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ScienceDirect
Epilepsy & Behavior 10 (2007) 328–332
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Assessment of cognitive functions before and after stereotactic interstitial radiosurgery of hypothalamic hamartomas in patients with gelastic seizures

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Received 6 November 2006; revised 19 December 2006; accepted 29 December 2006
Available online 20 February 2007

Abstract

We assessed cognitive functions before and 3 months after interstitial radiotherapy in 14 patients with gelastic seizures caused by hypothalamic hamartoma. Cognitive functioning was assessed before temporary implantation of ^{125}I-seed and 3 months after seed explantation. Performance was compared with that of a selected control group of conservatively treated patients with symptomatic focal epilepsy tested before add-on treatment with a new antiepileptic drug and after reaching steady state. No short-term negative side effects of the interstitial radiosurgery could be observed for the domains of attention and executive functions and verbal and figural memory performance. Cognitive development of the patients treated with seeds was comparable to that of the control group at both assessments. Thus, the stereotactic implantation of ^{125}I-seeds in this patient group with gelastic seizures caused by hypothalamic hamartoma provides a well-tolerated minimally invasive method in the treatment of this severe epileptic syndrome without negative cognitive side effects.

Keywords: Cognition; Interstitial radiosurgery; Hypothalamic hamartoma; Epilepsy

1. Introduction

In the past 2 years, interstitial stereotactic radiosurgery using temporary implantation of ^{125}I-seeds has become a promising option in the treatment of gelastic seizures caused by hypothalamic hamartoma (HH). This method has been successfully used to treat patients with this rare but highly pharmacoresistant type of focal epilepsy [1]. Apart from its positive effect on seizure frequency and severity, a positive effect on behavior and subjective handicaps of epilepsy was described in a previous work by our group as well [2]. Seizure-free patients and patients who experienced auras only showed a remarkable reduction in epilepsy-related behavioral problems, experienced less restrictions in social activities, and reported a more positive self-perception.

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1525-5050/$ - see front matter
doi:10.1016/j.yebeh.2006.12.009

Because of the critical localization of hypothalamic hamartomas, and particularly because of their close proximity to the mammillary bodies, lesioning of the hamartoma may result in cognitive side effects, and severe memory disturbances have been observed after microsurgical approaches [3]. Here we report the short-term consequences in a group of 14 juvenile and adult patients with gelastic epilepsy caused by hypothalamic hamartoma to assess the risk of interstitial stereotactic radiosurgery with respect to cognitive performance.

2. Methods

Fourteen adult patients, 15–43 years of age, with gelastic seizures caused by hypothalamic hamartomas were investigated (for clinical data, see Table 1). Before the temporary implantation of a ^{125}I-seed into the hamartoma, all patients received a complete presurgical workup, including high-resolution magnetic resonance imaging (MRI), continuous video/EEG telemetry, and a comprehensive neuropsychological assessment. According to the classification of Valdueza et al. [4], and based on high-resolution MRI, all hamartomas were located intrahypothalamically and were classified as type IIb. Ten of the patients with HH received a stable number of antiepileptic drugs (AEDs) within the observed period, three patients changed from two to one AED, and one patient changed from three to one AED postintervention. This change in the number of AEDs is not statistically significant ($\chi^2(1) = 2.57$, $P = \text{ns}$). Neuropsychological assessment was performed twice, prior to interstitial radiosurgery (T1) and 3 months afterward (T2). To improve statistical power, a number of neuropsychological tests were aggregated reflecting different cognitive domains. The following domains were assessed:

2.1. Attention

Selective attention was measured with the d2-Concentration Endurance Test [5]: This test requires the cancellation of a target letter embedded in distracter letters. The total performance score, standardized for sex and age, reflects cognitive speed. A second value, reflecting concentration, was determined by total performance minus omissions and errors.

2.2. Working memory

Verbal working memory performance was assessed with the subtest Digit Span Backward from the German version of the Wechsler Memory Scale—Revised [6]. This test requires the repetition of an increasing number of digits backward. Each correct repetition is scored 1 point. Visual working memory was assessed with the Spatial Span of the Wechsler Memory Scale—Revised. It requires repetition of a demonstrated block-tapping sequence of increasing length in a forward condition. Each correct repetition is scored 1 point.

