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Frequent Clinical and Radiological Progression of Optic Pathway/Hypothalamic Pilocytic Astrocytoma in Adolescents and Young Adults

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Abstract

Most cases of optic hypothalamic pilocytic astrocytoma (OHPA) develop during childhood, so few cases of histologically verified OHPA have been described in adolescents and young adults (AYA). To elucidate the clinical features of OHPA with histological verification in AYA, we reviewed the clinical and radiological finding of OHPA treated at our institute from January 1997 and July 2017. AYA are aged between 15 and 39 years. The clinical courses of 11 AYA patients with optic hypothalamic glioma (OHG) without neurofibromatosis type 1 were retrospectively reviewed. About six patients were diagnosed in childhood and followed up after 15 years of age, and five patients developed OHPA during AYA. Histological diagnosis, verified at initial presentation or recurrence, was pilocytic astrocytoma in 10 and pilomyxoid astrocytoma in one. After initial treatment including debulking surgery and/or chemotherapy, tumor progression occurred 16 times in seven patients as cyst formation, tumor growth, and intratumoral hemorrhage. Five of 10 patients suffered deterioration of visual function during AYA. One of 10 cases had endocrinopathies requiring hormone replacement at last follow-up examination. In conclusion, histological diagnoses of OHG before and in AYA were pilocytic astrocytoma or pilomyxoid astrocytoma. Both pediatric and AYA-onset OHPA demonstrate high incidences of tumor progression and visual dysfunctions in AYA, so that long-term follow up is essential after the completion of treatment for pediatric and AYA-onset OHPA. The optimal timing of debulking surgery and radiation therapy should be established to achieve the long-term tumor control and to preserve the visual function.

Key words: optic hypothalamic pilocytic astrocytoma, adolescent and young adult, clinical feature

Introduction

Adolescents and young adults (AYA) are the individuals in a population aged between 15 and 39 years of age.[1)] AYAs with cancer are reported to have a different spectrum of cancer types, tumors, and host biology, specific late adverse effects, and clinical outcomes compared to the other age groups.[2)] AYA have poorer clinical outcomes for acute myeloid and lymphoblastic leukemia, orbit cancer, Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma than younger patients, and for breast and anus cancer than older adults.[3)] The true mechanisms for these poor clinical outcomes remain unknown, but presumably reflect the differences in tumor and host biology.[3,4)] The cancer incidence data obtained from the monitoring of Cancer Incidence in Japan show that central nervous system (CNS) tumors account for a significant proportion of cancers in AYA.[5)]

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However, investigations focusing on CNS tumors in AYA are limited. The Brain Tumor Registry of Japan and the Central Brain Tumor Registry of United States suggest that pilocytic astrocytoma is one of the most common intracranial tumors in the population under 15 years, accounting for 11.9–12.9% of all intracranial tumors, whereas this entity is relatively rare in AYA, accounting for only 2.3–2.9% of all intracranial tumors.[6,7]

Pilocytic astrocytoma is considered indolent in the World Health Organization (WHO) classification of tumors of the CNS,[8] and curable by complete surgical resection. However, complete surgical resection of optic hypothalamic pilocytic astrocytoma (OHPA) is difficult in most cases. Consequently, combinations of chemotherapy, debulking surgery, and radiation therapy are adopted. The majority of studies of OHPA focused on pediatric cases[9–11] from the susceptible age of <15 years, and a few case series[12–14] described OHPA in AYA. Some studies suggested that OHPA was a static pathology at adulthood, and intense long-term follow up was not required after adolescence based on the findings that tumor recurrence occurs within 5–6 years in young children and adolescents,[12,15] and that some cases of OHPA with and without neurofibromatosis type 1 (NF1) regress spontaneously before adolescence or during AYA.[16,17] In contrast, seven cases of OHPA have been reported with optic hypothalamic glioma (OHG) without histological verification and without NF1, demonstrating that a significant percentage of AYA with OHG can suffer progression, visual decline, or both.[18] However, these conclusions cannot apply to OHPA in AYA because the study may have included cases of heterogeneous OHG with histological diagnosis of low-grade glioma, not pilocytic astrocytoma.[18]

The present study reviewed the clinical course and radiological findings of OHPA without NF1 treated in childhood and monitored until young adulthood (pediatric-onset OHPA), and newly diagnosed OHPA in AYA (AYA-onset OHPA), to elucidate the clinical features of OHPA in AYA.

