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Predictors of cognitive function in patients with hypothalamic hamartoma following stereotactic radiofrequency thermocoagulation surgery

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SUMMARY

Objective: To determine the predictors of cognitive function in patients with drug-resistant gelastic seizures (GS) related to hypothalamic hamartoma (HH) before and after stereotactic radiofrequency thermocoagulation surgery (SRT).

Methods: We studied 88 HH patients who underwent SRT between October 1997 and December 2014. Patients received neuropsychological tests preoperatively and postoperatively. Based on the preoperative measures, patients were categorized as "high-functioning" (full-scale intelligence quotient [FSIQ] ≥70; n=48) and "low-functioning" group (FSIQ <70; n=40). Univariate and multivariate linear regression analyses determined the clinical, electroencephalographic (EEG), and imaging factors associated with preoperative cognitive function as well as postoperative cognitive change.

Results: Eighty-seven (98.8%) patients were followed postoperatively for an average of 3.3 years, and 75 (85.2%) of them achieved GS remission at the last hospital visit. Neuropsychological performance was significantly improved after surgery in both groups. Multivariate linear regression analysis showed that a smaller HH size (p=0.002) and a smaller number of antiepileptic drugs (p<0.001) were preoperatively associated with better neuropsychological performance. Multivariate linear regression analysis showed that better postoperative improvement in cognition was associated with a shorter duration of epilepsy (p=0.03).

Significance: Cognitive impairment related to epileptic encephalopathy may improve following SRT in substantial proportions of HH patients. Reduced improvement in postoperative cognitive function in patients with longer duration of epilepsy warrants further studies to determine if earlier SRT provides a greater chance of postoperative cognitive improvement in patients with HH.

INTRODUCTION

Hypothalamic hamartoma (HH) is a rare congenital brain lesion.[1] Whereas one hallmark of HH syndrome is intractable gelastic seizures (GS), about half of HH patients exhibit cognitive impairment and behavioral disorders, referred to as epileptic encephalopathy.[2,3] Both drug-resistant GS and epileptic encephalopathy caused by HH are believed to be surgically treatable.[2,4] Stereotactic radiofrequency thermocoagulation surgery (SRT) is now recognized as an established therapy for intractable GS related to HH;[2] however, the predictors of cognitive profiles before and after SRT remain unclear. Previous studies of HH patients who underwent open or gamma knife surgeries reported that postoperative cognitive function was associated with several factors, including "anatomical features of HH", "age at epilepsy onset", "age at surgery", "duration of epilepsy", "presence of central precocious puberty", "number of antiepileptic drugs", and "preoperative cognitive function".[5-7] Since relatively small numbers of HH patients were included in the past studies, we expected that our longitudinal data derived from a large number of patients uniformly undergoing SRT would independently determine the factors predictive of cognitive function in patients with HH. Our central hypothesis, based on our clinical practice and the previous reports noted above, was that patients with a shorter duration of epilepsy would benefit from cognitive improvement following SRT more than those with a longer duration of disease. In other words, we hypothesized that the cognitive impairment in patients with severe epileptic encephalopathy may be less reversible, even after remission of GS by SRT. Univariate and multivariate analyses were employed to determine the clinical, imaging, and

electroencephalographic factors independently predictive of cognitive function before and after SRT.

MATERIALS AND METHODS

Patient selection

A total of 127 patients with HH underwent SRT for drug-resistant GS between October 1997 and December 2014 in the Hypothalamic Hamartoma Center, Nishi-Niigata Chuo National Hospital, Niigata, Japan. The present study included 88 Japanese patients. We excluded 39 patients who were unable to undergo the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), Wechsler Intelligence Scale for Children-Third Edition (WISC-III), or Tanaka-Binet Intelligence Scale (TBIS), because of the presence of severe cognitive deficit or because their primary language was other than Japanese. Clinical and neuropsychological data at 1 year and at the last hospital visit following SRT were reviewed. One patient was followed at another hospital postoperatively. Thereby, the mean follow-up period for 87 patients was 3.38 years (standard deviation [SD]: 1.8 years). One-year postoperative follow-up data was available in 84 out of the 87 patients. All patients (or parents of pediatric patients) gave written informed consent before presurgical evaluation and surgical treatment.

