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ORIGINAL ARTICLE

Cognitive and social functions of craniopharyngioma and germ cell tumor differ in patients with and without apathy

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Abstract

Aim: Apathy, the quantitative reduction of self-generated voluntary and purposeful behaviors, can affect social functions in patients with acquired brain injury. However, how apathy impairs social life in patients with craniopharyngioma and germ cell tumor (diencephalon tumor) remains unclear. Therefore, this study investigated patients with diencephalon tumors to assess the impact of apathy on their neurocognitive, social cognitive, and social functions.

Methods: Patients with diencephalon tumors treated at Kyoto University Hospital were enrolled in this observational study. Apathy was assessed using the Apathy Scale, while neurocognitive functions were evaluated using the Wechsler Adult Intelligence Scale-IV (WAIS-IV), Wechsler Memory Scale-Revised (WMS-R), and Behavioural Assessment of the Dysexecutive Syndrome. Social cognitive functions were evaluated by means of an emotion perception task and a theory of mind (ToM) task. Finally, social functions were evaluated using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0, where a high score indicates greater functioning difficulties experienced.

Results: Apathy was observed in 11 (45.8%) of 24 patients (15 males), with a mean (standard deviation) age of 35.83 (14.79) years. Patients with apathy scored significantly lower on the Verbal Comprehension Index (WAIS-IV), Working Memory Index (WAIS-IV), Attention (WMS-R), and ToM task than those without apathy ($P = 0.03$, 0.04, 0.01, and 0.046, respectively). Further, they scored significantly higher on the WHODAS 2.0 than patients without apathy.

Conclusion: Apathy manifests as a neuropsychological complication and affects social functions in patients with diencephalon tumors. Effective interventions for apathy may ameliorate the social dysfunctions of patients with diencephalon tumors.

KEYWORDS
apathy, cognitive function, craniopharyngioma, germ cell tumor, social function

INTRODUCTION

Apathy is conventionally conceptualized as an "absence or lack of feeling, emotion, interest, or concern." Marin describes apathy as a "primary absence of motivation not caused by a disturbance in intelligence, emotion, or level of consciousness".[1,2] Levy and Dubois define it as "a quantitative decrease in voluntary and purposeful behaviors," making apathy an observable syndrome.[3] Apathy is often observed as a complication after acquired brain injury (ABI),[4] caused by damage to the prefrontal cortex or the basal ganglia.[3] It is also observed in patients with cerebral stroke and traumatic brain injury (TBI)[5–7] because of damage sustained to the frontal lobe.[8,9] However, it has recently been discovered that apathy is not just caused by frontal lobe damage but can also be caused by lesions in the diencephalon.[10] Brain tumor occurring in the diencephalon is a typical disease that causes damage to this portion of the brain, with examples including craniopharyngioma or germ cell tumor (brain tumors are a type of ABI, along with TBI and stroke[11]). Furthermore, hydrocephalus and hypopituitarism have been found to be factors associated with apathy in pediatric patients with brain tumors.[10,12]

Patients with pediatric brain tumors have high unemployment rates, especially those with germ cell tumors.[13] Patients with childhood- or adolescent-onset craniopharyngioma have a higher risk for apathy[14] and lower cognitive and social functions than the healthy population.[15] As craniopharyngioma and germ cell tumors (diencephalon tumors) have a good prognosis and commonly occur in the diencephalon,[16] it is important to evaluate complications that may affect social function to support long-term lives after treatment. In patients with ABI, apathy is a syndrome that affects cognitive and social functions. However, the relationship between cognitive and social functions and apathy in patients with diencephalic tumor remains unclear. Furthermore, apathy in patients with adulthood-onset diencephalic tumors has not been investigated; its frequency is unknown among patients with childhood- and adulthood-onset brain tumors. Therefore, this study aims to clarify the prevalence of apathy and impact of apathy on neurocognitive, social cognitive, and social functions in patients with diencephalon tumors.

MATERIALS AND METHODS

Study design and patients

We conducted a prospective single-center observational study, which was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (approval number: R2052, date: July 19, 2019. This study was carried out in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. Our study specifically excluded minors. Patients treated for diencephalon tumors at Kyoto University Hospital were surveyed. The recruitment period for this study spanned from July 19, 2019 to June 15, 2022, and the sample size was determined based on the number of patients that could be recruited at Kyoto University Hospital within this period. Study eligibility criteria included the following: (a) diagnosis of a diencephalon tumor; (b) prior history of treatment for a diencephalon tumor; and (c) provision of written informed consent. Patients were excluded from the study if (a) their tumor lesions were outside the diencephalon; (b) they had a prior history of cognitive dysfunction; (c) they suffered cerebrovascular complications during treatment; (d) new lesions arose after informed consent was provided; and (e) they were deemed unsuitable by the researchers and/or the attending physician. Participants' medical records were accessed for research purposes from July 19, 2019 to January 6, 2025. The authors had access to information that could identify individual participants during and after data collection.

