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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Surgical Results of Pediatric Patients with Hypothalamic Hamartoma

Pediatrik Hipotalamik Hamartomlu Olgularda Cerrahi Sonuçlarımız

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Summary

Objectives: Hypothalamic hamartomas (HH) are congenital lesions present with gelastic seizures and precocious puberty. Disconnective surgery is a safe and effective treatment method in patients with HH. In this study, we aim to share demographic information, presenting symptoms, surgical complications and surgical outcomes in pediatric patients with HH who were operated in our clinic.

Methods: In this retrospective study, 12 pediatric patients with HH, who were operated in Acibadem University, School of Medicine, Department of Neurosurgery, Division of Pediatric Neurosurgery and Epilepsy Surgery Clinic between years 2007–2018 were included. All clinical materials, including patient notes, cranial magnetic resonance imaging, electroencephalogram recordings and endocrinological data of patients, were collected. Variables evaluated in the statistical analysis were age, sex, presenting symptom, radiological appearance, treatment outcome. Surgical outcome was evaluated by the Engel classification system. Statistical analysis was performed using SPSS 20.0 software.

Results: There were eight (66.7) males and four (33.3%) females within the patient cohort. Median age at the time of diagnosis was 3.1 years (4 months–6 years). Median follow-up period was 98.3 months (24–177 months). Presenting symptoms were gelastic seizures in six (50%) patients, precocious puberty in three (25%) patients and both gelastic seizures and precocious puberty in three patients. All patients had disconnective surgery for HH. None of the patients had a postoperative neurological deficit. The seizure outcome in seven (77%) of the nine patients with seizure were Engel class 1 after the surgery. Signs and symptoms of precocious puberty persist after surgery in three (50%) of six patients who had presented with precocious puberty in the preoperative period. There was no statistically significant relationship between age, sex and type of HH ($p>0.05$). There was also no significant relationship between the type of HH and presenting symptom, operation route or treatment outcome ($p>0.05$).

Conclusion: Disconnective surgery is a safe and effective treatment method in pediatric patients with HH. Since most of the patients presents with seizures and/or endocrinological problems, thorough preoperative and postoperative neurological and endocrinological follow-up is recommended.

Keywords: Disconnective surgery; gelastic seizure; Hypothalamic hamartoma; precocious puberty.

Özet

Amaç: Hipotalamik Hamartomlar (HH) genellikle jelastik nöbet ve erken ergenlik ile bulgu veren konjenital lezyonlardır. Hipotalamik hamartom hastalarında diskonnektif cerrahi güvenli bir tedavi yöntemidir. Bu çalışmadaki amacımız, kliniğimizde opere edilen pediatrik yaş grubundaki hipotalamik hamartomlu hastaların demografik verileri, başvuru şikayetleri, cerrahi komplikasyonları ve sonuçlarını paylaşmaktır.

Gereç ve Yöntem: Bu geriye dönük çalışmaya Acıbadem Üniversitesi Tıp Fakültesi Pediatrik Beyincerrahsi Bilim Dalı ve epilepsi cerrahisi kliniğinde 2007-2018 yılları arasında ameliyat edilen 12 pediatrik HH hastası dahil edilmiştir. Olguların dosyaları, beyin manyetik rezonans görüntülemeleri, elektroensefalogram kayıtları ve endokrinolojik tetkik ve konsültasyonları değerlendirilmiştir. Nöbet şikayeti olan hastalarda cerrahi nöbet başarısı Engel sınıflandırma sistemi ile değerlendirilmiştir. İstatistiksel analizler için SPSS 20.0 programı kullanılmıştır.

Bulgular: Çalışmada sekiz (66.7) erkek ve dört (33.3%) kadın hasta bulunmaktadır. Tanı anındaki ortanca yaş 3.1 yıldır (4 ay–6 yıl). Ortanca takip süresi 98.3 aydır (24–177 ay). Başvuru anında altı (50%) hastada jelastik nöbet, üç (25%) hastada erken ergenlik bulguları ve üç (25%) hastada hem jelastik nöbet hem de erken ergenlik bulguları mevcuttu. Tüm hastalara diskonnektif cerrahi uygulanmıştır. Nöbet şikayeti olan dokuz hastanın yedisi (77%) ameliyat sonrasında nöbet açısından Engel sınıf 1'dir. Erken ergenlik bulguları olan altı hastanın üç (50%) tanesinde bu bulgular ameliyat sonrası devam etmiştir. Hastaların yaşı cinsiyeti ile HH tipi arasında istatistiksel ilişki saptanmamıştır ($p>0.05$). Ayrıca HH tipi ile başvuru şikayeti, operasyon türü ve operasyon başarısı arasında ilişki saptanmamıştır ($p>0.05$).