Clinical history and video-electroencephalography (EEG) monitoring characterized GS and non-GS type seizures including complex partial seizures, tonic-clonic seizures, atypical absence, tonic seizures, atonic seizures, myoclonic seizures, and spasms. Video-EEG, recorded with the EEG1100 system (Nihon Kohden, Tokyo, Japan), determined the distribution of interictal epileptiform discharges. Preoperative evaluation also included neuropsychological tests, ictal/interictal single-photon emission computed tomography

(SPECT) with ^{99m}Tc-ethyl cysteinate dimer using the Symbia S system (Siemens Japan, Tokyo, Japan), and magnetic resonance imaging (MRI) using the Signa HDxt 1.5T system (GE Healthcare Japan, Tokyo, Japan). The MRI sequences included a 3D T1-weighted and fluid-attenuated inversion recovery images. MRI subtypes were categorized as intrahypothalamic, parahypothalamic, or mixed hypothalamic type according to the MRI criteria in the previous report.[2]

Neuropsychological examination

A neuropsychologist examined each patient's cognitive function with WAIS-III, WISC-III, or TBIS. In general, patients who were <7 years old were exclusively examined with TBIS; patients between 7 and 15 years old were examined with WISC-III, and patients ≥16 years were examined with WAIS-III. Patients with severe mental retardation who could not be examined with WISC-III or WAIS-III were examined with TBIS, even if they were ≥7 years old. In this study below, "FSIQ" was defined as "full-scale intelligence quotient" on WISC-III and WAIS-III or "IQ" on TBIS. "Postoperative cognitive change" was defined as subtraction of "preoperative FSIQ" from "FSIQ at 1 year after surgery or at the last hospital visit". The outcome measures of interest included "preoperative FSIQ" and "postoperative cognitive change".

Patient categories

Based on the result of IQ tests employed preoperatively, patients were categorized into "high-functioning" group (FSIQ≥70; n=48) and "low-functioning" group (FSIQ <70; n=40) because mental retardation is defined by the criterion of mental retardation in ICD-10.[8]

Statistical analysis

Continuous variables were reported as mean and SD, and categorical variables were reported as a number and percentage. The two-sample t-test was used to compare the distributions of continuous variables (e.g.: clinical profiles such as age) between the two patient groups. Fisher's exact test was used to test the equality of proportions of categorical variable (e.g.: gender) between two groups. The paired t-test was used to compare distributions in the same patient between two time points (i.e.: before and after surgery). Univariate and multivariate linear regression analyses using the variable reduction method were performed to determine the factors independently predictive of "preoperative FSIQ" and "postoperative cognitive change".[9] The predictor variables, incorporated into the regression analyses, included: (1) age at onset of GS, (2) duration of GS, (3) duration of non-GS type seizures, (4) maximum diameter of HH, and (5) number of antiepileptic drugs (AEDs) before surgery. The following categorical variables were also incorporated in the regression model: (6) gender, (7) attachment side of HH (bilateral attachment treated as attachment to both left and right side), (8) presence of precocious puberty, and (9) presence of preoperative interictal scalp EEG interictal epileptiform discharges. In addition to the aforementioned variables, (10) preoperative FISQ were also incorporated in the regression model to determine the factor independently predictive of "postoperative cognitive change".

In addition, we determined the factor independently predictive of the verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) by employing regression analyses in patients who were examined with WISC-III and WAIS-III.

Statistical analyses were conducted with EZR (Saitama Medical Center, Jichi Medical

University, Saitama, Japan). EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[10] Statistical significance was set at $p < 0.05$.

RESULTS

Patient profiles

Univariate analyses suggested difference in clinical profiles between the patient groups (Table 1). Those in the “high-functioning” group had a shorter duration of non-GS than those in the "low-functioning" group ($p = 0.009$; two-sample t-test). Seventy-seven patients with HH had non-GS type seizures. The percentage of patients showing interictal epileptiform discharges on scalp EEG was significantly higher in the “low-functioning” group than in the “high-functioning” group ($p = 0.005$; Fisher’s exact test). Preoperatively, patients in the “high-functioning” group took a smaller number of AEDs than those in the “low-functioning” group ($p = 0.006$; two-sample t-test).

Preoperative cognitive function and cognitive change following SRT

Eighty-four patients (95%), including 46 in the “high-functioning” group and 38 in the “low-functioning” group, were evaluated at a 1-year follow-up. The mean postoperative follow-up period between SRT and the last visit was 3.4 years. FSIQ in each patient group was significantly improved postoperatively at 1 year as well as at the last hospital visit (Fig. 1A and Table 2). Between the groups, there was no significant difference in the degree of improvement in FSIQ at postoperative 1 year or at the last visit (Table 2).

Significant postoperative improvement in FSIQ was noted in those with GS remission after SRT (preoperative: 72.8 ± 25.1 vs. postoperative at the last visit: 81.2 ± 26.7; $p < 0.001$;

paired t-test) but not in those failing to achieve GS remission (preoperative: 68.8 ± 23.3 vs. postoperative at the last visit 71.1 ± 24.1: p=0.36; paired t-test).