2.3. Executive functions

Executive functions were assessed with three tests. (1) In the Phonemic Verbal Fluency task from the Leistungsprüfsystem, a German intelligence test [7], patients have to produce and write down as many words as possible beginning with the letters L, P, and R, respectively F, K, and R. Time for word production for each letter was 1 min. (2) The Labyrinth Test [8] consists of three labyrinths of increasing difficulty. The patient has to find his or her way from the center to the exit as fast and as accurately as possible. The time in seconds needed for completion and errors are recorded. (3) The subtest Block Design from the German Version of the Wechsler Adult Intelligence Scale—Revised [9] assesses visual–spatial integration by requiring an individual to reproduce abstract patterns.

2.4. Learning and memory

Verbal learning and memory performance were assessed with the Verbal Learning and Memory Test (VLMT) [10]. The test comprises five trials in which the patient learns a list of 15 unrelated words that he or she has to reproduce after every oral presentation. After a distraction task and a free recall procedure 30 min after learning, the patient has to recognize the

Table 1
Demographic and clinical data

	Patients with HHs treated by radiotherapy ($N = 14$)	Patients with focal epilepsy treated pharmacologically ($N = 15$)
Chronological age	25.4 (10.5)[a]	35.6 (9.8)[a,b]
Sex (men/women)	8/6	6/9
Professional status		
Regular school/interrupted/protected	2/2/1	1/2/0
Professional training	1	2
Regular job	3	6
Protected institution	3	0
Retired/out of work	2/0	0/1
Epilepsy		
Age at onset	4.2 (3.9)[a]	17.7 (12.1)[a,c]
Duration	21.2 (10.8)[a]	17.3 (13.7)[a]
Estimated seizures per month (min/max/mean)		
Simple partial seizures	0/300/78	0/130/15[b]
Complex partial seizures	0/90/18	0/9/4[c]
Secondarily generalized seizures	0/8/1.4	0/2/0.1
Interval between tests (days)	165.6 (67.7)[a]	172.4 (83.3)[a]
Lesion		
Volume of hypothalamic hamartoma (ml)	0.971 (0.879)[a]	
Lesion temporal/extratemporal/no lesion		9/5/1

[a] Mean (SD).
[b] $P < 0.05$.
[c] $P < 0.01$.

Table 2
Performance of patient groups in single cognitive functions[a]

Cognitive function	Patients with HHs		Conservatively treated patients	
	T1	T2	T1	T2
Speed	50.8 (39.4)	59.1 (42.6)	50.2 (35.7)	48.9 (35)
Concentration	52.9 (40.2)	62.3 (43.3)	52.1 (37.7)	51.8 (37.3)
Verbal working memory	23 (31.1)	23.1 (27.7)	36.3 (27.4)	38.1 (23.6)
Visual working memory	33.8 (34.4)	26.7 (28.7)	37.6 (34)	33.3 (34)
Planning	47.4 (35.1)	39.6 (38.3)	36 (34.8)	40.6 (30.4)
Visuo-construction	38.8 (34.2)	36.9 (29.7)	43.7 (31.2)	49.9 (33)
Phonemic fluency	40 (26.6)	41.1 (33.3)	59.7 (24.6)	62.6 (19.4)
Verbal learning	31.8 (30.3)	26.4 (29.3)	35.3 (37.2)	37.3 (32.4)
Verbal recognition	25.3 (21.8)	25.7 (24.9)	34.7 (28.6)	28.3 (24.8)
Visual learning/memory	14.9 (21.9)	11.6 (25.3)	25.9 (25.9)	26.4 (26.9)

[a] All values are mean (SD) percentage ranks.

words among a list of 50 words also containing semantically or phonemically related words. The total number of words correctly recalled from the learning trials serves as a measure of verbal learning; verbal memory performance was scored as the number of correctly recognized words in the recognition paradigm.

Visual memory performance was assessed with the DCS, a visual learning and memory test for neuropsychological assessment [11]. Patients are shown nine geometrical drawings in succession that they afterward have to reproduce using five wooden sticks. There are six learning trials. The total number of correctly reproduced items during the six trials serves as a measure of visual learning and memory abilities.

All test results are expressed as percentage ranks with a mean of 50 and SD of 34 (see Table 2). The mean value for each cognitive domain is calculated by summing up the results for each test (percentage rank) and dividing this total by the number of tests reflecting the cognitive domain. At the second neuropsychological assessment, parallel versions of the VLMT, DCS, and word fluency test were administered. For all other tests, no parallel versions exist. Therefore, to control for possible learning effects that could falsely be interpreted as improvements in cognitive functioning, we selected a control group of 15 outpatients with focal epilepsy (for clinical and demographic data, see Table 1). These patients also underwent neuropsychological testing twice, before medical treatment with an antiepileptic drug (T1) and after reaching the steady state of the individual target dosage (T2). At T2, 10 control patients were on AED polytherapy, and 4 patients were on monotherapy. In most patients ($N = 11$), Levetiracetam was added or given as single medication. Other AEDs were Oxcarbazepine, Pregabalin, Valproate, and, in one case, Barbexaclone, a prodrug of Phenobarbital that used to be a common antiepileptic drug in Germany.

