Interdisciplinary Neurosurgery 15 (2019) 101–105

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery

journal homepage: www.elsevier.com/locate/inat

Technical Notes & Surgical Techniques

Successful step-by-step treatment of multiple tumours in neurofibromatosis type 2

Andrii Sirko[a,b,*], Dmytro Romanukha[a], Grigoriy Pilipenko[a,b], Natalia Sklyar[c]

[a] Nervous Diseases and Neurosurgery Department, Postgraduate Education Division, Dnipropetrovsk Medical Academy, Ministry of Healthcare of Ukraine, Dnipro, Ukraine
[b] Cerebral Neurosurgery Department No. 2, Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipro, Ukraine
[c] Radiotherapy Department No. 1, SE Clinical Oncology Dispensary, Dnipropetrovsk Regional Council, Dnipro, Ukraine

ARTICLE INFO

Keywords:
Neurofibromatosis type 2
Vestibular schwannoma
Brain meningiomatosis
Spinal tumour

ABSTRACT

A clinical study on successful treatment of multifocal brain and spinal cord lesions in neurofibromatosis type 2 in a woman aged 35 years is presented. Magnetic resonance imaging showed bilateral vestibular schwannomas, brain meningiomatosis and multiple spinal intramedullary tumours. The treatment comprised four stages: removal of giant dextral vestibular schwannomas, removal of convexital cerebral meningiomatosis, *whole-brain radiation therapy and follow-up*. The spinal cord mass was asymptomatic during the entire follow-up. These steps enabled achievement of a long relapse-free period and resulted in good functional outcomes.

1. Introduction

Neurofibromatosis type 2 (NF2) is a rare, genetically determined, autosomal dominant disease with an incidence of 1:56,000 and a male-to-female ratio of 1:1.29 [1]. 22q12 gene damage resulting in merlin protein tumour suppressor (schwannomin) synthesis causes benign tumour growth in the nervous tissue and skin [2]. NF2 tumour cells have a higher degree of division and consequently, more intensive growth than similar masses encountered as independent nosological forms [3].

Bilateral vestibular schwannomas (VS) are a characteristic NF2 feature and the most frequent clinical manifestation.

Treating patients with NF2 is difficult as they are predisposed to new central nervous system tumour development, making complete recovery impossible and affecting survival. The overall 5-, 10- and 20-year survival rate after diagnosis was 85%, 67% and 38%, respectively [4]. Newer data was obtained in 2015 and was used to estimate the survival rate of patients with NF2 meningiomatosis following Gamma Knife radiosurgery (12–14 Gy). Four (33%) of 12 patients died within the 14-year follow-up. Average age at the time of death was 39 (37–46) years; average time from the beginning of treatment to death was 103 (93–115) months. Lethality in all cases was caused by meningiomatosis progression [5].

2. Case presentation

A 35-year-old woman was admitted to the clinic with headaches, severe dizziness, unsteady walking, right ear hearing loss, impaired left ear hearing, and weakness in upper and lower extremities.

Her medical history included a progressive decrease in right ear hearing approximately 3 years ago with follow-up by an ENT specialist. Impaired left ear hearing and headaches developed 6 months previously. Acute dizziness, unsteady walking and weakness in the extremities developed 2 months ago. As multiple mass lesions were revealed on brain and spinal cord magnetic resonance imaging (MRI), she was directed to our clinic.

The patient's neurological status was minor right-sided facial nerve paresis (House–Brackmann Grade II), right-sided deafness, left-sided hypoacusis, tetraparesis (extremities strength, 4), bilateral pyramidal insufficiency and expressed coordination deficiency. MRI showed bilateral VS, brain meningiomatosis and multiple spinal intramedullary tumours.

The right-sided VS was large (42 × 37 × 39 mm), with an expressed brainstem and IV ventricle compression, corresponding to the T4b type according to M. Samii's classification [6]. The left-sided VS was smaller (10 × 7 × 6 mm; the T2 type according to M. Samii) (Fig. 1).

