Cerebellar anaplastic astrocytoma in adult patients: 15 consecutive cases from a single institution and literature review

Artem Belyaev[a], Dmitry Usachev[a], Marina Ryzhova[a], Gleb Gulida[a], Vasilisa Skvortsova[b], Igor Pronin[a], Grigory Kobiakov[a]

a Burdenko Neurosurgery Center, Moscow, Russia Federation
b Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London, United Kingdom

Highlights:

- cerebellar anaplastic astrocytomas are extremely rare entities
- incidence of IDH-1 mutation in cAA is higher than in cerebellar glioblastomas
- patients with cAA tend to have a more frequent multifocal presentation at diagnosis
- overall survival rates for patients with cAA was compatible to the control group with supratentorial anaplastic astrocytomas

Abstract: Adult cerebellar anaplastic astrocytomas (cAA) are rare entities and their clinical and genetic appearances are still ill defined. Previously, malignant gliomas of the cerebellum were combined and reviewed together (cAA and cerebellar glioblastomas (cGB), that could have possibly affected overall survival (OS) and progression-free survival (PFS). We present characteristics of 15 adult patients with cAA and compared them to a series of 45 patients with a supratentorial AA (sAA) in order to elicit the effect of tumor location on OS and PFS. The mean age at cAA diagnosis was 39.3 years (range 19-72). A history of neurofibromatosis type I was noted in 1 patient (6.7%). An IDH-1 mutation was identified in 6/15 cases and a methylated MGMT promoter in 5/15 cases. Patients in study and control groups were matched in age, sex and IDH-1 mutation status. Patients in a study group tended to present with longer overall survival (50 vs. 36.5 months), but the difference did not reach statistical significance. In both cAA and supratentorial AA groups presence of the IDH-1 mutation remains a positive predictor for the prolonged survival. The present study suggests that adult cAA constitute a group of gliomas with relatively higher rate of IDH-1 mutations and prognosis similar to supratentorial AA. The present study is the first to systematically compare cAA and supratentorial AA with respect to their genetic characteristics and suggests that both groups show a similar survival prognosis.

Key words: cerebellar anaplastic astrocytoma, IDH-1 mutation, MGMT methylation, multifocal glioma.

Introduction

Anaplastic astrocytomas of the cerebellum (cAA) are extremely rare entities with just a few case reports or case series published so far [1,3,4,7,9,10,12,14,18,22-25,30,31]. Given the relative weight of the cerebellum (approximately 10% of the brain), one could expect 10% of anaplastic astrocytomas to arise from cerebellum [16]. However, no incidence of cAA has been reported due to its' utmost scarcity. This is not surprising that literature dealing with malignant gliomas of the cerebellum mostly consists of cerebellar glioblastomas, including both pediatric and adult patients, and brainstem tumours involving cerebellum [5,8,11,15,17,21,31,34].

Meanwhile, cerebellar glioblastomas themselves represent a rare form of neoplasms with reported incidence rate of 0.24-4.1% from all primary glioblastomas [19]. Sporadic articles devoted to the cAA were published decades ago and combined cGB and cAA in the analysis due to insufficient number of patients in each group. In total only 45 cases of cAAs have been documented in the literature (see Table 1). Importantly, previous studies lack any genetic characteristics of cAA and no standard therapeutic approach has been developed or advocated.

Here we leverage on the unique opportunity to follow up 15 patients with cAA who received treatment at Burdenko Neurosurgery Center.

Table 1. Cerebellar anaplastic astrocytoma patients (global experience)

##	Author	Year of publication	Age	Sex	Treatment	OS, wks
1	Budka [3]	1975	41	F	STR	1
2	Preissig [20]	1979	52	M	STR, BCNU	13
3	Salazar [23]	1981	8	F	STR, PFI	48
4			6	F	STR, WBI	52
5			7	M	STR, PFI	45
6			10	M	STR, PFI	87
7			16	M	STR, SCI	216
8			13	M	STR, SCI	117
9			10	M	2xSTR, SCI	156
10	Alpers [1]	1982	26	F	STR,RT,BCNU	1
11	Kopelson [15]	1982	15	M	STR,RT	459
12			60	M	RT	52
13			30	M	STR	4
14			67	M	biopsy	4
15	Zito [35]	1983	77	F	STR,RT	12
16			85	M	STR	1