The mean test–retest intervals of the two patient groups did not differ significantly (Table 1). Because gelastic epilepsy is caused by HHs, the two groups could not be matched with respect to onset of epilepsy, chronological age at testing, and frequency of simple and complex partial seizures.

All patients with HHs were stereotactically implanted with ^{125}I-seeds with a diameter of 0.5 mm. The radioactive seed remained within the HH for 3–4 weeks and was than removed under local anesthesia. The reference dosage chosen was 60 Gy at the outer margin of the hamartoma; the exact position of the seeds was ascertained by MRI 1 day after implantation.

Data were analyzed using a 2 (seed vs conservative patients) × 2 (time of assessment: preintervention (T1), 3 months after intervention (T2) × 4 (cognitive domains: attention, working memory, executive functions, learning and memory) analysis of variance. To assess changes in seizure frequency from T1 to T2, seizure development over time was rated as substantial reduction in seizure frequency (⩾50% reduction), no substantial changes, or substantial increase in seizure frequency (⩾100% increase).

3. Results

At the follow-up examination 3 months after intervention (T2), five patients with HHs had a ⩾50% reduction in seizures, and nine patients experienced no substantial changes in seizure frequency. Although none of the patients with HHs experienced a ⩾100% increase in seizure frequency, one patient did experience a nearly 80% increase (gelastic seizures as well as secondarily generalized seizures). In the conservatively treated patient group, nine patients experienced a ⩾50% decrease in seizure frequency, seizure frequency remained unchanged in five patients, and one patient had a substantial increase in the frequency of simple partial seizures. There was no statistical difference between the two groups with respect to seizure development over time ($\chi^2(2) = .325$, $P = \text{ns}$).

Results of the ANOVA indicated no significant main effects between the two patient groups ($F(1,27) = 0.453$, $P > 0.05$) and time of assessment ($F(1,27) = 0.962$, $P > 0.05$). Additionally, there were no significant interactions between groups and time of assessment. A significant main effect was observed for the cognitive domains ($F(3,81) = 10.08$, $P < 0.001$; partial $\eta^2 = 0.255$). After Bonferroni correction, pairwise post hoc comparisons revealed

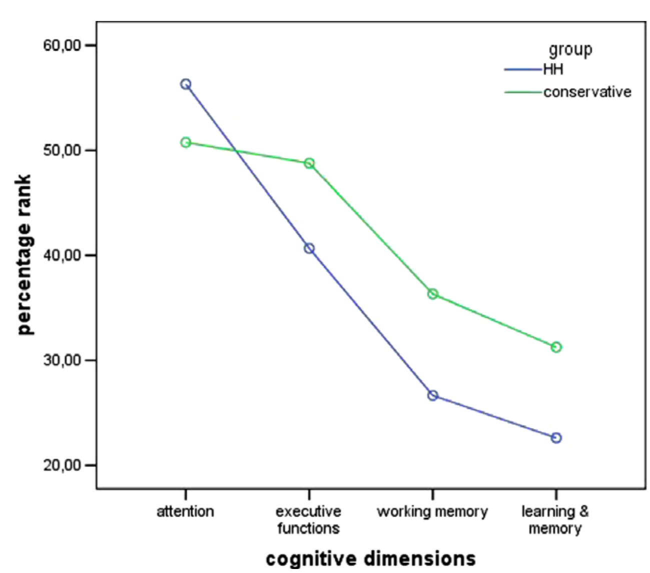

Fig. 1. Comparison of performance of patient groups among different cognitive domains.

significantly lower working memory and learning and memory performance compared with executive functions ($P < 0.05$) and attention ($P < 0.01$, Fig. 1). No performance differences were observed between attentional processes and executive functions ($P > 0.05$). On repetition of these analyses and with the change in seizure frequency from T1 to T2 as covariate, no significant effect on cognitive functioning was noted ($F(1,26) = 0.327$, $P > 0.05$).