Patients and Methods

Patients

This retrospective and single institute study examined the medical records of patients with clinically or histologically diagnosed OHG treated at Tohoku University Hospital between January 1997 and July 2017. The study included consecutive patients diagnosed in childhood and followed up after age 15 years, and patients who initially presented during age 15–39 years. Patients with NF1 were excluded because of the different clinical features.[11,14,17–19] This study was approved by the Institutional Ethics Committee of Tohoku University Hospital. This retrospective observational study did not require patient consent, but means to opt out were provided on the internet to the patients.

Treatments

During the period of this study, we treated patients with newly diagnosed and progressive tumors by debulking surgery and/or chemotherapy to avoid the radiation therapy. Patient with newly diagnosed OHPA were treated with only debulking surgery, debulking surgery, followed by chemotherapy, or biopsy, followed by chemotherapy. Patients with tumor progression were first treated by debulking surgery and/or chemotherapy. Radiation therapy was performed only if the tumor became uncontrollable after multiple debulking surgery or chemotherapy treatments.

Patients with impending neurological symptoms due to cyst formation, intratumoral hemorrhage, or significant mass effect underwent debulking surgery via craniotomy or trans-sphenoidal approach performed by M.K., R.S., Y.O., Y.S., and T.K. Other patients underwent stereotactic biopsy or endoscopic biopsy with or without septostomy by M.F. to verify the histology. The histological diagnoses were established from the specimens obtained by endoscopic or stereotactic biopsy, or resection via craniotomy, according to the WHO classification of tumors of the CNS.[8] Ventriculoperitoneal shunting was performed in some patients to control acute hydrocephalus. Carboplatin monotherapy was used for newly diagnosed and recurrent disease after 2006. It was given to one patient using carboplatin 560 mg/m^2 which is reported to be effective and tolerable in pediatric (<10 years) patients with progressive OHGs.[20] AYA patients tend to experience severe myelosuppression (Case 10 in Table 1), so reduced dosage of carboplatin 450 mg/m^2 (20% reduction) was administered every 4 weeks for 1 year to AYA patients.

Radiation therapy 50 Gy was given to the tumor site in patients with progressive disease after multiple debulking surgery and carboplatin chemotherapy.

Assessment of tumor control, visual and endocrine function

We reviewed tumor control, visual and endocrine function before treatment and at the most recent examination. Tumor control was evaluated as the responses to chemotherapy and radiation therapy as estimated by MacDonald's criteria[21] by M.K. and R.S. Tumor progression was defined as

Table 1 Clinical features of patients with optic hypothalamic pilocytic astrocytoma in adolescent and young adults

Case no.	Sex	Age at diagnosis (years)	Tumor site*		Symptom at presentation				Symptoms at last follow-up				Histological finding at progression	Age at last follow-up (years)
					Visual acuity (Rt., Lt.)	Visual field	Elevated ICP	Other symptoms	Visual acuity (Rt., Lt.)	Visual field	Elevated ICP	Other symptoms		
1	M	4	2a	Solid	N.E.	N.E.	Yes		N.E.	N.E.	No			17
2	M	10	3b	Cystic	1.5, 1.5	Rt. hemianopsia	No		1.2, 1.2	Rt. hemianopsia	No		Regressive changes	19
3	M	11	3b	Solid	0.01, 0.2	Lt. hemianopsia	Yes	PH	LS, 0.02	Lt. hemianopsia	No	PH, Lt. hemiparesis		19
4	F	11	2a	Cystic	1.5, 1.5	Rt. hemianopsia	Yes		1.0, 1.0[a]	Rt. hemianopsia	No		Regressive changes	23
5	F	11	3b	Cystic	N.E.	N.E.	No	Seizure	0.06, 0.3[b]	Lt. hemianopsia	No	Lt. hemiparesis	Cellular appearance	33
6	F	11	2a	N.A.	0.02, 0.01	Concentric contraction	Yes		Blind		No		Regressive changes	40 (dead)
7	M	17	2b	Solid	1.2, 1.5	Rt. hemianopsia	No		N.E.	Rt. hemianopsia	No			23
8	M	18	2a	Solid	1.0, 0.9	Rt. hemianopsia	Yes		1.5, FC	Rt. hemianopsia	No		Regressive changes	29
9	F	19	2a	Solid	1.0, 1.0	Rt. upper quadrantanopsia	Yes		0.8, 0.7	Rt. upper quadrantanopsia	No		Regressive changes	39
10	F	26	2a	Solid	1.5, 1.5	Rt. lower quadrantanopsia	Yes		1.2, 1.2	Rt. lower quadrantanopsia	No		Regressive changes	40
11	F	36	2a	Solid	1.2, 1.2	Normal	No		0.4, 0.3	normal	No			37