Sonuç: Pediatrik HH olgularında diskonnektif cerrahi güvenli ve etkili bir tedavi metodudur. Hastaların genellikle nöbet ve/veya erken ergenlik bulguları ile başvurduğu için ameliyat öncesi ve sonrası tüm hastaların detaylı bir çocuk nörolojisi ve çocuk endokrinolojisi muayenesinde geçmesi gerekmektedir.

Anahtar sözcükler: Diskonnektif cerrahi; erken ergenlik; hipotalamik hamartom; jelastik nöbet.

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Introduction

Hypothalamic hamartomas (HH) are rare congenital, non-neoplastic lesions, organized as clusters of both neuronal and glial cells within walls or floor of the third ventricle.[1] They generally present with gelastic seizures (GS) and/or precocious puberty (PP).[2,3] Less frequently, they may also present with cognitive dysfunction and behavioral disturbances.[4,5] Epilepsy in HH generally stars as GS in early years of life and later it may evolve into other types of seizures, which may result in epileptic encephalopathy.[1,2] Epilepsy that arises from HH is generally refractory to antiepileptic drugs (AED). Surgery, stereotactic radiosurgery, interstitial brachytherapy, radiofrequency thermocoagulation and laser interstitial thermal therapy are treatment options in patients with symptomatic HHs, especially with refractory epilepsy. In this study, we aimed to report our clinical experience with 12 pediatric hypothalamic patients all of whom were treated with disconnective HH surgery.

Materials and Methods

In this study, we reviewed the clinical data of 12 pediatric patients with a diagnosis of hypothalamic hamartomas who were operated at Acibadem University, School of Medicine, Department of Neurosurgery, Division of Pediatric Neurosurgery and Epilepsy Surgery clinic between 2007-2018. This retrospective study was approved by the medical ethical committee at Acıbadem University School of Medicine, Istanbul, Turkey.

Pre-surgical patient evaluation

All the patients had 3 Tesla magnetic resonance imaging (MRI), including sagittal, axial section turbo spin echo (TSE) T2 weighted imaging, coronal section fat-sat TSE T2 weighted diffusion, sagittal section 3-dimensional (3D) Turbo-FLAIR T2 with reconstructions, sagittal section 3D turbo flash T1 with reconstructions, axial section 3D susceptibility-weighted imaging and diffusion tensor imaging tractography protocol as described in our previous publication.[6] Delalande radiological classification system was employed.[1] All patients presented with seizures had at least 48-hour, 21 channel video electroencephalogram (EEG) monitoring with at least three ictal recordings. They all had preoperative blood tests for hemogram, electrolyte, bleeding parameters and serology. All patients presented either with seizures and/or precocious puberty had through pediatric endocrinological evaluation and they were evaluated by a clinical pediatric psychologist as a member of the pediatric neurosurgery and epilepsy surgery team.

Surgery

Patients were operated through one of the interhemispheric, pterional, subtemporal or subfrontal approaches. All patients had disconnective surgery, which aimed just to sever the connection of HH with the hypothalamus without removing the whole HH tissue. Only one patient who needed a second surgery for seizure control had resective surgery for HH during the second operation. All operations were performed by the senior author (MMÖ).

Postoperative follow-up

Each patient was observed in the pediatric neurosurgical intensive care unit for 24 hours and four days in the patient ward. All patients who presented with epilepsy continued their antiepileptic drugs with the same doses after surgery. They were followed by a pediatric endocrinologist concerning hormonal abnormalities, especially diabetes insipidus postoperatively. During routine follow-up, all patients were evaluated by a pediatric neurosurgeon, and patients who presented with seizure also evaluated by pediatric epileptologist every three months during the first postoperative year, every six months during the second postoperative year and yearly thereafter. All patients presented with seizure had control EEG recordings starting from three months after the surgery. Antiepileptic dose adjustments were performed according to EEG results by the pediatric epileptologist.