Measurements

We used the following measurements to evaluate the frequency of apathy and its effects on neurocognitive, social cognitive, and social functions in patients with diencephalon tumors. Proficient occupational therapists performed all assessments. They conducted the assessments over a few days to limit the sessions to less than 3 h per day considering the mental and physical conditions of the participants.

Apathy

Apathy was assessed using the Japanese version of the Apathy Scale,[6] originally devised by Starkstein et al. to measure apathy.[17,18] The cut-off score of the Japanese version is 16 points, with higher scores indicating more apathy (range 0–42). This scale is widely used in the evaluation of patients with ABI and its reliability and validity have been confirmed.[6,17]

Neurocognitive functions

Neurocognitive functions were evaluated using the Japanese version of the Wechsler Adult Intelligence Scale-IV (WAIS-IV), Wechsler Memory Scale-Revised (WMS-R), and Behavioural Assessment of the Dysexecutive Syndrome (BADS). The WAIS-IV, WMS-R, and BADS assess general intelligence,[19] memory function,[20] and executive function,[21] respectively. These measures are standardized, comprehensive neuropsychological test batteries used worldwide and their reliability and validity have been confirmed.[19–21]

Social cognitive functions

Social cognitive functions were assessed by means of an emotion perception task and a theory of mind (ToM) task. The emotional perception task consisted of a total of 48 photographs composed of six basic emotions, including disgust, fear, surprise, anger, sadness,

and happiness. These photographs were chosen from the standard facial image set of Ekman and Friesen[22] and Matsumoto and Ekman,[23] and were used as stimuli. The patients were asked to select which of these six labels best described the emotion shown in each photograph. The ToM task consisted of 36 photographs of eyes. The patients were asked to select which of the four simultaneously presented words best described the mental state of the photographed person.[24] These tests are frequently used in studies involving patients with ABI.[25–27]

Social functions

Social function was assessed using the World Health Organization Disability Assessment Schedule (WHODAS) 2.0. This tool provides a standardized method for measuring health and disability across cultures and is a reliable and valid generic assessment instrument developed by the World Health Organization.[28] WHODAS 2.0 captures the summary score and the level of functioning in six domains of life, including cognition (understanding and communicating), mobility (moving and getting around), self-care (attending to one's hygiene, dressing, eating, and staying alone), getting along (interacting with other people), life activities (domestic responsibilities, leisure, work, and school), and participation (joining in community activities, participating in society).[28] We used the full version of WHODAS 2.0, which has 36 questions related to the functioning difficulties experienced by patients in the six domains of life during the previous 30 days. There are three modes of administering WHODAS 2.0; we used the Japanese versions of the self- and proxy-administered versions. These self- and proxy-administered versions of WHODAS 2.0 were completed by the patients themselves and family members of patients, respectively. The summary and domain scores range from 0 to 100, with a high score indicating that patients experienced relatively more functional difficulties.

Statistical analyses

Patients were divided into "apathy" and "nonapathy" categories according to their score on the Apathy Scale, based on the cut-off score of 16 points. For demographic and clinical characteristics, *t*-test and chi-square test were performed between the apathy and nonapathy groups. The Apathy Scale scores were normally distributed according to the Shapiro–Wilk test, therefore we used a parametric test for analysis. Parametric variables were expressed as a mean and standard deviation (SD) or a number (percentage of the total). In addition, differences in apathy according to the age at diagnosis, diagnosis, surgery type, radiation, chemotherapy, and diagnosis of panhypopituitarism and hydrocephalus were also compared by performing the *t*-test. Patients were divided into "childhood-onset" and "adulthood-onset" groups according to their age at diagnosis, with onsets occurring at the age of 18 years or over being the criterion for adulthood onset. Moreover, data for neurocognitive, social cognitive, and social functions were not normally distributed, therefore we used a nonparametric test. Nonparametric, unpaired data were analyzed by performing the Wilcoxon rank-sum test for comparing patients with and without apathy. All analyses were performed using the JMP software for Windows version 16.2 (SAS Institute). We set the *p*-value for statistical significance at <0.05 (two-tailed test). A post hoc statistical power calculation was performed using ClinCalc (https://clincalc.com/Stats/Power.aspx).

RESULTS

Demographic and clinical characteristics

Between August 2019 and June 2022, 34 patients with diencephalon tumor treated at Kyoto University Hospital provided informed consent and were enrolled in this study. Ten patients were excluded due to the following reasons: progressive tumor lesions outside the diencephalon ($n = 4$), a prior history of cognitive dysfunction ($n = 2$), cerebrovascular complications during treatment ($n = 2$), and diagnosis of other brain diseases (radiation brain necrosis, radiation-induced tumor) after informed consent was provided ($n = 2$). A post hoc analysis was performed to confirm whether the statistical power was sufficient. With α set at 0.05, β was calculated to be 87.5%, demonstrating that the sample size was adequate; hence, no additional cases were considered.