*According to modified Dodge classification.[22] a: Left visual acuity improved from 0.02 to 1.0 after ventriculoperitoneal shunting and local irradiation. b: Bilateral visual acuity declined after 25 years of age, and improved partially after treatment. Regressive changes = calcification, hyalinization, microcystic formation, or the increase of Rosenthal fibers and/or eosinophilic granular bodies. Cellular appearance = morphological changes from fibrillary appearance of delicate spindle cells to cellular appearance composed of slight plump spindles cells without nuclear atypia and mitotic figures. N.A.: not available, N.E.: not examined, ICP: intracranial pressure, PH: panhypopituitarism, LS: light sense, FC: finger counting, Rt.: right, Lt.: left.

intratumoral hemorrhage and cyst formation as well as progressive disease using MacDonald's criteria. Visual function included both of visual acuity and visual field. Endocrine function was evaluated by measuring the serum levels of growth hormone, insulin-like growth factor-1 (IGF-1), adrenocorticotropic hormone, cortisol, follicle-stimulating hormone, luteinizing hormone, testosterone or estradiol, thyroid stimulating hormone, free triiodothyronine, free thyroxine, and prolactin without stimulation test in nine patients and with stimulation test in one.

Results

Patient characteristics of OHPA in AYA

Clinical diagnoses of OHG were established during the selected follow-up period in 27 patients. About 13 patients were excluded because of age <15 years at last follow-up and three because of age >40 years at onset. Therefore, 11 patients were included in this study.

These 11 patients were diagnosed with pediatric-onset OHPA and AYA-onset OHPA. Clinical characteristics, including age, sex, tumor location,[22] and clinical symptoms before and after treatment are summarized in Figs. 1 and 2 and Table 1. Cases 1–6 had pediatric-onset OHPA, and Case 7–11 had AYA-onset OHPA. Median follow-up period was 12 years, ranging from 1 year to 29 years.

Histological diagnosis of OHPA in AYA

Histological diagnosis was verified in all patients at initial presentation or recurrence as pilocytic astrocytoma in 10 patients and pilomyxoid astrocytoma in one. No patients had high grade glioma.

Tumor control of OHPA in AYA

Tumor progression occurred 16 times in seven patients with AYA (Figs. 1 and 2). Salvage treatment for tumor progression consisted of only debulking surgery in nine, debulking surgery followed by chemotherapy in three, debulking surgery followed by radiation therapy in one, carboplatin monotherapy in two, and only radiation therapy in one (Figs. 1 and 2). Two patients (Cases 5 and 6) had tumor progression more than 10 years after initial treatment. Tumor progression in AYA developed 10 times in four patients with pediatric-onset OHPA (Fig. 1), and six times in three patients with AYA-onset OHPA (Fig. 2). In the pediatric-onset OHPA, three (Cases 2, 5, and 6) of the four recurrent patients with pediatric-onset OHPA did not have tumor progression before 15 years of age. These findings suggested that pediatric and AYA-onset OHPA frequently demonstrated tumor progression in AYA, and that pediatric-onset OHPA remaining static before AYA could show tumor progression in AYA.

