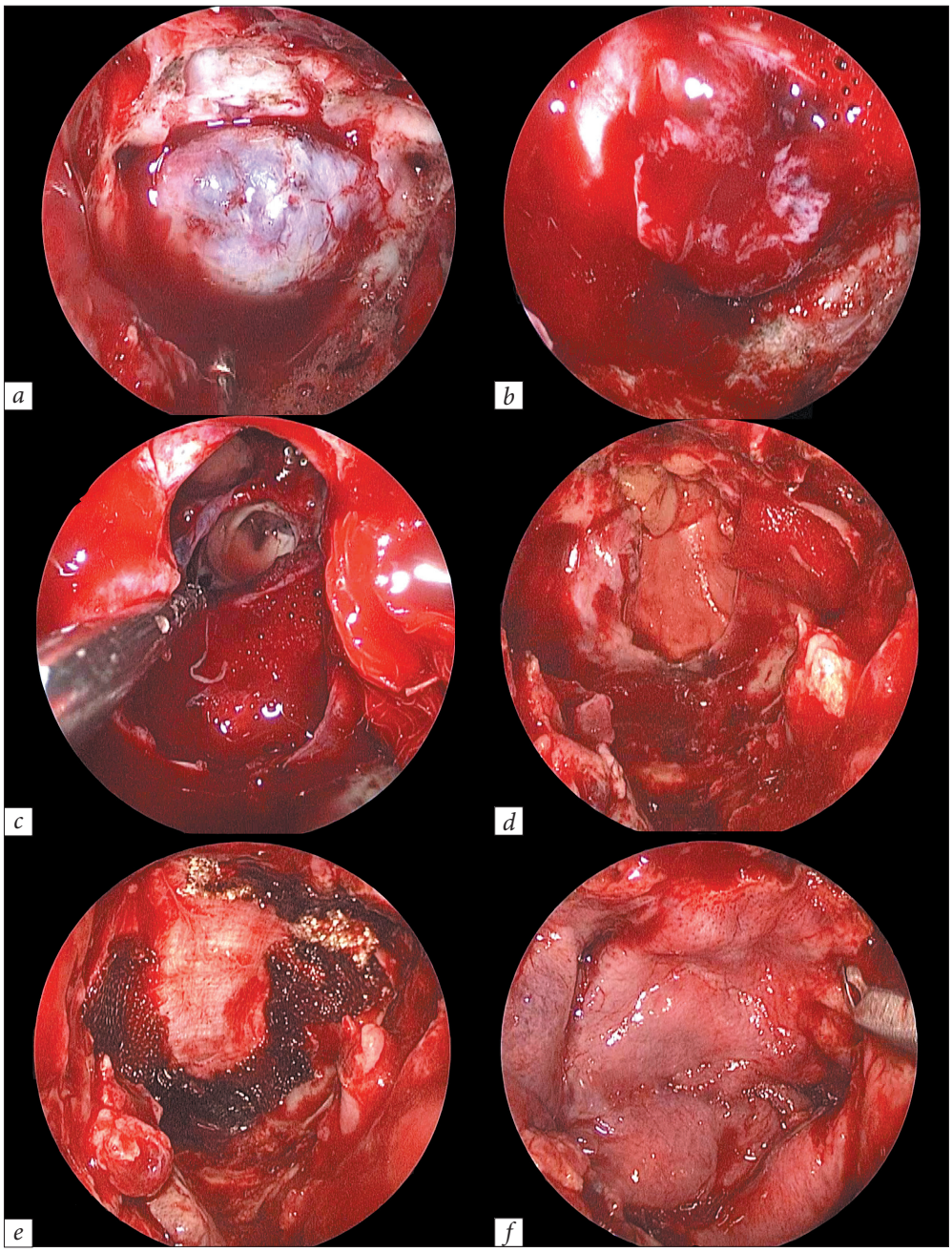

Fig. 4. Intraoperative images. (*a*) The bone of the sellar floor and part of tuberculum sella were removed. Bone window was enlarged to the right cavernous sinus. (*b*) Dura incision, adenoma mass. (*c*) The view of the third ventricle. (*d*) Inlay closure with the use of fat and artificial dura. (*e*) An outlay fragment of fascia lata and oxygenated cellulose. (*f*) Nasoseptal flap

leak. The lumbar drainage was removed on the 7th postoperative day with no evidence of a CSF leak.