This study thus included 24 patients with diencephalon tumor with a mean (SD) age of 35.83 (14.79) years (Supplementary Table A1). Table 1 shows the demographic and clinical characteristics of patients divided into the apathy and nonapathy groups. All patients were native Japanese, and diagnosed with craniopharyngioma and germ cell tumor. The patients with craniopharyngioma had undergone tumor removal and the patients with germ cell tumors had received chemotherapy (Supplementary Table A2). The *t*-test and chi-square test results revealed no significant differences in demographic and clinical characteristics between the apathy and nonapathy groups. Administering the Beck Depression Inventory, second edition, we found no patients with symptoms of severe depression.

Prevalence of apathy in patients with diencephalon tumor

Figure 1 shows the frequency of apathy and the Apathy Scale scores together with the *t*-test results. Patients' mean score on the Apathy Scale was 13.38 (SD = 5.55) and the frequency of apathy was 45.8% (11 patients; Figure 1a). Apathy was identified in seven (63.6%) of the 11 childhood-onset patients. The apathy scale scores of childhood-onset patients (mean = 16.55, SD = 3.21) and adulthood-onset patients (mean = 10.69, SD = 5.78) differed significantly ($t = 2.99$, $r = 0.54$) (Figure 1b). However, the Apathy Scale scores did not differ

TABLE 1 Demographic and clinical characteristics of the apathy and nonapathy groups.

	Apathy (n = 11)					Nonapathy (n = 13)					
	Mean	SD	n	%	Range	Mean	SD	n	%	Range	p
Age (years)	33.73	15.01	–	–	19–65	37.62	14.98	–	–	19–62	0.53
Sex											0.46
Male	–	–	6	54.55	–	–	–	9	69.23	–	
Female	–	–	5	45.45	–	–	–	4	30.77	–	
Education (years)	12.91	1.64	–	–	12–16	14.15	2.23	–	–	12–18	0.14
Age at diagnosis (years)	20.00	15.94	–	–	7–59	29.46	17.42	–	–	3–59	0.18
Post diagnosis period (days)	3924.45	4191.20	–	–	184–14,145	1990.69	1529.37	–	–	135–5598	0.14
Diagnosis											0.77
Craniopharyngioma	–	–	7	63.64	–	–	–	9	69.23	–	
Germ cell tumor	–	–	4	36.36	–	–	–	4	30.77	–	
Tumor region											
Thalamus	–	–	0	0.00	–	–	–	0	0.00	–	–
Hypothalamus	–	–	1	9.09	–	–	–	1	7.69	–	0.90
Pituitary	–	–	4	36.36	–	–	–	1	7.69	–	0.08
Suprasellar	–	–	9	81.82	–	–	–	9	69.23	–	0.48
Sellar	–	–	4	36.36	–	–	–	2	15.38	–	0.24
Pineal gland	–	–	3	27.27	–	–	–	5	38.46	–	0.56
3rd ventricle	–	–	1	9.09	–	–	–	5	38.46	–	0.098
Tumor volume (mm^3)	10010.84	9828.51	–	–	–	8250.53	10648.62	–	–	–	0.70
Surgery type											0.85
Biopsy	–	–	2	18.18	–	–	–	2	15.38	–	
Tumor removal	–	–	9	81.82	–	–	–	11	84.62	–	
Radiation	–	–	9	81.82	–	–	–	10	76.92	–	0.77
Chemotherapy	–	–	4	36.36	–	–	–	4	30.77	–	0.77
Panhypopituitarism	–	–	8	72.73	–	–	–	7	53.85	–	0.34
Diabetes insipidus	–	–	7	63.64	–	–	–	8	61.54	–	0.92
Hydrocephalus (n = 22)	–	–	3	30.00	–	–	–	3	25.00	–	0.79
Recurrence	–	–	2	18.18	–	–	–	4	30.77	–	0.48
BDI-II score[a]											0.07
Extremely mild symptoms	–	–	6	54.55	–	–	–	12	92.31	–	
Mild symptoms	–	–	2	18.18	–	–	–	1	7.69	–	
Moderate symptoms	–	–	3	27.27	–	–	–	0	0.00	–	
Severe symptoms	–	–	0	0.00	–	–	–	0	0.00	–	

Note: t-test and chi-square test.

Abbreviation: BDI-II, Beck depression inventory-second edition.

