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Characterization of Adult Patients with Pilocytic Astrocytoma with an Aggressive Clinical Course. Retrospective Cross-Sectional Study. Single Center Experience

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ABSTRACT

Background: Pilocytic astrocytoma (PA) is a common tumor of the central nervous system and is considered a benign condition. However, in some cases PA can demonstrate aggressive clinical behavior.

Aim: To analyze and correlate factors leading to an aggressive course of disease in patients with PA.

Methods: As part of a retrospective study, medical records of adult patients (over 18 years of age) with a histological diagnosis of pilocytic astrocytoma were examined. The clinical course of the disease was analyzed for the 5-year follow-up period of patients operated on in 2018. A comparison was made of the anatomical location of the tumor, demographic data and proliferative activity index between the group of "normal" and "aggressive" course of the disease.

Results: 19 patients with signs of an aggressive course of the disease were identified. It was found that the age of the patients did not differ significantly between the groups. The most common location of the tumor was the cerebellum. The proliferative activity index (Ki-67) was slightly higher in the aggressive group (7.4% ± 4.3 to 4.12% ± 1.6). It was found that high Ki-67 was more common among young patients (under 30 years of age). In a number of cases, the histological data indicated anaplastic morphology in the presence of signs of PA, and therefore the presence of malignant astrocytoma with piloid features (HGAP) can be assumed.

Conclusion: A small percentage of PA are prone to an aggressive clinical course. One should be more wary of patients with a "benign" diagnosis. It is advisable to conduct large studies aimed at identifying factors characterizing the malignant course of PA. The introduction of molecular genetic diagnostic methods will make it possible to reliably distinguish PA from HGAP.

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Introduction

The fifth edition of the World Health Organization (WHO) classification of tumors of the central nervous system (CNS) identified a new type of glial tumor called high-grade astrocytoma with pyloid features, or HGAP. This type of tumor occurs in children and adults and has a poor prognosis [1].

HGAP has a cytomorphology similar to PA and cannot be distinguished from PA without additional molecular genetic studies. This once again raises the extremely important issue of identifying malignant tumors among cytomorphologically benign tumors. Since 1970, cases of malignant course of PA after surgical and radiotherapeutic treatment have been described. More recent studies have shown that about 5% of all PA have a malignant clinical course [2].

In two fundamental publications the main markers characterizing this subtype of tumor were described [3,4]. The basis for these publications is a set of clinical observations and several works on the morphological and genetic nature of PA. There are no multicenter prospective works on this topic, making it difficult to judge the true prevalence and epidemiology of this specific tumor subtype. According to the study conducted by Bender et al, the detection of HGAP does not exceed 0.63% among the pool of all confirmed glial tumors [5].

Data suggests that PA in adult patients tends to be more aggressive and leads to earlier mortality, according to Johnson et al., 2012 [6].

This study demonstrated that the 5-year survival rate for patients aged 5 to 19 years was greater than 96%, while for older patients (over 60 years of age) it was 53%. At the same time, in the study of Boschetti et al, it was demonstrated that anatomical location in adult patients does not fundamentally affect the risk of recurrence, provided radical removal is achieved [7].

The purpose of this work was to conduct a retrospective analysis of a group of patients with surgically removed PA and analyze the incidence of aggressive disease course, anatomical localization, age of patients, presence of signs of anaplasia and to assess continued proliferative tumor growth.

Materials and Methods

Medical records of patients with a histological diagnosis of pilocytic astrocytoma (ICD-O code 9421/1) were selected. The following Inclusion criteria were applied: patients over 18 years of age; male and female; availability of histological examination results; availability of surgical records indicating the extent of tumor resection; patients for whom it was possible to obtain follow-up data (5-year follow-up).

Patients were divided into 2 groups: patients who did not receive adjuvant treatment during the follow-up period and were alive for 5 years, and patients with delayed relapse, continued growth or metastasis until 2023. The extent of resection was determined based on surgical records and, if available, postoperative imaging. Anatomical localization was established through surgical records and preoperative imaging. Data on adjuvant therapy were obtained from the medical records. Patients' history was collected by researchers with the participation of attending physicians.