Evaluation of outcome and statistical analysis

Statistical analysis was performed with SPSS 20. Variables evaluated in the statistical analysis were age, sex, presenting symptom, radiological appearance, treatment outcome. Seizure outcome was evaluated according to Engel's classification.[7]

Results

Clinical data of the patients are summarized in Table 1. Total number of patients in the study group was 12. There were eight (66.7%) males and four (33.3%) females. Median age at the time of diagnosis was 3.1 years (4 months–6 years). Median follow-up period was 98.3 months (24–177 months). Presenting symptoms were gelastic seizures in six (50%) patients (case 1, 2, 8, 9, 10 and 11), precocious puberty in three (25%) patients (case 4, 5 and 7) and both gelastic seizures

Table 1. Clinical data of the patients

Case	Age (years)/ Sex	Presenting symptom and seizure frequency	HH Type	No. of HH operations	Time period between operations (mo)	Operation Route	Post-op Engel score	Current AED	Resolution of PP	Follow-up time (mo)
1	0.6/M	GS (3 /day)	4	2	46	IH+IH	3	Levetirecetam + Sultiam	N/A	55
2	6/M	GS (10/day)	2	2	118	IH+IH	1	No	N/A	165
3	4.6/M	GS/PP (2/day)	3	1	N/A	IH	1	No	Yes	84
4	4.4/F	PP (N/A)	2	1	N/A	IH	N/A	N/A	No	109
5	1/F	PP (N/A)	1	1	N/A	PTR	N/A	N/A	Yes	24
6	1.5/M	GS/PP (10/week)	4	1	N/A	IH	1	No	No	78
7	4/M	PP (N/A)	1	1	N/A	SUBF	N/A	N/A	Yes	112
8	3.8/F	GS (4/day)	2	1	N/A	IH	1	Levetirecetam	N/A	24
9	3.3/M	GS (6/day)	2	1	N/A	IH	1	No	N/A	116
10	0.4/F	GS (40/day)	4	2	44	IH+IH	1	Carbamazepin	N/A	159
11	4.4/M	GS (15/day)	3	2	31	SUBT+IH	2	Carbamazepin+ valproic acid	N/A	177
12	3.6/M	GS/PP (7/day)	2	1	N/A	IH	1	No	No	78

AED: Antiepileptic drug; F: Female; M: Male; GS: Gelastic seizure; HH: Hypothalamic hamartoma; IH: Interhemispheric; mo: Month; N/A: Not applicable; PP: Precocious puberty; PTR: Pterional; SUBF: Subfrontal; SUBT: Subtemporal.

and precocious puberty in three (25%) patients (case 3, 6 and 12). Radiologically all lesions were isointense to surrounding brain parenchyma in T1 and T2 weighted MR images without contrast enhancement. The radiological diagnosis of patients was consistent with type 1 HH in two (16.7) patients, type 2 HH in five (41.7) patients, type 3 HH in two (16.7) patients and type 4 HH in three (25%) patients. All patients were operated within three months after diagnosis. Nine patients (75%) were operated through interhemispheric approach, one patient (8.3%) was operated through subfrontal approach, one patient (8.3%) was operated through the pterional approach and one patient (8.3%) was operated through the subtemporal approach (Fig 1–4). Four (33.3%) patients were operated twice. One of these patients (case 2) had been operated and also had postoperative stereotactic radiosurgery (SRS) treatment in another institution previously. Since his symptoms persisted, he had his second operation in our clinic. Case 11 was operated through the subtemporal approach for HH disconnection during the first operation. Since his seizures had persisted, he had the second operation through interhemispheric approach for total resection of HH. There was no postoperative neurological deficit in any patient. Post-operative seizure outcomes of nine patients who had gelastic seizures were Engel class 1 in seven (77%) patients, Engel class 2 in one patient and Engel class 3 in one patient. Three patients, the one with type 4 HH (case 1) and two other patients with type 2 HHs (case 9 and 12), had early postoperative diabetes insipidus, which mandated nasal antidiuretic hormone usage. Diabetes insipidus was resolved completely in all patients within two weeks after surgery. Cases 3–4–5–6–7–12 presented with precocious puberty (PP). Precocious puberty was completely resolved in cases 3, 5 and 7 within three months after surgery, but it persists in cases 4, 6 and 12 in whom LHRH releasing hormone treatment were indicated.

There was no statistically significant relationship between age, sex and type of HH ($p>0.05$). There was also no significant relationship between type of HH and presenting symptom, operation route or treatment outcome ($p>0.05$).