Patients with a history of non-SRT interventions, including partial removal of HH, gamma knife surgery, focused resection, corpus callosotomy, and biopsy, had lower preoperative FSIQ than those without (no past intervention: 75.7 ± 22.1 vs. with past intervention: 62.7 ± 28.9; p=0.03; two-sample t-test). Nonetheless, SRT improved postoperative FSIQ even in patients with a previous history of non-SRT interventions (preoperative: 62.7 ± 28.9 vs. postoperative at last visit 72.5 ± 31.6; p <0.001; paired t-test). There was no difference in the postoperative change in FSIQ between patients with and without past non-SRT interventions (past non-SRT interventions 9.9 ± 7.3 vs. no past intervention: 6.7 ± 8.8; p=0.13; two-sample t-test).

We have provided the detailed results of neuropsychological measures other than FSIQ in online supplementary documents (Table S1).

Predictive factors of postoperative cognitive changes

Univariate linear regression analysis, employed to 84 patients, showed that duration of non-GS type seizures (p=0.03) and preoperative number of AEDs (p=0.03) predicted postoperative change of FSIQ at 1 year following SRT. These predictor variables were negatively correlated to the outcome measure. Multivariate linear regression analysis showed that duration of non-GS type seizures (p=0.03) independently predicted postoperative change of FSIQ at 1 year following SRT (Table 3).

Univariate linear regression analysis, employed to the “high-functioning” group, showed that preoperative FSIQ (p=0.04) predicted postoperative change of FSIQ at 1 year

following SRT. Multivariate linear regression analysis showed that preoperative FSIQ (p=0.01), interictal epileptiform discharges (p=0.04), and mixed hypothalamic type of HH (p=0.04) independently predicted the change in FSIQ postoperatively at 1 year. Likewise, the postoperative FSIQ change at last visit can be independently predicted by preoperative FSIQ (p=0.03) and mixed hypothalamic type of HH (p<0.001) (Table 3).

Univariate linear regression analysis, employed to the "low-functioning" group, showed that preoperative FSIQ (p=0.03), age at onset of GS (p=0.04) and preoperative number of AEDs (p=0.04) predicted postoperative FSIQ change at 1 year following SRT. Multivariate linear regression analysis showed that duration of non-GS (p=0.007) and age at onset of GS (p=0.006) predicted the postoperative FSIQ change at 1 year (Table 3).

Supplementary Table S2 provides the results of univariate and multivariate linear regression analyses to determine the factors independently predictive of the changes in FSIQ, VIQ, and PIQ.

Predictive factors associated with preoperative cognitive function

Univariate linear regression analysis, employed to all 88 patients, showed that interictal epileptiform discharges on scalp EEG (p=0.03), intrahypothalamic type of HH (p=0.003), mixed hypothalamic type of HH (p=0.02), preoperative number of AEDs (p=0.002), maximum HH diameter (p=0.01) and precocious puberty (p=0.04) maintained their independent predictive variable status for preoperative FSIQ. Multiple linear regression analysis showed that preoperative number of AEDs (p<0.001) and maximum HH diameter (p=0.002) predicted preoperative FSIQ (Table 4). These predictor variables were negatively correlated to preoperative FSIQ. Univariate linear regression analysis, employed to the "low-

functioning" group, showed that age at onset of GS (p=0.04) and maximum HH diameter (p=0.04) predicted preoperative FSIQ. Multiple linear regression analysis showed that age at onset of GS (p=0.006), duration of GS (p=0.04), that of non-GS (p=0.04) and intrahypothalamic type of HH (p=0.03) predicted preoperative FSIQ (Table 4).

Supplementary Table S3 provides the results of univariate and multivariate linear regression analyses, employed to the patients examined with WISC-III and WAIS-III, to determine the factors independently predictive of preoperative FSIQ, VIQ, and PIQ.

DISCUSSION

To our knowledge, this is the first large case-series study to report the changes in cognitive function among patients with HH following SRT. Thereby, we determined the predictors of postoperative cognitive change. Our findings may help to identify patients with HH who are more likely to benefit from SRT in terms of cognitive function, and may also help to explain the pathophysiological mechanism of epileptic encephalopathy associated with HH.