After the surgery, the visual acuity remained the same in the left eye and impaired in the right eye (Vis OD = 0; OS = 1.0). The visual field was not determined in the right eye, and partial temporal hemianopia was detected in the left eye (Fig. 5).

At the discharge, no symptoms of headache or weakness were manifested, and visible improvement of the left eye's vision with a widening field of view was registered.

A standard pathohistological examination with IHC and proliferation markers was performed. A pathohistological diagnosis was null cell adenoma (ICD-O 8272/0). The assessed tissue contained predominantly solid neoplasm formed by monomorphous cells with small hyperchromatic nuclei and poorly developed cytoplasm. Mitosis and ne-

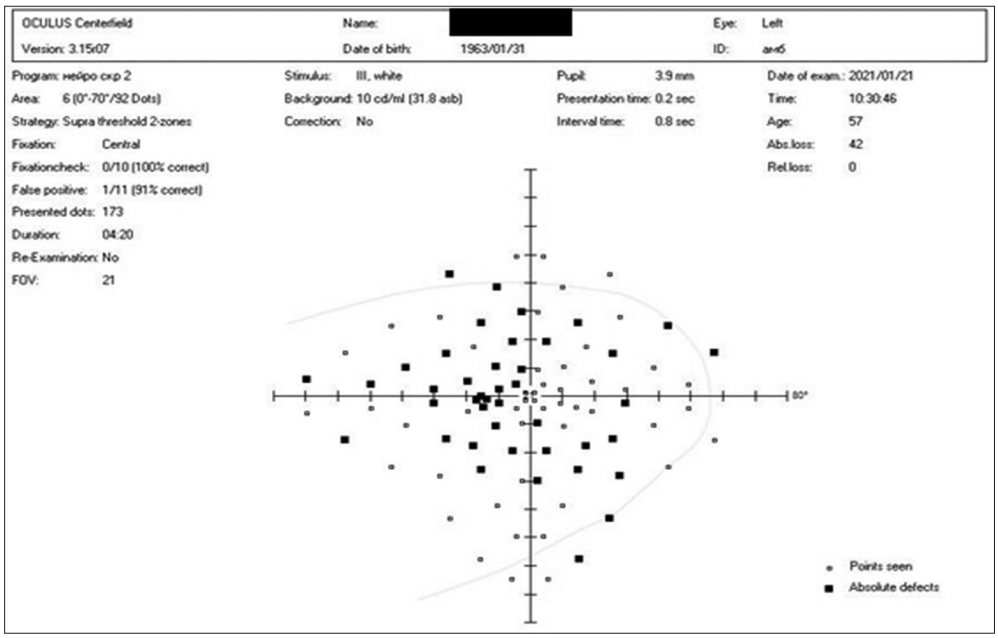

Fig. 5. Postoperative automated perimetry showing widening field of view in comparison with preoperative automated perimetry in the left eye