Mass lesions with thickened adjacent dura mater were detected on the right side of the caudal cranial fossa, in posterior horn of left lateral ventricle, bilaterally in the region of the anterior clinoid processes,

* Corresponding author at: Cerebral Neurosurgery Department No. 2, Mechnikov Dnipropetrovsk Regional Clinical Hospital, 14 Soborna Square, Dnipro, 49005, Ukraine.
E-mail address: sirkoscience@gmail.com (A. Sirko).

https://doi.org/10.1016/j.inat.2018.10.011
Received 9 August 2018; Received in revised form 6 September 2018; Accepted 14 October 2018

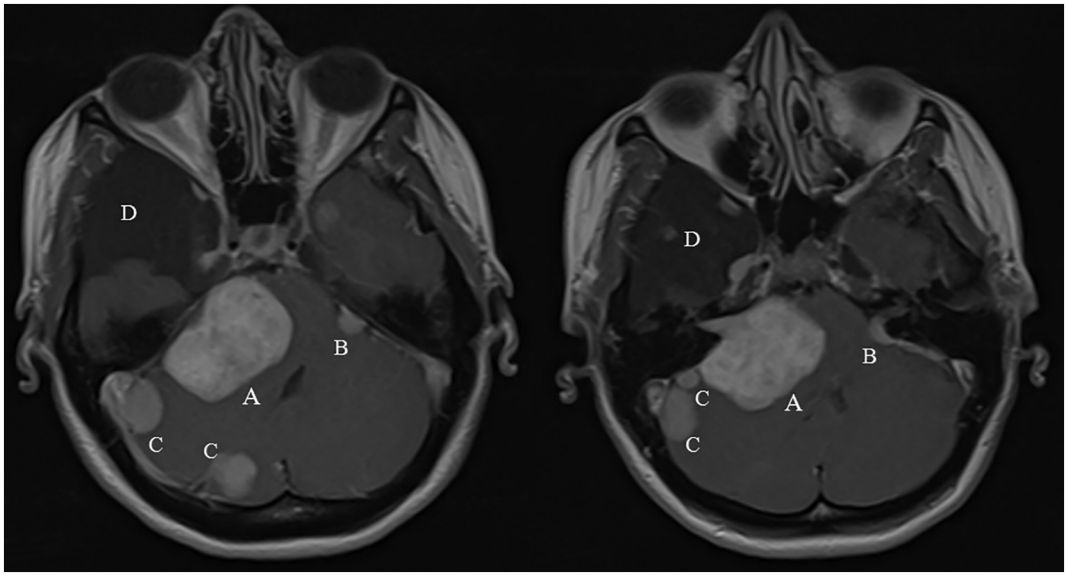

Fig. 1. Preoperative MRI, T1 + Gd: Two-sided VSs in a patient with NF2.
(A) Giant right-sided VS. (B) Small left-sided VS. (C) Right-sided caudal cranial fossa meningiomas. (D) Congenital arachnoid cyst of the right temporal lobe.