17	Steinberg [25]	1985	15	M	STR,PFI,BCNU,VCR	30
18			6	F	GTR,PFI	182
19	Itoh [9]	1988	1	F	STR	1
20	Jaskolski [10]	1988	52	F	2xSTR, BCNU	30
21	Shinoda [24]	1989	12	F	STR,RT	26
22			12	F	biopsy	13
23	Chamberlain [4]	1990	14	?	2xSTR, PFI,ChT	100
24			21	?	2xSTR, BCNU	546
25			44	?	STR,PFI,ChT	221
26			39	?	STR,PFI,ChT	928
27			25	?	2xSTR, RT,ChT	139
28			33	?	STR,PFI,ChT	26
29			38	?	STR,PFI,ChT	22
30			29	?	2xSTR, PFI,ChT	169
31			33	?	2xSTR, PFI	1568
32	Marchese [17]	1990	11	?	STR, WBI	115
33	Tsunoda [30]	1992	44	M	STR,WBI,PFI,ChT	64
34	Djalilan [7]	1996	63	F	STR, PFI	12
35	Walid [31]	2008	14	M	STR,ChT	>25
36	Morgan [18]	2016	47	M	2xSTR, RT,ChT	>92
37	Kozhuki [14]	2018	75	M	STR,RT,ChT	>105
38-45	*Rizk [22]*	*1994*	*8 patients*			

Abbreviations: BCNU – carmustine, ChT – chemotherapy, GTR – gross total resection, OS – overall survival, PFI – posterior fossa irradiation, RT – radiotherapy, SCI – spinal cord irradiation, STR – subtotal resection, VCR – vincristine, WBI – whole brain irradiation.

The aim of the present study was to describe genetic and clinical characteristics of 15 adult cAA patients and to compare them both qualitatively and quantitively to those of a series of patients with supratentorial anaplastic astrocytomas with an emphasis to overall survival, multifocal location and IDH-1 mutational status.

Materials and methods

The database of Burdenko Neurosurgery Center was screened from January 2000 to March 2020 and a total of 15 cAA patients met our criteria: 1. AA was located in cerebellar vermis or

hemispheres (patients presenting with tumours involving both brainstem and cerebellum were excluded from the study); 2. all patients were evaluated by MRI before admission 3. all but one patient underwent tumor resection; 4. all but one patient received adjuvant (chemo- and radiotherapy) in the post-operative period. Biopsy results were reviewed by 3 independent experienced neuropathomorphologists.

A consecutive series of 45 adult patients with supratentorial hemispheric anaplastic astrocytomas not involving basal ganglia and/or midline structures were extracted from our database and used as a comparative group. Two patients in the main group presented with multiple lesions (parietal lobe in one case with unconfirmed supratentorial tumour biology and frontal lobe + corpus callosum in another case with glioblastoma histology); in the control group there were also 2 patients with multiple supratentorial AAs. All specimens – both in study and control group – were available for molecular analysis. The groups matched by patient gender, age and IDH-1 mutation status.

Statistical methods

Survival curves analyses and Cox regression models were performed using R-package (version 3.3.3 (R Core Team, 2017) with package "survival" [27,28].

For the Cox regression investigating the status of the IDH-1 across two groups we performed a regression with clustering patients within each group for the purposes of a robust variance estimation) [29].

For MGMT Cox regression model one of the patients was excluded because of the missing MGMT status leaving 14 patients for the analysis.