[a]Mild symptoms of depression: 14–19, moderate symptoms of depression: 20–28, severe symptoms of depression: 29 or higher.

significantly between groups based on the following characteristics: craniopharyngioma (mean = 12.56, SD = 6.40) and germ cell tumor (mean = 15.00, SD = 2.98; t = 1.02, r = 0.21) (Figure 1c); tumor removal (mean = 12.90, SD = 5.78) and biopsy (mean = 15.75, SD = 3.86; t = 0.94, r = 0.20) (Figure 1d); radiotherapy (mean = 13.68, SD = 4.98) and nonradiotherapy (mean = 12.20, SD = 7.95; t = 0.52, r = 0.11) (Figure 1e); and chemotherapy (mean = 15.00, SD = 2.98) and nonchemotherapy (mean = 12.56, SD = 6.40; t = 1.02, r = 0.21)

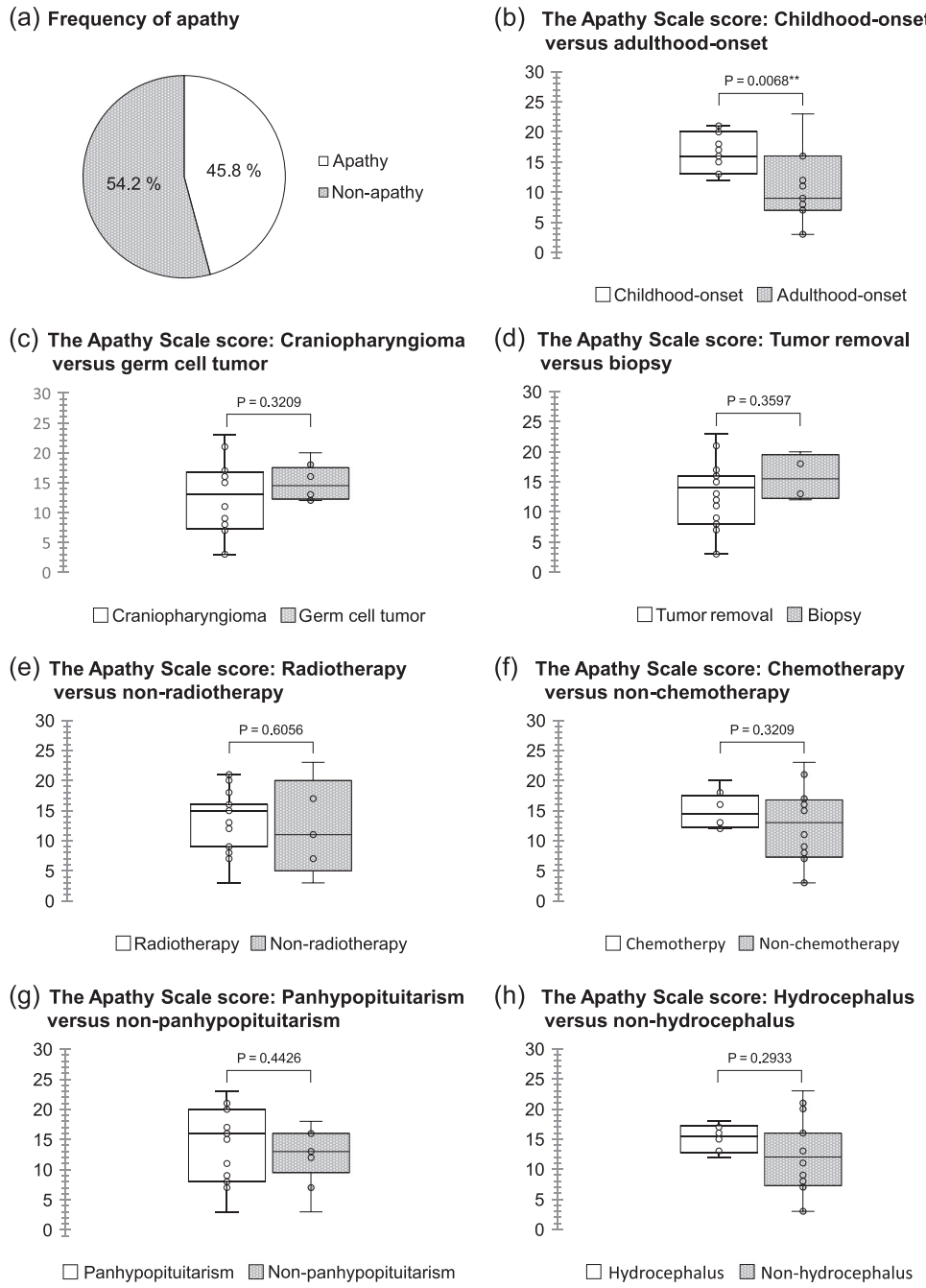

FIGURE 1 Prevalence of apathy among patients with diencephalon tumor. (a) The frequency of apathy among all patients ($n = 24$). (b) The difference in the Apathy Scale scores between childhood- and adulthood-onset patients. Comparison of the Apathy Scale scores of patients with craniopharyngioma versus germ cell tumor (c), patients who underwent tumor removal versus biopsy (d), those who received radiotherapy and those who did not (e), those who received chemotherapy and those who did not (f), patients with and without panhypopituitarism (g), and those with and without hydrocephalus (h). **P < 0.01, *t*-test.