Predictors of postoperative cognitive changes

The results of our multivariate regression analyses led to the following hypotheses. Ultimately, we hypothesize that early intervention will optimize the degree of postoperative cognitive improvement following SRT. The present study provided some evidence that warrants early intervention with SRT for intractable GS with HH. First of all, SRT surgery improved cognition in patients with a shorter duration of epilepsy more than in those with a longer duration (Tables 2 and S2; Fig.1B). Patients with intractable GS related to HH has

increased risk of progressive worsening of EEG abnormalities and secondary epileptogenesis.[11,12] Their academic performance and social skills tend to be impaired by such disease progression, similar to patients with childhood-onset temporal lobe epilepsy.[13]

We also hypothesize that severe epileptic encephalopathy may be irreversible, even after achieving GS freedom (Table 3 and Fig.1C). Our study showed that cognitive function of "low-functioning" patients remained lower, even after SRT, than those of "high-functioning" patients. Among "low-functioning" patients, poor preoperative FSIQ was associated with reduced cognitive improvement following SRT (Fig.1A and 1C). In contrast, regression analyses, employed to "high-functioning" group alone, revealed that patients with lower preoperative FSIQ enjoyed greater cognitive improvement following SRT (Fig. 1A and 1C). Our observations are consistent with those in previous studies in other institutions. For example, Wethe et al. reported that patients with lower preoperative cognition improved more than those with higher cognitive function,[6] and their study population can be treated as "high-functioning", based on our study criteria. Lack of cognitive improvement in patients with the most severe cognitive deficit in the "low-functioning" group warrants further studies to determine if earlier SRT provides a greater chance of postoperative cognitive improvement to the patients with HH. Taken together,[14,15] we wish to propose that we should consider early intervention for patients with HH before they develop severe and irreversible cognitive deficits.

Patients with interictal epileptiform discharges on scalp EEG had lower preoperative cognition than those without interictal epileptiform discharges in the present study. The relationship between the severity of cognitive deficit and interictal EEG abnormality has been reported by previous studies of HH[4,16] as well as in the other epilepsy

syndromes.[17,18] Cognitive deficits associated with focal seizures and focal epilepsies may be related to the dysfunction of a network of cortical and subcortical brain structures induced by epileptic activity.[19,20] Among the "high-functioning" patients, the presence of interictal epileptiform discharges on scalp EEG was associated with better cognitive improvement following SRT. This finding may be attributed to the notion that SRT terminated propagation of epileptic discharges from HH to other structures. We previously proposed that the mediodorsal nucleus of the thalamus is important for epileptic encephalopathy associated with HH because the mediodorsal nucleus of the thalamus has been implicated as the key nucleus in intractable GS with HH.[21] EEG–functional MRI study in patients with HH also supports our hypothesis.[22] Schizophrenia and Korsakoff"s syndrome, which are often associated with cognitive dysfunction and behavior disorders, also involve dysfunction of the mediodorsal thalamus.[23,24] The observation that inhibition of the thalamic mediodorsal nucleus impairs cognition of animals also supports our hypothesis.[25] Further investigation into the precise pathophysiological mechanism of epileptic encephalopathy caused by HH is needed.

Clinical change in cognitive function following SRT

The goal and strategy for patients with intractable GS associated with HH are GS remission after SRT and the expectation of cognitive improvement. We believe that freedom from GS may be an important key to optimize the cognitive improvement following SRT, whereas a previous study reported that postoperative seizure outcome was not necessarily associated with postoperative cognitive improvement.[6] Univariate analysis, in the present study, suggested that failure to achieve GS remission at the last visit was associated with

reduced cognitive improvement after SRT. History of past surgical intervention did not negatively impact the cognitive improvement following SRT.

Predictors of preoperative cognitive function

The present study found that larger HHs were associated with poorer preoperative cognitive function, as has been previously reported.[3] In our previous study, the maximum diameter of the HH, once associated with poor preoperative FSIQ (Table 4), was instead a positive predictor of postoperative cognitive change in VIQ and PIQ (Table S2). Although larger HHs are perceived to be difficult to treat surgically,[26] we have a track record of successful treatment of giant HH of which diameter is greater than 30 mm.[27]

In concurrence with our previous report,[28] the findings of the current study support the classification of HH as being well correlated with preoperative cognitive function. Specifically, intrahypothalamic type HH was associated with better intellectual function compared to the other types (Tables 4 and S4). We also found that mixed hypothalamic type HH was associated not only with lower preoperative cognition but also with lower postoperative change of cognitive function (Table 3).

The use of multiple AEDs is associated with worse cognitive function.[5] Most patients with GS take multiple AEDs prior to surgery because GS is usually resistant to AEDs.[28] We hypothesize that early intervention by SRT would reduce the risk of cognitive decline attributed to the effects of multiple AEDs.