Results

Characteristics of 15 patients with cerebellar anaplastic astrocytomas and 45 patients with supratentorial anaplastic astrocytomas are presented in Table 2

Table 2. Patients' characteristics - study and control groups

(for study group patients index numbers are given in **bold**)

Patients	Personal cancer History	Sex	Age	Tumor Location	Multiple (Supratentorial) Tumor	Surgery	IDH-1 mutaion	MGMT methylation	Adjuvant treatment	OS (mounths)

1	No	M	27	H, V	left frontal lobe +CC	GTR,S	+	-	C,R	9
2	No	M	39	H, V	No	B,S	-	-	C	48,9
3	No	F	31	H, V	No	GTR	-	-	R	5,4
4	No	F	47	H	No	GTR	+	+	C,R	110,6 alive
5	No	F	54	H, V	No	STR,S	+	+	C,R	6,3
6	No	M	42	V	No	GTR	-	-	R	8,1
7	No	M	72	1-H 2-H,V,BrSt	No	1-GTR 2-STR	-	-	No	20
8	No	M	21	V	No	GTR,S	+	-	C,R	100,4 alive
9	No	F	58	H	No	GTR	-	+	C,R	7,4
10	Cr uteri	F	51	H, V	No	GTR	-	+	C,R	62,7
11	No	F	40	H	right parietal lobe	GTR	+	-	C,R	9,3
12	No	M	21	V	No	STR	+	?	C,R	159 alive
13	No	M	19	H	No	GTR	-	-	C	30,8
14	No	M	46	V	No	GTR	-	+	C,R	??
15	NF-1	F	22	H, V	No	STR	-	-	C,R	121,8 alive
1	No	M	24-29	F	No	GTR	+	-	C,R	43
2	No	M	25-30	P	No	GTR	+	-	C,R	38
3	No	M	25-30	F	No	STR	+	?	C	9,6
4	No	M	36-41	F	No	GTR	-	-	C,R	43,8
5	No	M	35-40	Oc	No	GTR	-	?	C,R	41
6	No	M	39-44	T	No	GTR	-	?	C,R	28,3
7	No	F	29-34	P	No	GTR	-	?	C,R	45,3
8	No	F	28-33	F	No	GTR	-	?	C,R	37
9	No	F	28-33	F	No	B	-	?	C,R	27
10	No	F	47-52	P	No	GTR	+	?	C,R	174
11	No	F	49-54	P	No	GTR	+	?	C,R	35
12	No	F	47-52	P	No	STR	+	?	C,R	36
13	No	F	51-56	F+P	Yes	GTR	+	?	C	11
14	No	F	53-58	P	No	GTR	+	?	C,R	29
15	No	F	53-58	F	No	GTR	+	?	C,R	49
16	No	M	41-46	T	No	GTR	-	?	C	7
17	No	M	35-40	P	No	STR, S	-	?	C,R	49
18	No	M	40-45	F	No	GTR	-	?	C,R	154
19	No	M	61-66	F	No	GTR	?	?	C,R	42,4

20	No	M	67-72	F	No	B	?	?	R	11
21	No	M	65-70	T	No	GTR	-	?	C	7,1
22	No	M	19-24	P	No	STR, S	+	?	C,R	39
23	No	M	25-30	P	No	GTR	+	?	C,R	35
24	No	M	17-22	F	No	GTR	+	?	C,R	27,7
25	No	F	53-58	P	No	GTR	-	?	C,R	25,7
26	No	F	56-61	T	No	GTR	-	?	C,R	27
27	No	F	57-62	P	No	STR	-	?	R	16,3
28	No	F	44-49	F+T	Yes	GTR	-	?	C,R	18,3
29	No	F	40-45	P	No	GTR	-	?	C,R	152,7
30	No	F	45-50	T	No	GTR	-	?	R	28
31	No	F	37-42	T	No	GTR	+	?	C	26
32	No	F	40-45	P	No	STR	+	?	C,R	37
33	No	F	37-42	F	No	GTR	+	?	R	2,4
34	No	M	19-24	F	No	STR	+	?	C,R	29
35	No	M	23-28	F	No	GTR	+	?	C,R	40
36	No	M	26-31	T	No	GTR	+	?	R	9,3
37	No	M	21-26	F	No	GTR	-	?	C,R	27,6
38	No	M	24-29	P	No	GTR	-	-	C,R	30
39	No	M	25-30	Oc	No	B,S	-	?	C,R	28
40	No	M	44-49	P	No	STR	-	?	C	5,7
41	No	M	48-53	T	No	GTR	-	?	R	16
42	No	M	44-49	F	No	STR	-	?	C,R	12,9
43	No	F	21-26	P	No	GTR	-	?	C,R	26
44	No	F	24-29	F	No	GTR	-	?	C,R	28
45	No	F	27-32	F	No	GTR	-	?	C,R	37,4