The progression patterns were cystic formation in seven occurrences, tumor growth in five, and

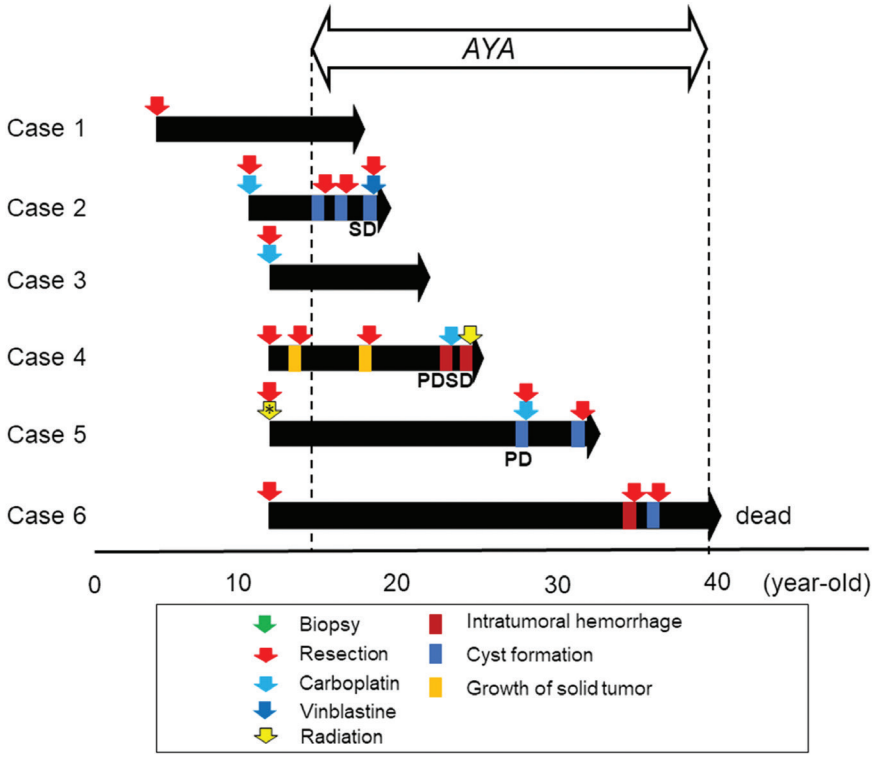

Fig. 1 Management history of non-neurofibromatosis type 1 related optic hypothalamic pilocytic astrocytoma treated in childhood and monitored until young adulthood. Vertical *arrows* and *bars* in the horizontal *black arrow* indicate active treatment and the pattern of failure. Treatment response is indicated below each bar, assessed according to the Macdonald criteria.[21] AYA: adolescents and young adults, PD: progressive disease, SD: stable disease. *Asterisk* in Case 5 indicates gamma knife surgery.

Fig. 2 Management history of non- neurofibromatosis type 1 related optic hypothalamic pilocytic astrocytoma which developed in adolescents and young adults. Vertical *arrows* and *bars* in the horizontal *black arrow* indicate active treatment and the pattern of failure. Treatment response is indicated below each bar, assessed according to the Macdonald criteria.[21] AYA: Adolescents and young adults, PD: progressive disease, SD: stable disease, ACNU: nimustine hydrochloride.