(Figure 1f). Apathy was identified in eight (53.3%) of 15 patients with panhypopituitarism and three (50.0%) of six patients with hydrocephalus. However, the Apathy Scale scores did not differ between patients with panhypopituitarism (mean = 14.07, SD = 6.05) and the nonpanhypopituitarism group (mean = 12.22, SD = 4.68; $t = 0.78$, $r = 0.16$) (Figure 1g) nor between those with hydrocephalus (mean = 15.17, SD = 2.32) and the nonhydrocephalus group (mean = 12.31, SD = 6.24; $t = 1.08$, $r = 0.22$) (Figure 1h).

Neurocognitive function decline in patients with apathy

Table 2 shows the median and interquartile range (IQR) of intelligence quotient, memory, and executive function scores of patients with and without apathy. The median full-scale intelligence quotient, processing speed index, and delay memory scores of patients with apathy were more than −1 SD lower than standard scores. Interestingly, the median of all results for nonapathy patients was within standard scores. The

TABLE 2 Neurocognitive assessment results of the apathy and nonapathy groups.

	Apathy (n = 11)			Nonapathy (n = 13)					
	25%	Median	75%	25%	Median	75%	z	r	P
WAIS-IV (n = 24)									
FSIQ	70.00	84.00	107.00	92.50	101.00	113.50	−1.91	−0.39	0.06
VCI	79.00	92.00	106.00	98.00	104.00	111.50	−2.12	−0.43	0.03
PRI	84.00	101.00	107.00	94.00	109.00	119.00	−0.84	−0.17	0.40
WMI	79.00	88.00	97.00	95.50	106.00	113.00	−2.04	−0.42	0.04
PSI	71.00	79.00	90.00	83.50	87.00	99.00	−1.43	−0.29	0.15
WMS-R (n = 24)									
Verbal memory	61.00	85.00	115.00	99.00	104.00	114.50	−1.51	−0.31	0.13
Visual memory	83.00	96.00	108.00	95.50	104.00	110.50	−1.51	−0.31	0.13
General memory	61.00	86.00	108.00	96.50	104.00	113.50	−1.68	−0.34	0.09
Attention	89.00	96.00	102.00	100.50	106.00	115.00	−2.46	−0.50	0.01
Delay memory	63.00	78.00	93.00	83.50	99.00	107.50	−1.65	−0.34	0.098
BADS (n = 24)									
General score	80.00	100.00	104.00	95.00	104.00	114.00	−1.75	−0.36	0.08

Note: Wilcoxon rank sum test. WAIS-IV, WMS-R, BADS; Mean = 100, SD = 15.

Abbreviations: BADS, behavioural assessment of the dysexecutive syndrome; FSIQ, full scale intelligence quotient; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; VCI, verbal comprehension index; WAIS-IV, Wechsler adult intelligence scale-IV; WMI, working memory index; WMS-R, Wechsler memory scale-revised.

TABLE 3 Social cognitive assessment results of the apathy and nonapathy groups.

	Apathy (n = 8)			Nonapathy (n = 9)					
	25%	Median	75%	25%	Median	75%	z	r	P
Emotion perception task (n = 17)									
Correct answers (%)	60.42	66.67	71.88	60.42	68.75	75.00	−0.58	−0.14	0.56
Theory of mind task (n = 17)									
Correct answers (%)	46.53	55.56	59.72	56.94	61.11	73.61	−1.99	−0.48	0.046

Note: Wilcoxon rank sum test. Emotion perception task,[29] mean = 90.2, SD = 4.7. Theory of mind task,[30] mean = 67.6, SD = 5.9.

Abbreviation: SD, standard deviation.

verbal comprehension index (VCI), working memory index (WMI), and Attention scores were significantly different between patients with apathy and the nonapathy group, with the results of the former being significantly lower than those of the latter. Other intelligence quotient, memory, or executive function scores were not significantly different between apathy and nonapathy patients.