Limitations

The results of this study need to be interpreted in light of several limitations. First, our findings were limited to patients who were examined, in Japanese, with WAIS-III, WISC-III, or TBIS. Patients who do not speak Japanese (i.e.: most patients from foreign countries) were excluded from this study. Second, the outcome measures were derived from the WISC-III/WAIS-III and IQs from the TBIS and defined them all as "FSIQ." A previous study reported a strong correlation between FSIQ on WISC-III and IQ on TBIS.[29] Third, we could not exclude a practice effect in long-term follow-up. Therefore, we compared the degree of postoperative improvement in the patients with postoperative GS remission vs. those without. Although WISC and WAIS are susceptible to practice effects,[30] the cognitive improvement in our series could not be explained only by practice effects because the degree of cognitive improvement was significantly better in patients with GS remission after SRT. Fourth, the outcome measures in the present study did not include memory or executive function, which might have been positively or negatively altered by epilepsy surgery.[6] Memory function was measured with the Wechsler Memory Scale only in 31.8% (28/88) of patients; thus, we focused on FSIQ in the present study. We plan to collect more pre- and post-operative measures on such neuropsychological sub-tests in order to better characterize the effect of SRT on cognitive function. Finally, we did not incorporate behavioral disorders as co-variables, although behavioral disorder is one of the typical symptoms in epileptic encephalopathy caused by HH.[2,7,31] Further research is clearly needed to enroll participants with a definitive behavioral disorder diagnosis, based on the formal assessment to explore the relationship between cognitive change after SRT and such disorders.[32]

CONCLUSION

The main aim of this study was to clarify the predictors that contribute to cognitive change following SRT. Cognitive impairment may improve following SRT in substantial proportions of HH patients. Patients with longer duration of epilepsy or those with severe mental retardation benefited smaller degree of cognitive improvement following SRT. Further studies will determine whether earlier SRT provides a greater degree of postoperative cognitive improvement in patients with HH.

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DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose concerning the subjects or methods used in this study or the findings specified in this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. We received no support or funding for this study.

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KEY POINTS

- Patients with intrahypothalamic type HH have better preoperative cognitive function
- Excessive medication with AEDs affects preoperative FSIQ
- SRT is effective not only for intractable GS but also for cognitive deficits caused by HH
- Patients with a shorter duration of epilepsy experience cognitive improvement following SRT

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A) Detailed scatter plots of preoperative and postoperative verbal IQ (VIQ) and performance IQ (PIQ) in order of preoperative PIQ in individual patients (n=64). Black plots show preoperative VIQ or PIQ; gray plots show VIQ or PIQ postoperatively at year 1 and white plots show VIQ or PIQ at the last visit after SRT. ◇ = PIQ; □ = VIQ (B) Detailed scatter plots of postoperative change in VIQ in order of preoperative VIQ in individual patients (n=64). Gray plots show VIQ postoperatively at year 1 and white plots show VIQ at last visit after SRT. ○ = patients with left attachment HH; △ = patients with right attachment HH

Table S1. Comparison of preoperative vs. postoperative cognitive function in the patients examined with WAIS/WISC.

Table S2. Predictors of postoperative change in FSIQ, VIQ and PIQ in the patients examined with WAIS/WISC by univariate and multivariate linear regression analyses.

Table S3. Predictors of preoperative of FSIQ, VIQ and PIQ in the patients examined with WAIS/WISC by univariate and multivariate linear regression analyses.

Appendix S1. Discussion about VIQ and PIQ in patients who were examined with WAIS/WISC.

Table 1. Clinical characteristics of patients

Clinical features	All patients n=88 Mean (SD)	High-functioning group (Preoperative FSIQ≧70) n=48 Mean (SD)	Low-functioning group (Preoperative FSIQ<70) n=40 Mean (SD)
Sex, female, n (%)	31 (35)	17 (35)	14 (35)
Age at surgery, y	16.2 (11.5)	15.3 (11.5)	17.3 (11.5)
Age at onset of GS/non-GS, y	2.3 (2.8)/6.9 (5.1)	2.6 (3.2)/7.8 (5.4)	2.0 (2.1)/5.9 (4.7)
Duration of GS/non-GS, y	13.9 (11.1)/8.5 (9.3)	12.7 (11.1)/**6.1 (7.9)**	15.4 (11.1)/**11.3 (10.1)**
Maximum diameter of HH, mm	15.8 (7.1)	14.8 (6.6)	16.9 (7.7)
Attachment side, n (%), right/bilateral/left	24 (27)/41 (47)/23 (26)	15 (31)/20 (42)/13 (27)	9 (23)/21 (53)/ 10(31)
MRI subtype, n (%), intra/mixed/para	24 (27)/58 (66)/6 (7)	17 (37)/28(58)/3 (6)	7 (18)/30 (75)/3 (8)
No interictal epileptiform discharges on scalp EEG, n (%)	12 (14)	**11 (23)**	**1 (3)**
Precocious puberty, n (%)	26 (30)	11 (23)	15 (38)
Number of preoperative of AEDs, n (%)	2.1 (1.1)	**1.7 (1.0)**	**2.4 (1.0)**
History of non-SRT interventions, n (%)	24 (27)	11 (23)	13 (33)
Seizure remission, n (%)			
At POY1: GS/All types of seizure	75 (85)/58 (66)	40 (83)/34 (71)	35 (88)/24 (60)
At last visit: GS/All types of seizure	75 (85)/57 (65)	42 (88)/**38 (79)**	33 (85)/**19 (49)**