Statistics

Data was checked with the Shapiro–Wilk test for normality. Mann–Whitney U-test for data violating the normal distribution. $P < 0.05$ were considered statistically significant. Computer software packages (SPSS software, v. 21; Chicago, IL) were used for the statistical analyses.

Results/Observations

Demographics

In 2018, 79 patients over 18 years of age with a diagnosis of pilocytic astrocytoma (PA) underwent surgical treatment. Six patients were removed due to incomplete medical records, another 6 were removed due to the inability to collect follow-up data. Sixty-seven patients were included in the analysis. This included 39 female patients and 28 male patients. The average age of the patients was 36 years.

The average age of patients with a "normal" clinical course was 35 [18; 66] years, among them 18 male and 30 female patients (n=48).

Among patients with clinically aggressive tumor behavior (n=19), the average age was 32 [18; 64] years, 11 males and 8 females. The average age of initial diagnosis was 30 years for men [9; 64] and 23.6 years for women [4; 52], with an overall average of 27 years [4; 64].

Thus, in our series, patients with an aggressive course of the disease, the average age of onset of disease was lower than in the group with a normal course (32 to 35) (P>0.05).

1 patient from the series had a diagnosis of neurofibromatosis. However, during the observation period there was no need for repeat operations or adjuvant therapy for PA.

Anatomical Localization

The most frequent anatomical localization for PA among patients in the series was the cerebellum (n=25), followed by the brainstem (n=14). In thirteen patients' tumor was localized in other areas of the brain (Table 1).

Table 1: Anatomical Localization of Tumors

Anatomical localization		n	%
Brain	Frontal lobe	3	20
	Temporal lobe	5	
	Parietal lobe	2	
	Occipital lobe	2	
	Corpus collosum	1	
Cerebellum		25	37
Optic chiasm and optic nerve		6	9
Thalamus		6	9
Brainstem	Midbrain	7	21
	Pons	5	
	Medulla oblongata	2	
Spinal cord	Cervical	2	4
	Thoracic	1	
		N=67	

When comparing the anatomical localization of PA with normal and aggressive course, it was not possible to identify significant differences (Figures 1 and 2). The correlation between gender and anatomical location could not be reliably identified due to the small sample size. However, it can be assumed that in male patients PAs localized in the chiasmal sellar region are somewhat more common than in female patients (Table 2).

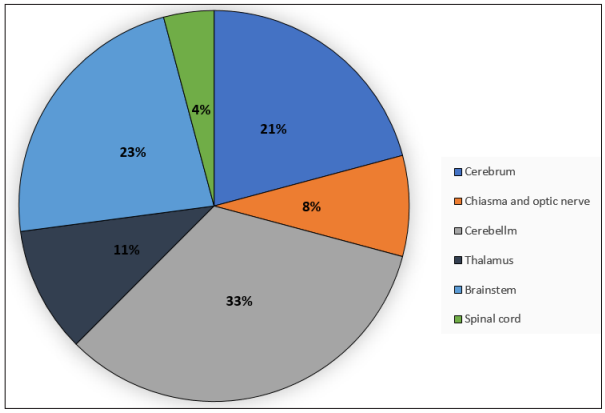

Figure 1: Anatomical Localization of PA in Normal Course Disease Progression Patient Group

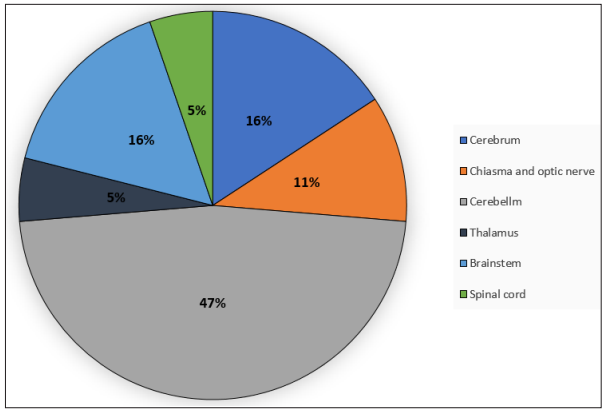

Figure 2: Anatomical Localization of PA in Aggressive Course Disease Progression Patient Group