4. Discussion

There is broad agreement that gelastic seizures caused by HHs do not respond to pharmacological treatment [12]. Hence, different neurosurgical and radiosurgical interventions are used to treat this severe epilepsy syndrome. Open resection of HHs via a pteryonal approach is frequently accompanied by such neurological complications as diabetes insipidus, hemiplegia, Korsakoff syndrome, and thalamic infarction in a considerable number of patients [13]. In particular, intrahypothalamic sessile hamartomas are often not completely respectable, resulting in a nonsatisfactory outcome with respect to epilepsy [4]. Rosenfeld and colleagues [14] recently reported the results of resection of HHs through an interforniceal approach to the third ventricle in 45 patients. Postoperative side effects, for example, diabetes insipidus in 2 patients and early short-term memory impairment in 16 patients with persistence in 6 patients, were observed. Recently, Ng and co-workers [15] reported transient memory disturbances in 58% of patients with HHs undergoing transcallosal resection of the lesion, with persistence in 8% of cases. Consequently, these studies emphasize the necessity of evaluating new techniques in the treatment of HHs with respect to early and late cognitive side effects.

The temporary implantation of ^{125}I-seeds into HHs is a new and promising minimally invasive method in the treatment of patients with gelastic seizures caused by HHs [1]. Our results indicate that this interstitial radiosurgical treatment generally is not accompanied by early short- or long-term memory impairments. Additionally, there were no changes in attentional or executive functions. Before and after interstitial radiosurgery, the patients with HHs exhibited cognitive performance in the selected cognitive domains comparable to that of conservatively treated patients who had been tested twice, before and after add-on treatment with AEDs. These patients were treated predominantly with second-generation AEDs with a low risk of impairing cognitive functioning [16]. We excluded all conservatively treated patients who were treated with AEDs known to have a high probability of causing cognitive disturbances, for example, Topiramate [16,17]. With this selection we aimed to guarantee that the conservatively treated patients were in optimal medical condition to show nonmedication effects on cognitive performance over time. For both groups, seizure status at T2 had no substantial impact on cognitive performance. Both patient groups had similar cognitive profiles with significantly lower performance in the domains of learning/memory and working memory than in attention and executive functions. Because the control group consisted mainly of patients with temporal lobe epilepsy (TLE), this pattern of cognitive impairments is not surprising. A huge body of literature indicates that because of the importance of the mesial temporal lobe in the processing of memory functions, memory disturbances especially are a constitutional element of TLE [18]. Because of the nature of seizure initiation and propagation in patients with HHs, a control group of patients with HHs and gelastic epilepsy undergoing medical treatment would have been more suitable for this study. However, one has to bear in mind that seizures in patients with HHs are highly pharmacoresistant [1]. Thus, from an ethical point of view, it would be very questionable to withhold from these patients a promising therapeutic option for their pharmacoresistant seizures.

In a recently published study by our group [19], we described in detail the cognitive profiles of 13 juvenile and adult patients with gelastic seizures caused by HHs. In summary, the most prominent cognitive deficits were observed in memory processing (77% of cases). Concordant with our results, Fratalli and co-workers [20] described a similar pattern of disturbed memory functions in a group of 8 pediatric patients with gelastic seizures and HHs. In both studies, the nature of the severe memory disturbances observed remained unexplained. On the basis of strong reciprocal interconnections between the hypothalamus and the medial temporal lobe [21], it was speculated that temporal ictal and interictal EEG abnormalities suspected of causing complex partial seizures in patients with HHs are involved in the genesis of memory disturbances [22,23]. In the current study, the reduction in seizure frequency did not have any substantial effect on memory performance. Considering the short follow-up interval of only 3 months, late positive effects of interstitial radiosurgery on memory performance could be possible, analogous to the effects of selective amygdalohippocampectomy (SAHE) on memory performance in patients with TLE. Restitution and increased memory performance after SAHE have been described at the 1-year follow-up, whereas memory performance at the 3-month follow-up was decreased compared with preoperative performance [24,25]. This observation points to the fact that release effects or restitution of memory functions is a time-dependent process and is not likely to be observed after a short interval of 3 months after an intervention.

In summary, the temporary implantation of ^{125}I-seeds in patients with gelastic seizures caused by HHs proved to be a powerful method for decreasing seizure frequency. Within a period of 3 months after interstitial stereotactic radiosurgery, our study observed no evidence of negative cognitive side effects from the treatment as compared with a well-established pharmaceutical intervention. It is necessary to evaluate these patients carefully in the long term to obtain valid data concerning seizure development and changes in cognitive capabilities.

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