Bolded format represents statistically significant findings in comparison between patients in “high-functioning” group and those in “low-functioning” group ($p<0.05$). AEDs: antiepileptic drugs. FSIQ: full-scale intelligence quotient. GS: gelastic seizures. HH: hypothalamic hamartoma. Intra: intrahypothalamic type. mixed: mixed hypothalamic type. MRI: magnetic resonance imaging. non-GS: non-gelastic seizures type seizures. para: parahypothalamic type. POY: postoperative year. PR: partial resection of HH. SD: standard deviation. SRT: stereotactic radiofrequency thermocoagulation.

Table 2. Comparison of preoperative vs. postoperative FSIQ

	Preoperative	POY1 n=84			Last visit n=87			Postoperative change	
		vs. preoperative			vs. preoperative			POY1	Last visit
Group	Mean (SD)	Mean (SD)	t (df)	p value	Mean (SD)	t (df)	p value	Mean (SD)	Mean (SD)
All patients	72.2 (24.6)	**78.6 (25.7)**	**11.3 (83)**	**<0.001**	**79.8 (26.5)**	**8.36 (86)**	**<0.001**	6.98 (5.65)	7.61 (8.49)
High-functioning	90.4 (12.6) [a]	**97.0 (12.1)**	**8.83 (45)**	**<0.001**	**98.2 (13.4)**	**7.02 (47)**	**<0.001**	7.07 (5.43)	7.83 (7.73)
Low-functioning	50.3 (16.4)	**56.3 (19.3)**	**7.07 (37)**	**<0.001**	**57.2 (20.4)**	**4.86 (38)**	**<0.001**	6.87 (5.99)	7.33 (9.43)

Bolded format represents statistically significant findings in comparison with preoperative cognitive function.

[a] $p < 0.05$, vs. in the "low-functioning" group

df, degrees of freedom; FSIQ, full-scale intelligence quotient; IQ, intelligence quotient; POY1, postoperative 1 year; SD, standard deviation

Table 3. Predictors of postoperative change by univariate and multivariate linear regression analyses

Independent variables	Postoperative 1 year n=84				Last visit n=88			
	Univariate		Multivariate		Univariate		Multivariate	
	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value
Female	0.86 (1.28)	0.51			0.56 (1.91)	0.77		
Age at onset of GS	0.35 (0.23)	0.13			0.51 (0.33)	0.12		
Duration of GS	–0.09 (0.06)	0.10			–0.02 (0.08)	0.77		
Duration of non-GS	**–0.14 (0.07)**	**0.03**	**–0.14 (0.07)**	**0.03**	-0.11 (0.10)	0.27		
Maximum diameter of HH	–0.005 (0.09)	0.96			0.02 (0.13)	0.85		
MRI subtype								
Intrahypothalamic type	1.02 (1.41)	0.47			2.30 (2.06)	0.27		
Mixed hypothalamic type	–1.67 (1.32)	0.21			–3.07 (1.91)	0.11		
Parahypothalamic type	3.00 (2.60)	0.25			3.64 (3.59)	0.31		

Attachment side of HH					
	Left side	–1.58	0.25	–3.65	0.07
		(1.38)		(2.01)	
	Right side	0.52	0.71	2.09	0.32
		(1.41)		(2.09)	
Interictal interictal epileptiform discharges on sEEG		1.91	0.28	–0.06	0.98
		(1.76)		(2.65)	
Precocious puberty		1.40	0.30	1.60	0.42
		(1.35)		(1.99)	
Number of preoperative AEDs		**−1.23**	**0.03**	–1.40	0.10
		(0.56)		(0.84)	
Preoperative FSIQ		0.01	0.68	0.01	0.72
		(0.03)		(0.04)	
Constant				**8.17**	

Table 3. Continued.