Table 2: Anatomical Localization of Tumors among Patients with Normal Course of Disease Progression PA Versus Aggressive Course of Disease Progression PA

Anatomical localization		Normal course		Aggressive course	
Sex		M	F	M	F
Brain	Frontal lobe		2		1
	Temporal lobe	1	3	1	
	Parietal lobe		2		
	Occipital lobe		1	1	
	Corpus Collosum	1			
Cerebellum		6	10	6	3
Optic chiasm and optic nerve		3	1	2	
Thalamus			5		1
Brainstem	Midbrain	2	3		2
	Pons	3	1	1	
	Medulla Oblongata	1	1		
Spinal cord	Cervical				1
	Thoracic	1	1		
		n=18	n=30	n=11	n=8

Ki-67 Expression

Information on Ki-67 expression was available in 10 out of 19 observations in the aggressive group and averaged 7.4% ± 4.3%. For the "normal course" group, Ki-67 expression was available in 45 cases and averaged 4.12% ± 1.6% ($P < 0.05$). Thus, due to the lack of significant differences, it is premature to talk about the role of Ki-67 in the current study.

Characteristics of Patients with Aggressive Clinical Behavior of Pilocytic Astrocytoma

We defined the "aggressive course" group of patients based on the presence of continued growth or distant recurrence or metastasis, the control of which required adjuvant therapy or repeated surgical treatment. 11 of 19 patients in the aggressive group were operated on at least once before 2018 with or without adjuvant treatment. The group also included patients who were first operated on in 2018, but had continued tumor growth during the observation period (5 years).

In total, 8 patients with primary PA were operated on in 2018. Ki-67 (available for 6 out of 8 patients) was 7.14 [5; 14]. The average age of these patients (n=8) was 34 years. One patient out of 8 died 15 months after surgery due to disease progression. One patient showed continued tumor growth on MRI and subsequently underwent radiation therapy after which was lost to follow-up. Anatomically, PA in 4 cases was localized in the cerebellum, in 2 cases in the brainstem, in 1 case in the optic chiasm, 1 case in the frontal lobe of the brain. In 2 cases, patients received radiotherapeutic treatment after surgery and underwent repeat operations after 3 and 5 years. In five patients, disease control was achieved with radiation therapy. In one case (deceased in 2020), the patient underwent combined chemo-radiation treatment without any significant effect.

Anaplastic cytomorphology was documented in 3 patients, but molecular genetic methods were not routinely used until 2021.

In the group of patients operated on before 2018 (n=11), the average age at the time of disease manifestation was 27 years [4; 58]. Average Ki-67 (available for 3 of 11 patients) was 8 [2; 20]. There were 2 deaths among patients, 1 and 2 years after surgery.

In this group, four patients underwent three operations and 7 patients underwent 2 operations. The time to relapse varied significantly from 14 years to 1 year. Three patients underwent repeat operations without adjuvant therapy, 6 patients underwent radiation treatment with a positive effect, 2 patients received combined chemo-radiation treatment. There was indication of anaplastic cytomorphology in 4 patients.

Discussion

As part of a retrospective cross-sectional study, demographic parameters, anatomical localization and expression of Ki-67 were compared in a group of patients who underwent surgical resection of PA with "normal clinical course" and in a group "aggressive clinical course". No significant differences were found in anatomical location. Ki-67 was not available for all patients; however, Ki-67 was slightly higher in the aggressive group. Anaplastic morphology was observed in 7 patients. Thus, it can be assumed that among the pool of aggressive PA, patients with high-grade astrocytoma with piloid features (HGAP) may be found which is considered as a tumor comparable in malignancy to IDH mutant type astrocytoma Grade 4 and has a treatment algorithm different from PA.

Patients with continued tumour growth, delayed relapse and metastasis were included in the aggressive clinical course group. This analysis showed that this group itself is very heterogeneous and requires additional examination. The approach to treatment of this group of patients will be fundamentally different from that for those with a normal clinical course of PA.

Conclusion

A small percentage of PA are prone to an aggressive clinical course. One should be warier of patients with a "benign" diagnosis and, at the first signs of relapse and continued growth, apply treatment protocols for malignant neoplasms.

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