Certain social cognitive functions were worse in patients with apathy than those without apathy

Social cognition tasks could not be evaluated for seven patients (patient numbers 2, 3, 4, 8, 9, 13, and 16 in Supplementary Table A1) because of their time constraints, therefore the results of only 17 patients were analyzed. Table 3 presents details on the social cognition tasks together with the results of the Wilcoxon rank-sum test for the apathy and nonapathy groups. There were no significant differences in the scores of the emotion perception task between patients with apathy and the nonapathy group, and both groups' scores were lower than those of healthy participants.[29] There was a significant difference in the score for the ToM task between the apathy and nonapathy groups, with the results of the former being significantly lower than those of the latter. Patients with apathy scored lower on the ToM task than healthy participants.[30]

Social function decline in patients with apathy

Figure 2 shows the social function outcomes reported by patients themselves and their family members together with the results of the Wilcoxon rank-sum test for patients with and without apathy. Two

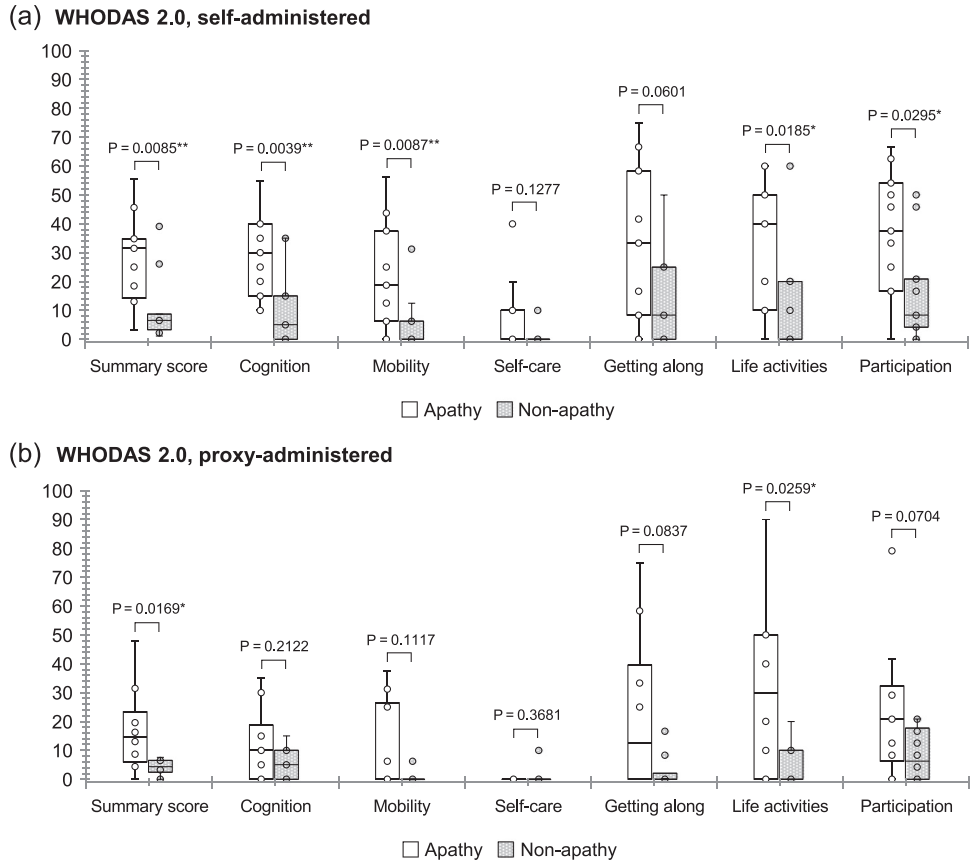

FIGURE 2 Social function decline in patients with apathy. Social function outcomes reported by patients themselves (a) and their family members (b), together with the results of the Wilcoxon rank-sum test in patients with and without apathy. *P < 0.05, **P < 0.01, Wilcoxon rank-sum test. WHODAS 2.0, The World Health Organization Disability Assessment Schedule 2.0.

patients (patient numbers 2 and 3 in Supplementary Table A1) did not provide reports for social function outcomes because of their time constraints, therefore the results of only 22 patients were analyzed for self-administered social functions (Figure 2a). The summary scores were significantly different between patients with apathy (median = 31.52, IQR = 14.13–34.78) and those without apathy (median = 6.52, IQR = 3.26–8.70; $z = -2.63$, $r = -0.56$). For each domain (cognition, mobility, life activities, participation), patients with apathy experienced significantly more social difficulties than those without apathy (in order, $z = -2.88$, -2.62, -2.35, and -2.18, $r = -0.61$, -0.56, -0.50, and -0.46). The other domains were not significantly different between the apathy and nonapathy groups.