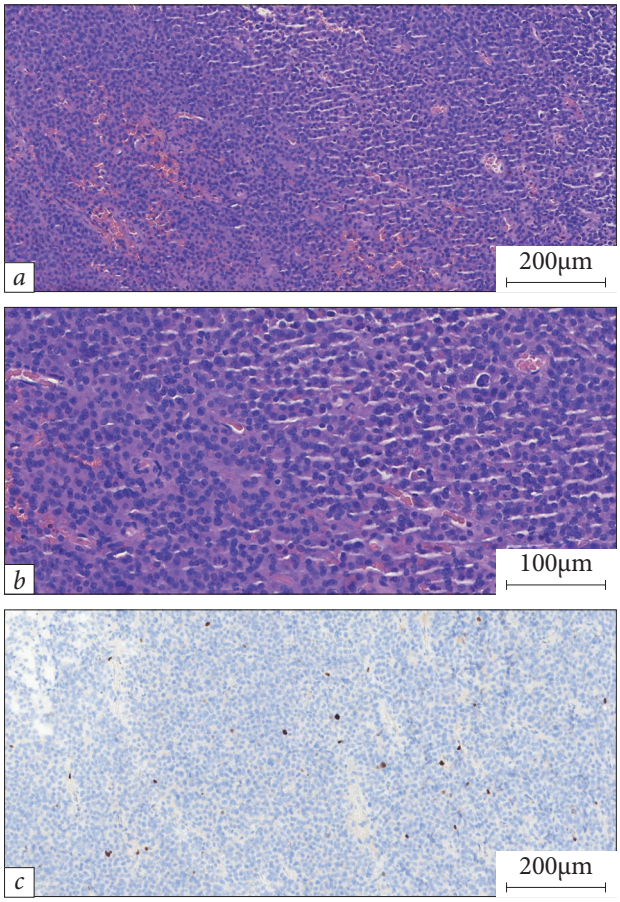

Fig. 6. (*a*) Solid sheets of monomorphous cells with the absence of acinar structure. Pituitary adenoma, H&E, x10. (*b*) Solid sheets of monomorphous cells with the absence of acinar structure. Pituitary adenoma, H&E, x20. (c) Low proliferative activity. Pituitary adenoma, Ki-67 = 5%, ×10

crosis were absent. Tumor cells were negative for pituitary hormones such as FSH, LH, PRL, GH, TSH, and ACTH, and no expression of transcription factors T-pit, SF-1, and Pit-1 was detected. The Ki-67 index was about 5% avg. (Fig. 6).

Three months after the surgery, serum hormone levels were estimated as follows: TSH 0.440 mlU/mL, GH 1.28 ng/dL, LH 8.36 mlU/mL, FSH 18.76 mlU/mL, PRL 1.24 ng/mL, cortisol 15.5 μg/dL, DHEA-S 107 μg/dL, IGF-1 60.8 ng/mL. All the levels were evaluated as normal. MRI control was performed as well (Fig. 7).

This particular case shows the natural history of NCPA including the onset of visual disturbances, hypopituitarism, the start of multi-vector invasiveness, and the stage of becoming giant. It also shows how aggressive and fast-growing NCPA can be. The doubling in size and invasion to the cavernous sinus extending to the third ventricle over 5 years is remarkable for aggressive PAs. Retrospectively, we insist that the attempt of medical treatment as well as "wait and see" tactics are not applicable for such pituitary macroadenoma.

Despite the absence of direct indications for immediate surgery for incidentalomas in modern guidelines, big series–based reports claim that early surgery in patients with such pathology leads to better outcomes, including lower postoperative endocrinological complications [7]. In most cases

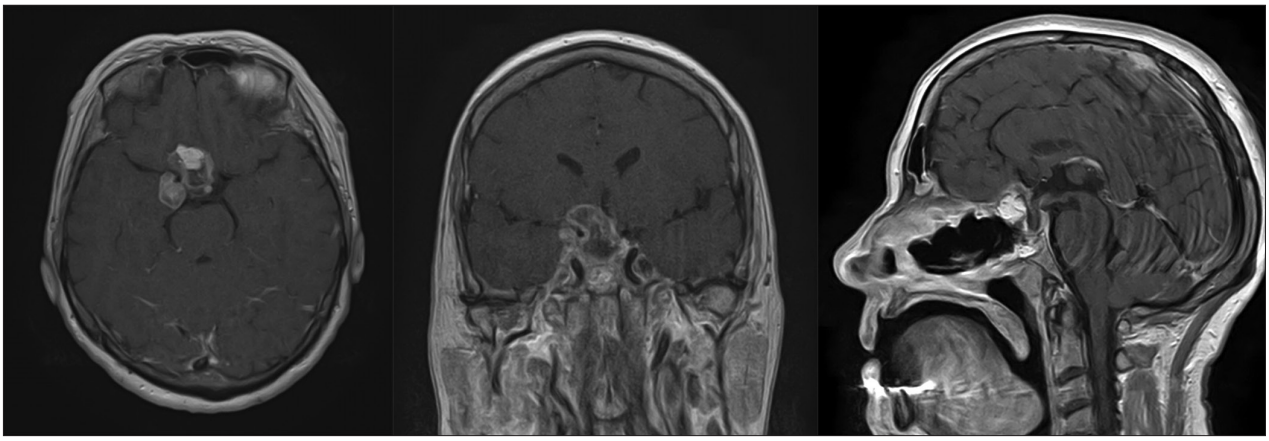

Fig. 7. April 2021. Non-enhanced axial, coronal, and sagittal T1-weighted MRI showing residual elements of pituitary adenoma in the right cavernous sinus three months after surgery

of early surgery, a nasal trauma could be minimized and the perioperative risks are lower. Even more so, the risks of the new onset of hypogonadism, hypothyroidism, hypoadrenalism, and diabetes insipidus in asymptomatic pituitary adenomas (incidentalomas) have been reported as 5.2%, 2.7%, 5.3%, and 6.8%, respectively [7].