Discussion

Hypothalamic hamartomas are congenital non-progressive malformations of anterior hypothalamus.[8] Although gelastic seizures are the most common presenting symp-

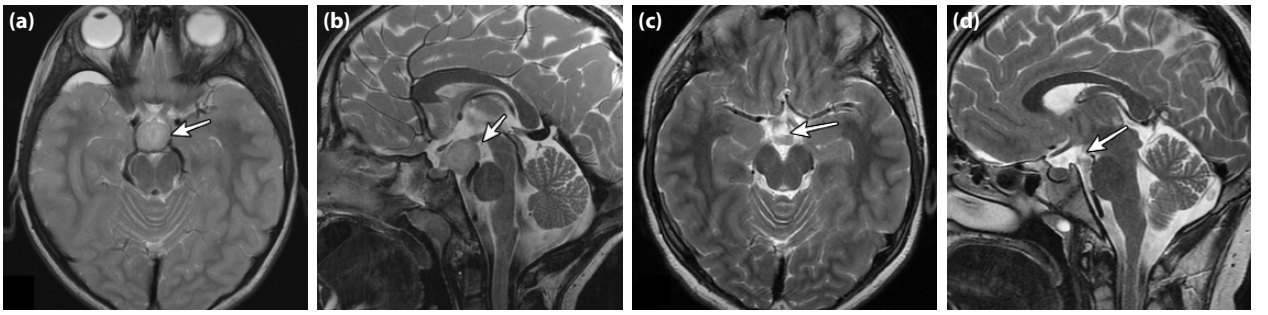

Fig. 1. **(a)** Axial section T2 weighted MRI of a patient with type 1 HH (arrow). **(b)** Sagittal section T2 weighted MRI of the same patient (arrow). **(c)** Axial section T2 weighted MRI of the patient after disconnection surgery through pterional route. Arrow designates disconnection plane. **(d)** Sagittal section T2 weighted MRI of the same patient after disconnection surgery. Arrow designates the disconnection plane.

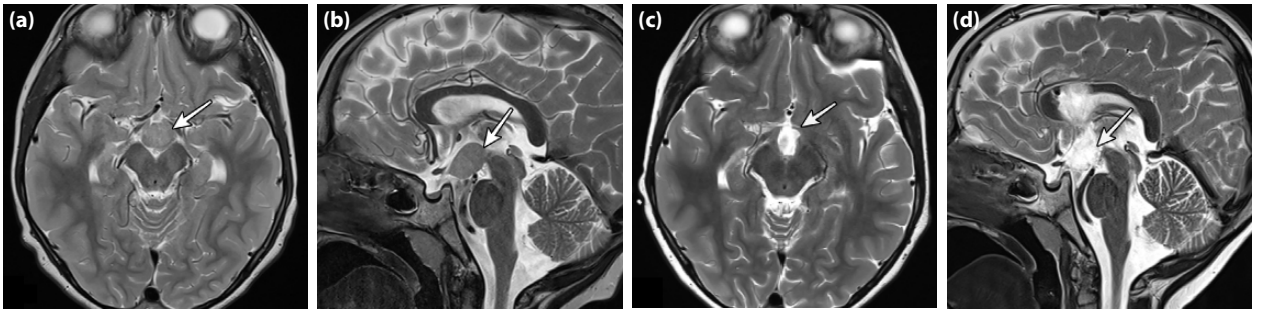

Fig. 2. **(a)** Axial section T2 weighted MRI of a patient with type 2 HH (arrow). **(b)** Sagittal section T2 weighted MRI of the same patient (arrow). **(c)** Axial section T2 weighted MRI of the patient after disconnection surgery through the interhemispheric route. Arrow designates disconnection plane. **(d)** Sagittal section T2 weighted MRI of the same patient after disconnection surgery. Arrow designates the disconnection plane.