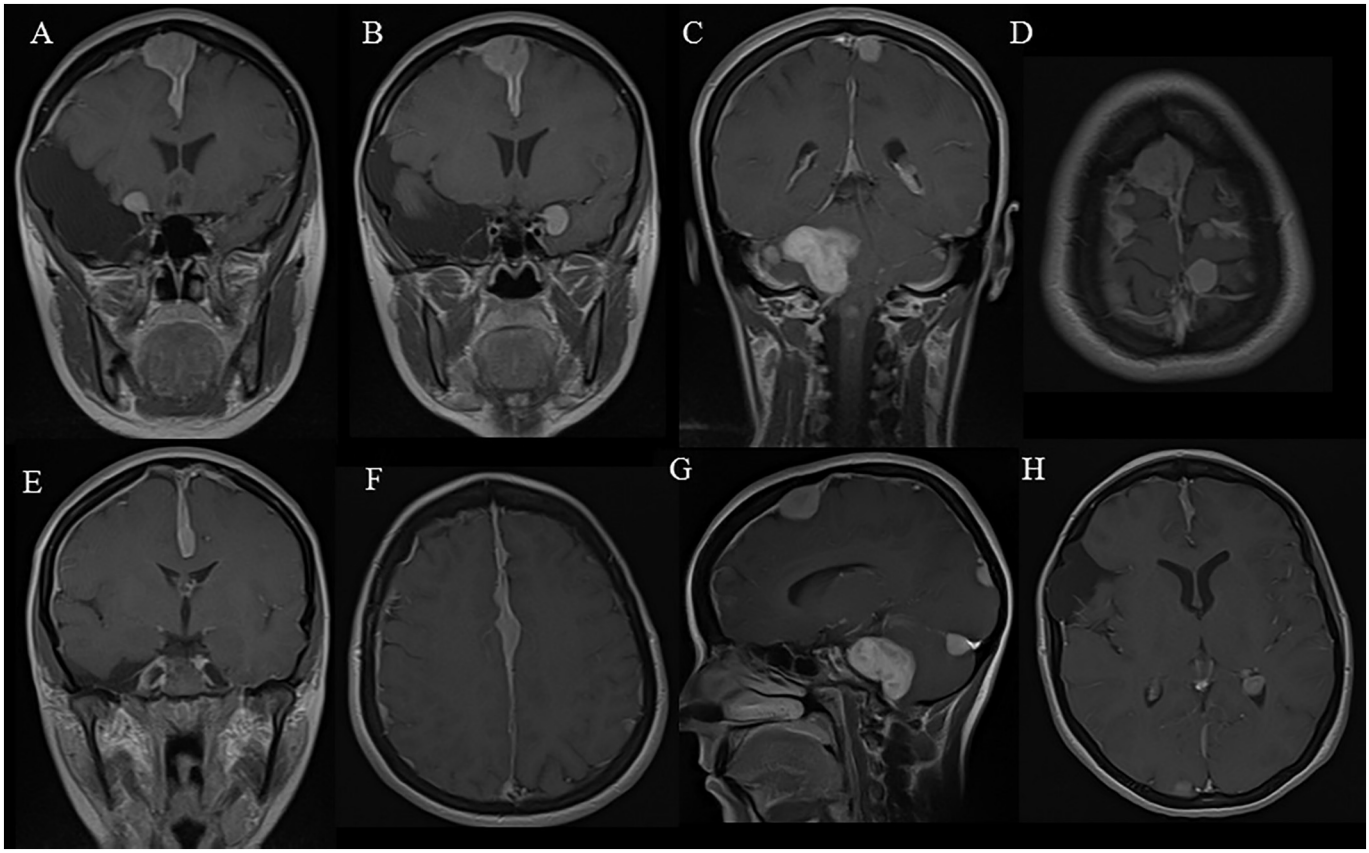

Fig. 2. MRI, T1 + Gd: Brain meningiomatosis in a patient with NF2.
(A, B) Bilateral meningiomas in the anterior clinoid process and right-sided parasagittal meningioma. (C) Left-sided parasagittal meningioma. (D) Convexital meningiomatosis. Nodular mass lesions, non-uniform thickening and contrast accumulation in the convexital dura mater. (E, F) Thickened cerebral falx. (G) Right-sided parasagittal meningioma in the occipital region and right-sided infratentorial meningioma. (H) Meningioma in the posterior horn of the left lateral ventricle.

parasagittally in frontal and parietal regions (bilaterally), on the right side of the occipital region and in the anterior and middle third of the cerebral falx. Fig. 2 denotes brain meningiomatosis.

Intramedullary spinal lesions were located in the craniovertebral junction (C1–C2), C5, C7 and Th1–Th3 (Fig. 3).

The patient underwent audiometry that revealed gross right-side damage to the auditory analyser down to the level of deafness (78 dB) and impaired left side function (17 dB).

According to the NIF, NNFF and Manchester criteria, NF2 was diagnosed [2,3]. Hereditary history was not aggravated; molecular