Independent variables	High-functioning group (Preoperative FSIQ≧70)								Low-functioning group (Preoperative FSIQ<70)							
	Postoperative 1 year n=46				Last visit n=48				Postoperative 1 year n=38				Last visit n=40			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value
Female	1.95 (1.65)	0.24			3.81 (2.29)	0.10			–0.47 (2.04)	0.82			–3.42 (3.14)	0.28		
Age at onset of GS	0.13 (0.26)	0.62			0.31 (0.35)	0.38			**0.90 (0.44)**	**0.04**	**1.21 (0.42)**	**0.006**	1.06 (0.71)	0.15		
Duration of GS	–0.04 (0.08)	0.52			0.02 (0.10)	0.82			–0.15 (0.09)	0.10			–0.08 (0.14)	0.59		
Duration of non-GS	–0.12 (0.11)	0.29			–0.08 (0.14)	0.56			–0.18 (0.09)	0.06	**–0.24 (0.09)**	**0.007**	–0.13 (0.15)	0.39		
Maximum diameter of HH	–0.09 (0.12)	0.45			–0.17 (0.17)	0.33			0.08 (0.13)	0.55			0.21 (0.20)	0.30		
MRI subtype																
Intrahypothalamic type	1.43 (1.68)	0.40			**5.91 (2.19)**	**0.01**			0.16 (2.70)	0.95			–5.52 (4.14)	0.19		
Mixed hypothalamic type	-2.54 (1.61)	0.12	**–3.11 (1.49)**	**0.04**	**–6.80 (2.06)**	**0.04**	**-7.72 (2.01)**	**<0.001**	–0.32 (2.32)	0.89			3.18 (3.59)	0.38		

Parahypothalamic type	6.73 (3.84)	0.09			5.16 (4.60)	0.27			0.50 (3.65)	0.89	2.17 (5.73)	0.71
Attachment side of HH												
Left side	–1.75 (1.74)	0.32			–4.61 (2.34)	0.05			–1.34 (2.31)	0.57	–2.17 (3.61)	0.55
Right side	–0.12 (1.80)	0.95			0.93 (2.53)	0.71			1.43 (2.30)	0.54	3.76 (3.58)	0.30
interictal epileptiform discharges on sEEG	3.43 (1.82)	0.07	**3.66 (1.68)**	**0.04**	1.55 (2.67)	0.56			–8.35 (5.99)	0.17	– 11.97(9.48)	0.21
Precocious puberty	2.47 (1.93)	0.21			0.45 (2.68)	0.87			0.66 (2.01)	0.75	2.93 (3.11)	0.35
Number of preoperative AEDs	–0.80 (0.76)	0.31			–0.33 (1.10)	0.76			**–1.95 (0.89)**	**0.04**	–2.83 (1.41)	0.05
Preoperative FSIQ	**-0.13 (0.06)**	**0.04**	**–0.16 (0.06)**	**0.01**	–0.12 (0.09)	0.19	**-0.18 (0.08)**	**0.03**	**0.13 (0.06)**	**0.03**	0.11 (0.09)	0.23
Constant			**20.36**				**28.69**				**7.19**	

Bolded format represents statistically significant findings.

AEDs, preoperative antiepileptic drugs; FSIQ, full-scale intelligence quotient; GS, gelastic seizures; HH, hypothalamic hamartoma; MRI, magnetic resonance imaging; non-GS, non-gelastic seizures type seizures; Reg, estimated regression coefficient; SE, standard error; sEEG, scalp