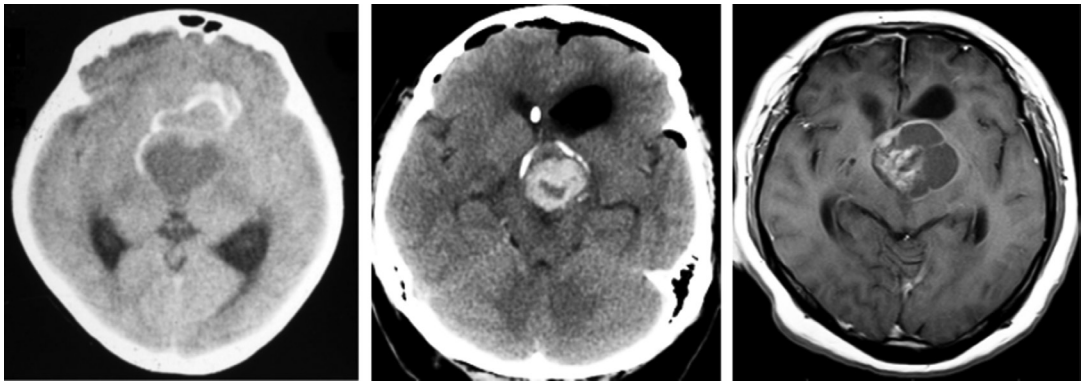

Fig. 3 Neuroimaging findings of the patient diagnosed in childhood and followed up after age 15 years (Case 6). CT scans at age 11 years (*left* panel), age 33 years when she presented with rapid visual decline, headache, and consciousness disturbance (*middle* panel), and age 34 years when she had consciousness disturbance (*right* panel), demonstrating intratumoral hemorrhage and cyst formation in young adults.

intratumoral hemorrhage in four (Figs. 1 and 2). Cyst formation or intratumoral hemorrhage occurred frequently in pediatric-onset OHPA during AYA, whereas tumor growth occurred in AYA-onset OHPA (Figs. 1 and 2). These findings suggested that rapid deterioration due to cyst formation or intratumoral hemorrhage could occur during AYA, especially in patients with pediatric-onset OHPA.

Eight patients received various types of chemotherapy in AYA: carboplatin monotherapy in six, nimustine hydrochloride in one, and vinblastine in one (Figs. 1 and 2). Progressive disease occurred in four of the six patients treated with carboplatin monotherapy (Cases 4, 5, 8, and 10; Figs. 1 and 3). These outcomes suggested that OHPA in AYA could be insensitive to carboplatin.

Two patients were treated with radiation therapy, and they did not experience further tumor progression.

One patient without pan-hypopituitarism died of sepsis. Six patients could live independently, and three patients were dependent due to visual disorder or hemiparesis.

We reviewed the histological findings of seven patients who underwent salvage surgery in AYA to

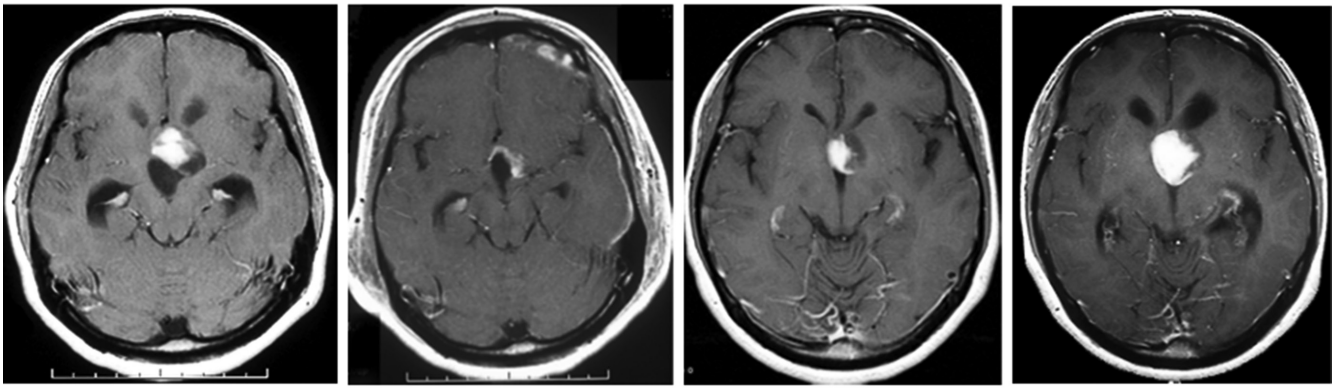

Fig. 4 Neuroimaging findings of the patient diagnosed in AYA (Case 10). T1-weighted MR images with gadolinium at age 26 years (*left* panel), after first debulking surgery (second panel from left), age 28 years when she was monitored without chemotherapy (third panel from left), and age 31 years when she received 18 cycles of carboplatin chemotherapy (*right* panel), demonstrating tumor growth with and without chemotherapy in young adults.

elucidate the mechanism of tumor progression. Regressive changes at progression were seen in six of seven patients, such as calcification, hyalinization, microcystic formation, or the increase of Rosenthal fibers and/or eosinophilic granular bodies (Table 1). Case 5 had morphological changes ranging from fibrillary appearance of delicate spindle cells to somewhat cellular appearance consisting of slight plump spindles cells without nuclear atypia and mitotic figures. None of patients had malignant features at progression.