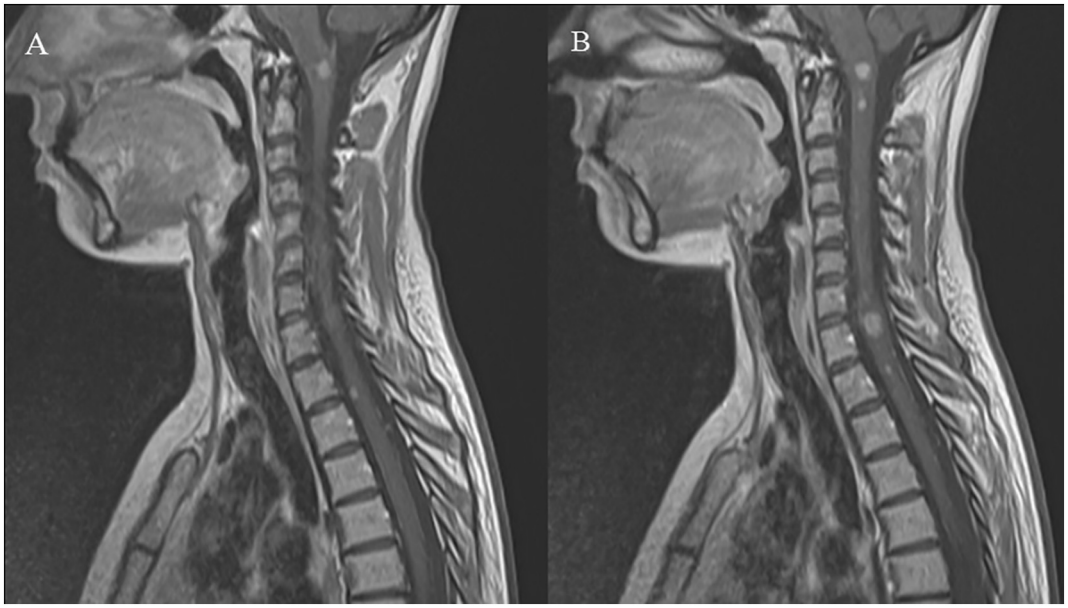

Fig. 3. MRI, T1 + Gd: multifocal spinal cord lesion in a patient with NF2.
(A) Intramedullary lesions (ependymomas) in the craniovertebral junction (C1 vertebra) and intervertebral disc of the Th1-Th2. (B) Intramedullary lesions in the craniovertebral junction (C1–C2), C5, C7, Th1 and Th2.

genetic studies on NF2 gene mutation were not performed (3).

2.1. Surgery stage I: giant right-sided vestibular schwannoma total excision

Using a standard retrosigmoid approach, the medullocerebellar cistern was opened and CSF was evacuated to relax the cerebellum. The OPMI VARIO 700 microscope (Carl Zeiss, Oberkochen, Germany) was used for tumour removal; facial nerve function was neurophysiologically monitored using Nim Response 3.0 (Medtronic, Minneapolis, USA) at all surgery stages. This approach enabled accessible right-sided caudal cranial fossa meningioma removal. The pathomorphological response corresponded to neurinoma and grade I fibrotic meningiomas.

2.2. Surgery stage II: convexital brain meningiomatosis removal

4-Month follow-up MRI in the right cerebellopontine angle showed postoperative changes. There was a significant increase in the signal intensity and contrast accumulation area because of convexital meningiomatosis and adjacent dura mater. Thickening along the falx and increased nodular thickening in the inferior part of the anterior and middle third of the falx were observed with a slight increase in convexital nodular tumour volume.

To evaluate superior sagittal sinus (SSS) permeability and collateral venous blood flow pathways, total cerebral angiography was performed. Occlusion was detected at the anterior and middle third interface of SSS; the distal occlusion level went beyond the coronary suture projection by 2 cm. Venous blood outflow occurred through superficial veins (including the superior anastomotic vein) into the middle third of SSS and deep cerebral veins.

Wide osteoplastic bifrontal temporal craniotomy was performed; the frontal parasagittal meningioma, invaded portion of SSS and meningioma of inferior sections of the anterior and middle third of the falx were removed stepwise. The falx infiltrated with the tumour, anterior third of SSS and pathologically altered duramater over the right and left cerebral hemispheres were dissected. SSS was resected until it regained function. Duraplasty was performed using autogenous tissue (periosteum); a pathomorphological study of the altered duramater and nodular lesions (grade I fibrotic psammous meningiomas) was performed.

On day 7 postoperatively, the patient began to develop mental disorders and expressed frontal ataxia. Follow-up CT and MRI in the haemorrhaging regions showed no frontal lobe ischaemia. Abnormalities detected were attributed to cerebral venous blood flow reorganisation after anterior third of SSS resection and meningiomatosis removal.

2.3. Treatment stage III: whole-brain radiation therapy

A tumour board was held at our clinic in which we decided to conduct a course of remote gamma therapy by irradiating the entire brain using the Elekta Synergy (Elekta, Stockholm, Sweden) linear accelerator. Such an approach was justified by the sufficiently large area, number of intracranial regions to be irradiated and more intensive tumour tissue growth due to the genetic nature of the disease.

One month following the second surgery, the patient was irradiated. The total percentage depth dose was 40 Gr (2 Gr/session). Thus, irradiation was applied to mass lesions not subjected to surgery and initial growth areas of the removed tumours. There were no complications with the applied irradiation mode.

2.4. Treatment stage IV: follow-up

The first follow-up was performed 6 months postoperatively. Her neurological status still included right facial nerve mild palsy (House–Brackmann Grade II), right-sided deafness (85 dB), and left-sided hypoacusia (15 dB), but coordination impairment had regressed. Follow-up MRI showed no tendency for VS, meningiomas or spinal cord tumour growth.

We would like to present the 5-year follow-up brain and spinal cord MRI of the patient (Fig. 4).