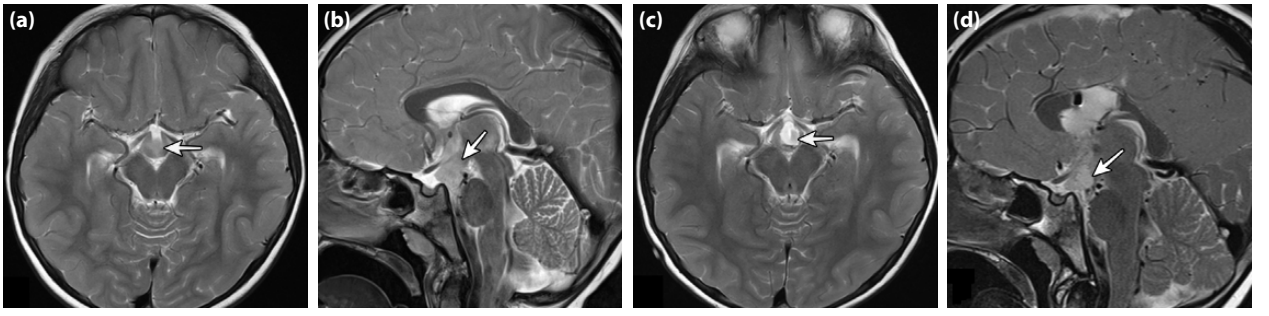

Fig. 3. **(a)** Axial section T2 weighted MRI of a patient with type 3 HH (arrow). **(b)** Sagittal section T2 weighted MRI of the same patient (arrow). **(c)** Axial section T2 weighted MRI of the patient after disconnection surgery through the interhemispheric route. Arrow designates disconnection plane. **(d)** Sagittal section T2 weighted MRI of the same patient after disconnection surgery. Arrow designates the disconnection plane.

tom, they may also present with precocious puberty, cognitive problems, such as speech retardation, learning difficulties and behavioral changes, such as difficulties in anger control, oppositional-defiant disorder.[4,5] Gelastic seizures are characteristic seizure types associated with HH.[9] They consist of short, repeated behaviors, which are like laughter, generally lasts 10–20s.[10] More than 80% of patients with gelastic seizures secondary to HH may also develop other types of seizures, which are very resistant to antiepileptic drug treatment and mandate HH disconnection surgery.[11,12]

Delalande et al.[1] classified HH into four main categories according to their insertion planes to the hypothalamus. They described type 1 as the one which has a horizontal im-

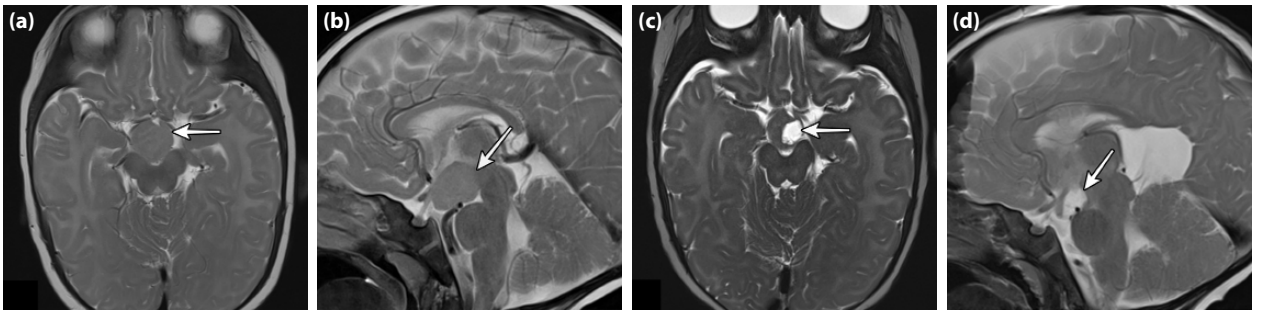

Fig. 4. **(a)** Axial section T2 weighted MRI of a patient with type 4 HH (arrow). **(b)** Sagittal section T2 weighted MRI of the same patient (arrow). **(c)** Axial section T2 weighted MRI of the patient after disconnection surgery through the interhemispheric route. Arrow designates disconnection plane. **(d)** Sagittal section T2 weighted MRI of the same patient after disconnection surgery. Arrow designates the disconnection plane.

plantation plane to the hypothalamus at the level of tuber cinereum. Type 2 was described as the one with a vertical insertion plane to the hypothalamus and located within the third ventricle. Type 3 was described as the combination with type 1 and 2. Type 4 describes the giant hamartomas. They recommended a pterional route for type 1 HH, endoscopic or interhemispheric microneurosurgical disconnection for type 2 HH, and staged surgery as a combination of pterional and interhemispheric approaches for type 3. They did not recommend any specific type of surgery for type 4 HH.[1] We had 2 type 1 HH (16.7%), 5 type 2HH (41.6%), 2 type 3HH (16.7%) and 3 type 4 HH (25%) in our patient cohort. One of the type 1 HH lesions was operated through pterional approach; the other type 1 HH patient hamartoma was operated through subfrontal approach. All of the remaining 10 patients were operated through the interhemispheric approach.