Visual and endocrine function of OHPA in AYA

Five (50%) of the 10 patients suffered deterioration of visual function (Cases 4, 5, 6, 8, and 11 in Table 1). The cause was tumor progression or intratumoral hemorrhage in three (Fig. 3) and surgical intervention in one, and unknown reason in one.

Endocrine function was examined in 10 patients during the follow up period. Case 3 was diagnosed with panhypopituitarism based on the low level of serum pituitary hormone after tumor resection and received hydrocortisone, levothyroxine, and testosterone replacements. Case 9 had low level of serum IGF-1. However, she was not diagnosed with growth hormone deficiency based on the findings of growth hormone-releasing peptide and glucagon stimulation test. Another eight patients, including the patients with long-term follow up after radiation therapy (Case 10), were not diagnosed with endocrinopathies requiring hormone replacement based on the findings of normal serum levels of pituitary hormones.

Representative cases

Case 6: An 11-year-old girl presented with severe decline in bilateral visual acuities and concentric visual field defects. Her corrected right and left visual acuities were 0.02 and 0.01, respectively. Computed tomography (CT) demonstrated mass lesion in the optic hypothalamic region extending to the left frontal lobe (left panel in Fig. 3). She underwent debulking surgery and ventriculoperitoneal shunting, but her visual function did not improve. Histological diagnosis was pilocytic astrocytoma. Thereafter, she did not develop tumor progression until age 32 years. She presented with headache, decline in visual acuity, and consciousness disturbance at age 33 years. Her right and left visual acuities at that time were hand movement and 0.01, respectively. CT demonstrated intratumoral hemorrhage (middle panel in Fig. 3), and she underwent emergent debulking surgery. She had postoperative meningitis, so adjuvant treatment was not performed. She presented with consciousness disturbance and gait disturbance at age 34 years. T1-weighted magnetic resonance (MR) imaging with gadolinium demonstrated cyst formation (right panel in Fig. 3). She underwent third debulking surgery. Subsequently, her neurological symptoms did not improve, and visual acuity became blind. Eventually, she died of sepsis at age 40 years.

Case 10: A 26-year-old female presented with headache and lower quadrantanopsia. T1-weighted MR imaging with gadolinium demonstrated enhanced lesion in the optic chiasma extending to the third ventricle (left panel in Fig. 4). She underwent debulking surgery (second panel from left in Fig. 4), and was diagnosed with pilocytic astrocytoma. She did not receive any adjuvant treatment. The residual lesion had grown gradually by age 28 years (third panel from left in Fig. 4). She received 18 cycles of carboplatin chemotherapy, but the response was progressive disease (right panel in Fig. 4).

She underwent debulking surgery followed by local radiation therapy at age 31 years. Subsequently, she did not have further progression, and maintained visual function. She does not suffer from endocrinopathy.

Discussion

The present study examined the clinical and radiological features of histologically verified OHPA in AHA and found frequent tumor progression and deterioration of visual function in AYA.

Histological diagnosis of OHG in AYA

The present study focused on the clinical and radiological characteristics of histologically verified OHPA without NF1 in AYA. Since many of the patients in this study had hydrocephalus, large cyst formation, or intracranial hemorrhage, we could obtain tumor specimens and establish the histological diagnosis in most cases with OHG. We found that all AYA patients with newly diagnosed OHG had histologically verified pilocytic astrocytoma or pilomyxoid astrocytoma. This histological distribution is different from OHPA patients aged over 40 years of age. Patients with high grade glioma in OHG were older than 40 years without exception.[23] The histological diagnosis of OHG in patients over 60 years was high grade glioma in two of four in previous reports[14] and two of three in our unpublished data. These findings suggested that the histological diagnosis of OHG in AYA was pilocytic astrocytoma or pilomyxoid astrocytoma in most cases, but that OHG in elderly patients was not always pilocytic astrocytoma.