Her neurological status remains stable and corresponds to the 6-month follow-up examination level. We intend to continue with follow-up.

3. Discussion

The clinical case is of interest regarding treatment tactics for multifocal extensive lesions in NF2. We faced many issues as there is still no consensus on multifocal mass lesion treatment in patients with NF2. In

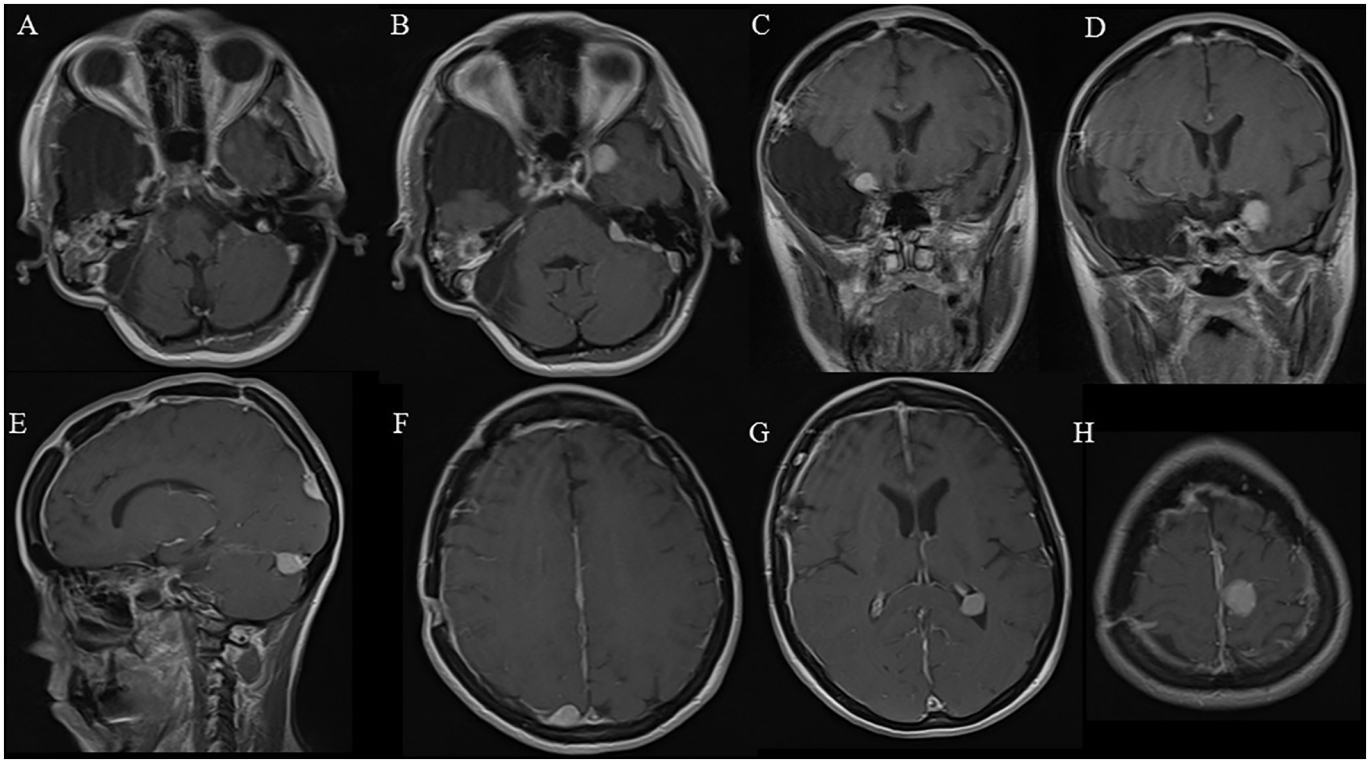

Fig. 4. Five-year follow-up brain MRI (T1 + Gd).
(A, B) No growth of bilateral VS. (C, D, E, F) No growth of removed convexital meningiomatosis, anterior third of falx and SSS, clinoid process meningiomas, parasagittal meningioma in occipital region and infratentorial meningioma. (G) No growth of meningioma in the posterior horn of the left lateral ventricle. (H) No growth of parasagittal meningioma in parietal region.

small or medium bilateral VS, tumour removal on the better hearing ear side is recommended for maintaining higher level of useful hearing on both sides [6]. However, the right-sided VS in our case was huge and there was total deafness on that side. Treatment was, thus, initiated from the right side, primarily to eliminate brainstem compression and also to preserve useful hearing at the expense of the contralateral ear. Large VS (diameter > 3 cm) is a direct surgical indication [2]. Radiosurgery, chemotherapy and expectant management are not reasonable at this treatment stage.