Four family members (patient numbers 2, 17, 21, and 22 in Supplementary Table A1) did not provide written consent for social function analyses, therefore we only analyzed the results of proxy-administered social functions for 20 patients (Figure 2b). The summary scores of patients with apathy (median = 14.67, IQR = 5.98–23.37) and the nonapathy group (median = 4.35, IQR = 2.45–6.52) were significantly different ($z = -2.39$, $r = -0.53$). The life activities score of apathy patients (median = 30.00, IQR = 0.00–50.00) was significantly higher than that of those without apathy (median = 0.00, IQR = 0.00–10.00; $z = -2.23$, $r = -0.50$). The other domains were not significantly different between the apathy and nonapathy groups.

DISCUSSION

In this study, apathy was present in 45.8% of patients with diencephalon tumors. A meta-analysis of patients with craniopharyngioma showed that 41.9% of patients had altered emotion control, including apathy.[10] The results of our study are consistent with previous work that demonstrates the frequency of apathy in patients with diencephalon tumors. In a meta-analysis of patients with craniopharyngioma, all types of alterations involving emotional expression/control were significantly higher at a younger age,[10] and those with childhood-onset craniopharyngioma were also found to have a higher risk of apathy compared to healthy controls.[14] In our study, apathy was identified in seven (63.6%) of the 11 childhood-onset patients, who had significantly higher scores on the Apathy Scale than adulthood-onset patients. Contrarily, no significant differences were observed in the Apathy Scale scores for diagnosis, surgery type, radiation, chemotherapy, panhypopituitarism, or hydrocephalus.

Furthermore, apathy in survivors of childhood brain tumors was strongly predicted by pituitary dysfunction, suggesting a relationship between apathy and pituitary dysfunction.[12] However, in our study, there was no significant difference in the proportion of patients with panhypopituitarism between the apathy and nonapathy groups. Additionally, there was no significant difference in the Apathy Scale

scores between patients with and without panhypopituitarism, therefore it should be noted that the onset of apathy is not necessarily related to the presence or absence of panhypopituitarism, and that even patients with diencephalon tumor without panhypopituitarism may develop apathy.

Levy and Dubois have classified the causes of apathy into three types, corresponding to functional anatomy.[3] The first is apathy related to disruption of "emotional-affective" processing, which is involved in the orbitofrontal circuit, the second is apathy related to disruption of "cognitive" processing associated with the dorsolateral prefrontal circuit, and the third is apathy related to an "auto-activation" deficit associated with the anterior cingulate circuit. Additionally, the definition of apathy was discussed at the European Psychiatric Association Conference in 2008, and similar to the definition of Levy and Dubois,[3] the three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) were presented.[31] In a previous study evaluating neurocognitive functions before treatment, patients with craniopharyngioma showed poorer performance across neurocognitive domains, including executive functions and working memory, compared to the normative mean.[32]

In our study, scores for neurocognitive and social cognitive functions, such as the VCI, WMI, attention, and ToM scores, were lower for patients with apathy than for those without apathy. Several regions, including the frontal and parietal lobe, are thought to be the neural basis of working memory. Previous studies have shown that in the frontal lobe, the dorsolateral prefrontal cortex is an important region for working memory,[33] and the medial prefrontal cortex (MPFC) is an important region for understanding the mental states of the self and others, which is necessary for ToM.[34] The thalamus, including the hypothalamus, is involved in the frontal–subcortical neuronal circuits,[35] and the hypothalamus itself has pronounced functional connectivity with widespread subcortical and cortical areas, including the prefrontal cortex and cingulum.[36] Even in the case of craniopharyngioma, a type of diencephalon tumor, it has been suggested that the prefrontal cortex and its subcortical pathways may be involved in cognitive function deficits.[37] Evidence suggests that abnormal functional connectivity within the hypothalamus–default mode network circuit, notably in the bilateral anterior cingulate cortices and posterior cingulate cortices, might be a functional mechanism leading to cognitive impairment in patients with craniopharyngioma.[36] Based on these results, a combination of factors, namely, dysfunctions of the frontal–subcortical neuronal circuits, such as the dorsolateral prefrontal circuit and anterior cingulate circuit, including the MPFC, may cause apathy in patients with diencephalon tumors.

Meanwhile, according to the results of the emotion perception task, emotion recognition was impaired in patients with diencephalon tumors, regardless of apathy. In patients with diencephalon tumors, even if there are no hypothalamic lesions, hypothalamo–hypophyseal functions could be impaired. In fact, 75.0% of the patients in this study had hypothalamo–hypophyseal dysfunction. Oxytocin production in the hypothalamus affects automatic processes of emotion recognition via long-range axonal projections directly to various other brain regions, such as the amygdala, septum, nucleus accumbens, and hippocampus.[38] As mentioned above, patients with diencephalon tumors may have impaired hypothalamo–hypophyseal functions, which produce oxytocin, and we believe that emotional recognition may be impaired due to decreased functions in these brain regions.