Valdueza et al.[13] classified the HH based on the localization. They describe the type 1 HH as small lesions with tiny attachments to the tuber cinereum, whereas type 2 lesions as relatively large 3rd ventricular lesions, which displaces the hypothalamus.[13] They also proposed that type 1 lesions are more commonly associated with PP, whereas type 2 lesions are commonly associated with gelastic and other seizure types.[13] Arita et al.[4] also classified HHs into two main groups as parahypothalamic HH and intrahypothalamic type. The parahypothalamic type is very similar to type 1 HH and intrahypothalamic one is very similar to type 2 HH described by Valdueza et al.[13]

Hypothalamic hamartomas located within the hypothalamus and 3rd ventricle are more commonly associated with seizures, whereas HHs located at the level of tubercinereum are more commonly presented with precocious puberty.[14] The gelastic seizures may be triggered by epileptogenic activity propagated in the HH through neuronal connections, which are present only in HHs or also may be triggered by direct hypothalamic compression by the HHs within third ventricle.[14] Precocious puberty may be caused by excessive GnRH secretion from the lesion or epileptic discharges stimulates neurons to secrete an excess amount of GnRH.

Since PP mainly encountered in parahypothalamic HHs, they can be easily accessed and safely disconnected through surgery to treat PP.[15–17] There was 2 Delalande type 1 HH (case 5 and 7) in our patient cohort, which can also be grouped as parahypothalamic hamartomas, and both of which were presented with PP. Precocious puberty was totally disappeared in both patients after HH surgery. There were also one type 2 HH patient (case 4) presented with PP and one type 2 HH patient (case 12) presented with both GS and PP. Precocious puberty did not resolved in both patients. There was one type 3 HH patient (case 3) presented with both GS and PP in whom PP was completely resolved after HH disconnection surgery. There was also one type 4 HH patient (case 6) presented with both GS and PP in whom PP did not resolve after HH disconnection surgery. Although symptoms of patients according to tol localizations were similar in our cohort, there was no statistically significant relationship between the type of HH and the presenting symptom of patients. This may be because of the small number of the patient group.

There are several types of surgical routes described to treat HH patients. In all of them, the main aim was the total removal of the HH since it is thought to be the reason for GS and PP.[18] Delalande et al.[1] proposed that complete remov-

al of the HH can be replaced by disconnection of HH from the hypothalamus either with craniotomy or endoscopic surgery. All of the cases included in our patient cohort had a disconnective type of surgery since the risk postoperative neurological deficit is lower than the resective surgery.[1] Overall success rates of all kinds of HH surgery concerning seizure reduction differ between 43%-68%.[18,19] In our patient cohort, 88.8% (8 in 9) of patients showed more than 90% seizure reduction (Engel class 1–2), and 77.7% (7 in 9) of patients with seizure were totally cured.

Stereotactic radiosurgery is also an alternative to HH surgery for patients who present with epilepsy. Régis et al.[20] reported their series of eight patients with HH who were treated with SRS. They reported a total cure in four patients, and moderate improvement in the remaining four patients in terms of epilepsy with a mean latency period of nine months. Recently, Régis et al.[21] published their experience with SRS in 57 HH patients and they reported more than 50% seizure reduction rate. Overall seizure reduction rates of SRS in HH patients are reported to range between 27%–66% in the literature.[22–25] However, the success rate of SRS in patients with type 4 giant HHs is still low.[21]

There was only one patient (case 2) in our cohort with type 4 HH, who had post-operative SRS treatment after a failed surgery performed in another institution. He did not benefit from both procedures and was re-operated in our clinic. Now, he is still free of seizures during 55 months of follow-up.

Radiofrequency thermocoagulation, laser interstitial thermal therapy and interstitial brachytherapy are other less commonly used treatment options in HH patients with epilepsy.[1,26]

Although there have been different kinds of treatment options for HHs, we recommend disconnective surgery as the first treatment of choice. If it fails besides successful disconnection surgery, SRS treatment may be employed.

Conclusion

Hypothalamic hamartomas are rare congenital lesions generally present with refractory epilepsy and/or precocious puberty. Disconnective surgery is the first-line treatment option with very low post-operative complications in symptomatic HH patients. Surgical approach depends on the type of HH. Detailed post-operative neurological and endocrinological follow-up is recommended. Stereotactic radiosurgery may be used as an adjunct treatment in patients with unsatisfactory surgical outcome.

Ethics Committee Approval

Ethics committee approved.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: B.T.; Design: B.T.; Supervision: M.M.Ö.; Materials: B.T.; Data collection &/or processing: B.T., M.M.Ö.; Analysis and/or interpretation: B.T., M.M.Ö.; Literature search: B.T.; Writing: B.T.; Critical review: M.M.Ö.

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