A 4-month follow-up MRI showed the progress of convexital meningiomatosis, which excluded the possibility of further follow-up and necessitated a second treatment stage [7]. Targeted therapy in contrast to the rather good outcome of VS treatment in NF2 was not effective for meningiomas [8]. Neither was radiotherapy. Previous studies have demonstrated the applicability of this method; however, the sample groups had numerous complications and unfavourable outcomes regarding survival [5]. Radiotherapy also shows much greater efficiency in VS treatment [2,3]. Surgery is not devoid of drawbacks either as evidenced by the patient's postoperative temporary neurological deficits resulting from venous microvasculature reorganisation. It is difficult to determine whether this or other complications (such as oedema or venous infarction) occurred during irradiation.

We found no examples of whole-brain radiation therapy for NF2 in the literature. However, the technique is used for sporadic meningiomatosis treatment [9]. The irradiation regime employed in this case targeted the meningiomas and left-sided VS, preventing further tumour growth.

Based on their radiological characteristics, intramedullary spinal tumours are ependymomas, which are generally located in cervical and upper thoracic segments of the spinal cord. As they grow from the central canal ependyma, they occupy the central part of the spinal cord and cause its symmetrical expansion. In majority observations, the tumours have asymptomatic progression and are subject to follow-up [3]. Our clinical case was no exception. During the observation period, the patient showed no signs of compression or intramedullary spinal cord lesion growth; therefore, we decided to refrain from any manipulation and performed follow-up.

4. Conclusion

Appropriate multifocal lesion treatment policy selection in NF2 including large right-sided VS removal, convexital brain meningiomatosis removal, *whole-brain radiation therapy* and follow-up enabled long relapse-free period achievement and ensured good functional outcome.

Conflict of interest

The article does not contain a conflict of interest.

References

[1] D.G. Evans, E. Howard, C. Giblin, T. Clancy, H. Spencer, S.M. Huson, et al., Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service, Am. J. Med. Genet. A 152A (2010) 327–332, https://doi.org/10.1002/ajmg.a.33139.
[2] D.G. Evans, Neurofibromatosis type 2 (NF2): a clinical and molecular review, Orphanet J. Rare Dis. 4 (2009) 16, https://doi.org/10.1186/1750-1172-4-16.
[3] D.G. Evans, Neurofibromatosis 2 [bilateral acoustic neurofibromatosis, central neurofibromatosis, NF2, neurofibromatosis type II], Genet. Med. 11 (2009) 599–610, https://doi.org/10.1097/GIM.0b013e3181ac9a27.
[4] G. Otsuka, K. Saito, T. Nagatani, J. Yoshida, Age at symptom onset and long-term survival in patients with neurofibromatosis Type 2, J. Neurosurg. 99 (2003) 480–483, https://doi.org/10.3171/jns.2003.99.3.0480.
[5] A. Liu, E.N. Kuhn, J.T. Lucas Jr., A.W. Laxton, S.B. Tatter, M.D. Chan, Gamma Knife radiosurgery for meningiomas in patients with neurofibromatosis Type 2, J. Neurosurg. 122 (2015) 536–542, https://doi.org/10.3171/2014.10.JNS132593.
[6] M. Samii, V. Gerganov, Surgery of Cerebellopontine Lesions, Springer-Verlag, Heidelberg, 2013, https://doi.org/10.1007/978-3-642-35422-9.
[7] S. Goutagny, A.B. Bah, D. Henin, B. Parfait, A.B. Grayeli, O. Sterkers, et al., Long-term follow-up of 287 meningiomas in neurofibromatosis type 2 patients: clinical,

radiological, and molecular features, Neuro-Oncology 14 (2012) 1090–1096, https://doi.org/10.1093/neuonc/nos129.
[8] F.P. Nunes, V.L. Merker, D. Jennings, P.A. Caruso, E. di Tomaso, A. Muzikansky, et al., Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients, PLoS ONE 8 (2013) e59941, , https://doi.org/10.1371/journal.pone.0059941.
[9] R.H. Wong, A.K. Wong, N. Vick, H.I. Farhat, Natural history of multiple meningiomas, Surg. Neurol. Int. 4 (2013) 71, https://doi.org/10.4103/2152-7806.112617.