In patients with diencephalon tumors, impaired social function has been reported,[39,40] but how apathy affects the social life of those patients remains unclear. However, the impact of apathy on social function has already been reported in patients with other ABI. For example, in patients with stroke and TBI, apathy has a significant direct negative effect on social functions such as activities of daily living (ADL) and employment status,[41,42] and is related to social cognitive functions.[43,44] In addition, a previous study of young adult survivors with pediatric brain tumors more than 5 years after onset indicated that executive dysfunction and apathy may have an impact on adaptive functioning.[45] We therefore believe that it is important to focus on apathy when supporting patients with diencephalon tumors, which are a type of ABI. The results of this study suggest that apathy may impair social function in patients with diencephalon tumors. Specifically, the summary scores of the self-administered form were higher in patients with apathy, and they experienced significantly more difficulty in cognition, mobility, life activities, and participation. Likewise, the summary scores of the proxy-administered form were also higher in patients with apathy, and they had significantly more difficulty with life activities.

As a matter of concern, the association between apathy and the level of caregiver burden is unclear in patients with diencephalon tumors. In patients with TBI, apathy does not only affect their social function but also increases the level of caregiver burden.[42,46] As patients with childhood-onset germ cell tumors tend to lose their jobs,[13] they need life support from their families. This indicates that it is necessary to understand the burden level of caregivers and consider more appropriate support systems for patients with diencephalon tumors and their families.

This exploratory study only revealed the frequency of apathy in patients with diencephalon tumors and reduced functions in patients with apathy; it did not provide clarity on how to support such patients and their families. Nonpharmacological treatment has been reported to be effective for apathy in patients with ABI.[47] As a specific example, incorporating motivational interviewing and external compensation to increase sustained activity toward cumulative goals improves apathy in patients with ABI.[48] However, the effectiveness of interventions for apathy has not been established,[49] and it is important to explore effective intervention methods to mitigate apathy and improve social participation in patients with diencephalon tumors.

Our study has several limitations that should be considered. First, as this study had a small sample size, the impact of not only lesions, treatments, histological differences, and complications but also traditional well-known prognostic factors such as residual tumors, damage to critical neuronal structures by a primary or recurrent

tumor, treatment-related hypothalamic lesions, dissemination of tumor, and lesion size[50–52] on apathy could not be fully examined. Second, as the sample size was insufficient to conduct a comprehensive analysis, type 1 errors may have occurred. In addition, since this was an exploratory study with a limited number of cases, we did not perform adjustments for multiple comparisons. Rigorous statistical validation will be necessary in future studies with larger sample sizes. Third, based on the differences in neurocognitive and social cognitive functions between patients with apathy and those without apathy, the dorsolateral prefrontal circuit as well as the anterior cingulate circuit, including the MPFC, may be impaired in apathy patients. The fact that five out of seven items in the self-administered version of WHODAS 2.0 were significant highlights the need to pay attention to these findings as an exploratory study. However, the functional connectivity associated with apathy in patients with diencephalic tumors remains unknown because we did not analyze brain function images in this study, therefore it is necessary to conduct additional large-scale studies to elucidate the mechanism of apathy development in such patients. Finally, the causal relationship between apathy and clinical outcome was unclear in our study, therefore in the future, longitudinal studies must be conducted to verify whether clinical outcomes change with interventions for apathy.

CONCLUSIONS

Apathy is frequently identified in patients with diencephalon tumors and is more severe in childhood-onset patients. Neurocognitive, social cognitive, and social functions may be more impaired in apathy patients, and this should be tested in larger studies. A possible mechanism could be dysfunction in the dorsolateral prefrontal circuit as well as the anterior cingulate circuit, including the MPFC. Effective interventions for apathy may ameliorate the social dysfunctions of patients with diencephalon tumors.

AUTHOR CONTRIBUTIONS

Ami Tabata: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, project administration, funding acquisition. **Keita Ueda**: Conceptualization, methodology, resources, writing—review and editing, supervision. **Katsutsugu Umeda**: Conceptualization, methodology, resources, writing—review and editing. **Takeshi Funaki**: Resources, writing—review and editing, visualization. **Tsukasa Ueno**: Resources, writing—review and editing. **Yohei Mineharu**: Resources, writing—review and editing. **Masahiro Tanji**: Resources, writing—review and editing. **Takayuki Kikuchi**: Resources, writing—review and editing. **Misa Komaki**: Investigation, writing—review and editing. **Susumu Miyamoto**: Writing—review and editing, supervision. **Toshiya Murai**: Writing—review and editing, supervision. **Yoshiki Arakawa**: Conceptualization, methodology, formal analysis, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL STATEMENT

This study was reviewed and approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (approval number: R2052, date: July 19, 2019).

PATIENT CONSENT STATEMENT

All patients provided written informed consent to participate in the study and for the publication of their anonymized data.

CLINICAL TRIAL REGISTRATION

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