It is recommended to undergo an MRI follow-up within 3—12 months, which is guided by the aggressiveness of the tumor, its adjacent structures, the prior tumor growth rate, and/or location [8].

Some studies and even guidelines over the past decade have underlined the importance of pituitary centers of excellence to set the initial strategy by a multidisciplinary team. In new guidelines, the requirements for transsphenoidal surgery to define it like a safe and effective procedure, considered as an initial treatment of choice for most sellar lesions only if performed by experienced neurosurgeons specially trained and actually working with a significant pituitary tumor practice [9—12]. Many endocrinologists report the recognition of their responsibility in choosing the "best" surgeon pituitary tumor cases, even referring outside their local service area, preferably big neurosurgical centers [4, 13, 14].

The reports of PAs that extend to the ventricular system are quite rare. As well, the incidence of NCPAs has been reported as 5% in cohort of NFPAs and 0.6% of all PAs [15]. The combination of such features in this case with long-term observation and throughout MR visualization is considered to be remarkable. The invasiveness, rapid growth, and recurrence potential are discussed as specific signs of NCPA [16]. The complex configuration, extending to the third ventricle, giant size, and tumor density constitute the additional technical issues for their removal. Despite aggressive behavior, the quality of life is prioritized. We tried to reach a satisfactory removal volume preventing visual deterioration and obstructive hydrocephalus. Obviously, gross total removal has not been considered accessible for such cases. We have chosen the extended endoscopic endonasal approach (incl. the transtuberculum transplanum corridor). The anatomical variant of prefixed chiasm gives a natural corridor for tumor growth in direction to the third ventricle. In our case, the onset of visual disturbances is associated with compression of the papillomacular bundle.

It is important to notice that there was visual field enlargement on the left eye only and no right eye vision improvement after surgery. That fact is associated directly with long-term optic nerve compression and, correspondingly, with late surgery. To conclude, the unsatisfactory outcomes in this case underline the importance of multidisciplinary management of such cases with an opportunity of timely surgical treatment.

We have found the importance of choosing the proper treatment modality earlier. The ineffectiveness of dopamine antagonist therapy and the tumor growth were recognized but had not been taken into account from the onset of the disease. Moreover, we could avoid right eye vision loss by applying surgery at the start of severe symptoms. We also realized that we had to perform much more complex and riskier surgery regarding the third ven-

tricle invasion, high-flow CSF leak, and multilayer closure because of such a long "wait-and-see" period. Finally, considering non-radical surgery because of cavernous sinus invasion and aggressive profile of the tumor, impracticality of medical treatment, postoperative radiotherapy is reserved as a probably only option for such patients. Obviously, we have bad outcomes for visual function, barely coming better after radiotherapy.

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Disclosures

There are no conflicts of interest for each author related to the manuscript or its subject matter.

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ТРИВАЛЕ СПОСТЕРЕЖЕННЯ ВЕЛЕТЕНСЬКОЇ НУЛЬ-КЛІТИННОЇ АДЕНОМИ ГІПОФІЗА

Пацієнти з велетенськими аденомами гіпофіза з поширенням у шлуночкову систему зустрічаються дуже рідко і, на нашу думку, даний випадок — унікальний. Доступні серії МРТ можуть бути корисними для нейрохірургів, офтальмологів, ендокринологів, а також для радіологів. Випадок велетенської нуль-клітинної аденоми гіпофіза з поширенням у третій шлуночок публікується вперше. Пацієнти з діагнозом аденома гіпофіза, встановленого на підставі радіологічного та клінічного обстеження, мають бути консультовані нейрохірургом, який має досвід в ендоскопічній ендоназальній хірургії, нейроендокринологом та офтальмологом. Відтермінування операції в таких випадках призводить до інвалідизації та погіршення якості життя. Хірургія велетенських аденом гіпофіза вимагає високої кваліфікації від нейрохірурга, з огляду на високий ризик післяопераційних ускладнень. Правильно підібране лікування, разом із ранньою хірургією, є важливим для поліпшення результатів для пацієнтів. Крім того, рання хірургія, безперечно, є технічно простішою і безпечнішою.

Ключові слова: велетенська аденома гіпофіза, нуль-клітинна, третій шлуночок, ендоскопічна ендоназальна хірургія.