electroencephalogram

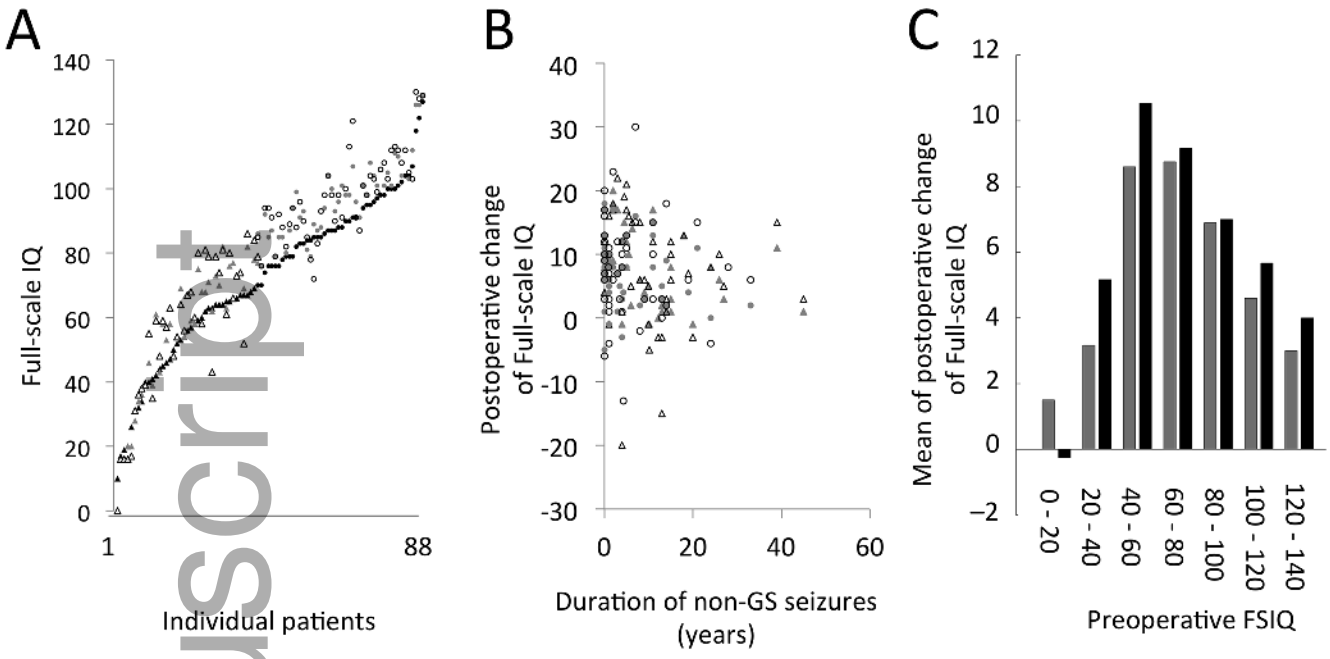
Table 4. Predictors of preoperative of FSIQ by univariate and multivariate linear regression analyses

Independent variables	All patients n=88				High-functioning group (Preoperative FSIQ≧70) n=48				Low-functioning group (Preoperative FSIQ<70) n=40			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value	Reg (SE)	p value
Female	–2.45 (5.53)	0.66			–3.31 (3.80)	0.39			–1.82 (5.49)	0.74		
Age at onset of GS	1.37 (0.95)	0.15			–0.12 (0.57)	0.83			**2.46 (1.20)**	**0.04**	**3.51 (1.21)**	**0.006**
Duration of GS	0.02 (0.24)	0.92			0.27 (0.16)	0.11			0.23 (0.24)	0.34	**1.11 (0.51)**	**0.04**
Duration of non-GS	–0.39 (0.28)	0.17			0.35 (0.23)	0.13			0.13 (0.26)	0.63	**–1.23 (0.58)**	**0.04**
Maximum diameter of HH	**–0.91 (0.36)**	**0.01**	**–1.08 (0.34)**	**0.002**	–0.31 (0.28)	0.27			**−0.69 (0.33)**	**0.04**		
MRI subtype												
Intrahypothalamic type	**17.30 (5.63)**	**0.003**			7.34 (3.67)	0.05			11.21 (6.65)	0.10	**14.04 (6.20)**	**0.03**
Mixed hypothalamic type	**−12.94 (5.40)**	**0.02**			–5.10 (3.64)	0.17			–6.77 (5.95)	0.26		

Parahypothalamic type	−8.23	0.43			−7.51	0.32	−5.04	0.61
	(10.44)				(7.48)		(9.91)	
Attachment side of HH								
Left side	−8.82	0.14			–4.88	0.21	–3.88	0.54
	(5.86)				(3.88)		(6.24)	
Right side	–0.59	0.92			2.10	0.61	–1.57	0.80
	(6.01)				(4.11)		(6.05)	
Interictal epileptiform discharges on sEEG	**−16.59**	**0.03**			2.73	0.53	–17.10	0.31
	(7.49)				(4.34)		(16.55)	
Precocious puberty	**−11.98**	**0.04**			–2.02	0.64	–7.99	0.14
	(5.65)				(4.35)		(5.26)	
Number of AEDs	**–7.41**	**0.002**	**–8.36**	**< 0.001**	–0.06	0.97	–4.64	0.07
	(2.34)		**(2.24)**		(1.79)		(2.46)	
Constant			**106.4**					**37.75**

Bolded format represents statistically significant findings.

AEDs, antiepileptic drugs; FSIQ, full-scale intelligence quotient; GS, gelastic seizures; HH, hypothalamic hamartoma; MRI, magnetic resonance imaging; non-GS, non-gelastic seizures type seizures; Reg, estimated regression coefficient; SE, standard error; sEEG, scalp electroencephalogram



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