Tumor control of OHPA in AYA

We found the frequent tumor progression during AYA in patients with non-NF1 related pediatric and AYA-onset OHPA, in contrast to the findings in patients with NF1-related OHG, in whom the tumor tended to remain stable during AYA.[14] In addition, patients with pediatric-onset OHPA with stable clinical course before AYA, could suffer rapid clinical deterioration due to cyst formation or intratumoral hemorrhage. This finding implies that long-term follow up is essential after the completion of treatment for pediatric and AYA-onset OHPA.

Chemotherapy with carboplatin, vinblastine, or nimustine hydrochloride achieved tumor control for more than 5 years in only one patient. In addition, no objective response to chemotherapy was observed (Figs. 1 and 2). The objective response rate to carboplatin-based chemotherapy in childhood and adolescence is reported as 27–56% and 56%, respectively,[10,12] but no standard regimen has been developed for OHPA in patients aged over 18 years.[14] Since adults are more intolerant to chemotherapy than children, we treated the patients in AYA with OHPA with carboplatin monotherapy with 20% lower dosage, compared to that for childhood OHPA.[20] Although the observed refractoriness could be attributed to the reduced dose of carboplatin, there could be the difference in sensitivity to chemotherapy between childhood and AYA OHPA.

The present histological findings showed that tumor progression was associated with regressive changes, rather than malignant transformation. Cases 2, 8, and 10 received chemotherapy before salvage surgery, but Cases 4, 6, and 9 had no prior chemotherapy or radiation therapy. The effectiveness of chemotherapy remains unclear, but tumor progression could be based on spontaneous regressive changes in OHPA in AYA.

Decline in visual function and endocrinopathies in AYA

It was reported that risk factors for the deterioration of visual function were younger age (<2 years), chiasmatic/hypothalamic tumor site, and intraconal tumor site in the pediatric optic glioma.[17] Our study demonstrated that visual decline during AYA after initial treatments developed in half of the AYA patients with pediatric and AYA-onset OHPA. One patient did not have any sign of tumor progression or receive radiation therapy, and we could not identify the definitive cause of the deterioration of visual function. Similarly, deterioration of visual function without tumor progression or prior radiation therapy has been reported in three of 11 patients during adolescence.[12] These undesirable clinical courses suggest that close monitoring of visual function is indispensable in patients with pediatric and AYA-onset OHPA patients.

In contrast to the previous report demonstrating as high as 64% of patients with OHG had endocrinopathies in childhood,[18] our study found that only 10% of AYA patients with OHPA had endocrinopathies during the follow-up period. Patients who received radiation therapy, especially below 10 years of age, carried high risk for endocrinopathies.[18,24] In our series, nine of 11 patients developed OHPA after 10 years of age, and only two patients received radiation therapy at 23 and 31 years of age. These patient backgrounds explain the difference in the prevalence of endocrinopathies.

Limitations

The first limitation of this study is that the number of the patients was small, but few cases of OHPA

occur in AYA. The second limitation is selection bias because our institute is a tertiary referral center, so our cases could be refractory to treatment. However, the treatment outcome of OHPA in AYA mainly depends on the proportion of the patients with NF1 and histological diagnosis of the tumor, and this study included homogeneous patient groups. In addition, most patients were followed up until adulthood. Therefore, the present information is useful for the management during AYA of non-NF1-related patients with pediatric and AYA-onset OHPA.

Conclusion

In this series, the histological diagnoses of OHG in AYA were pilocytic astrocytoma or pilomyxoid astrocytoma. Both pediatric and AYA-onset OHPA demonstrated high incidences of tumor progression and visual dysfunctions during AYA, so that long-term follow up is essential after the completion of treatment for pediatric and AYA-onset OHPA. The optimal timing of debulking surgery and radiation therapy should be established to achieve the long-term tumor control and to preserve the visual function.

Conflicts of Interest Disclosure

All authors declare that they have no conflicts of interest, are members of the Japan Neurosurgical Society, and registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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