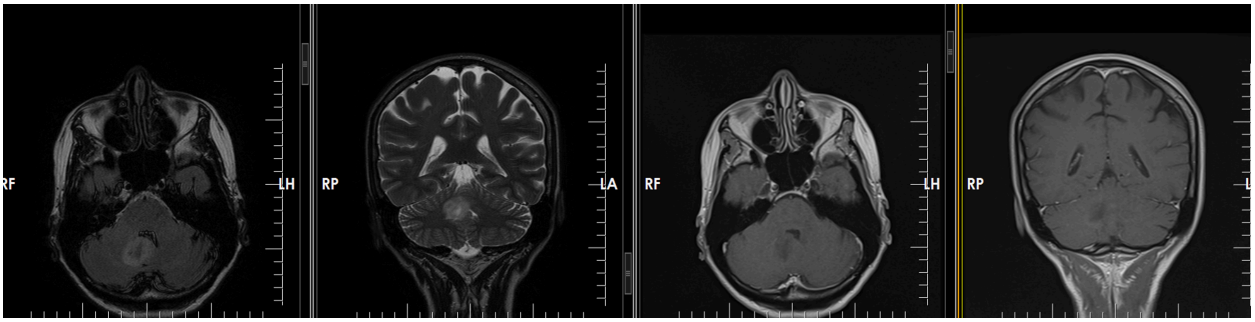
Abbreviations: B – tumour biopsy, BrSt – brainstem, C – chemotherapy, CC – corpus callosum, F -frontal lobe, GTR – gross total resection, H - cerebellar hemisphere, NF-1 – neurofibromatosis type I, Oc – occipital lobe, OS – overall survival, P – parietal lobe, R – radiotherapy. S - shunt placement, STR – subtotal resection, T – temporal lobe, V - cerebellar vermis.

Clinical characteristics and imaging findings

The mean age at diagnosis was 39 years (range 19-72 years). There were 8 men and 7 women. A personal history of neurofibromatosis type I (NF1) was noted in 1 patient (6.7%), as well as a personal history of previous cancer (cervical cancer). Clinical manifestation consisted mostly of intracranial hypertension syndromes (nausea, vomiting) 60% of cases and cerebellar symptoms (gait and writing disturbances) 47% of cases. One of two patients with concomitant supratentorial tumors experienced seizures.

MRI results usually reveal infiltrating mass, more often occupying both the cerebellar vermis and (partially) the hemispheres, sometimes located in the hemisphere or vermis only. Tumors represent a mixed iso-hypointense mass on T1WI and heterogeneously hyperintense mass on T2WI and T2-

FLAIR regimes. Patterns of contrast enhancement are various, but most of the cAA showed a mild or no enhancement (Figure 2).



FLAIR T2WI T1+C

Figure 2. Patient 45-49 years; pre-op MRI revealed space-occupying lesion in the cerebellar vermis and right hemisphere with no perifocal edema and moderate contrast enhancement. The tumor was completely resected. Biopsy report – anaplastic astrocytoma.

Histological and molecular characteristics

Biopsy samples were reviewed by 3 independent neuropathomorphologists and patents were included into study group only upon consensus regarding tumour type (in accordance with WHO 2016 classification of CNS tumours). Median Ki67 labeling index was 15% (range 8-50%). Molecular analysis revealed that 6 patients had IDH-1 mutation; methylated MGMT-promoter was identified in 5 patients and H3F3AK27 mutation was revealed in 1 patient.

Treatment and outcome

One patient underwent tumour biopsy, in 3 patients subtotal resection (STR) was performed, and in 11 patients surgery consisted of gross-total resection (GTR) based upon surgeon's impression. In one patient repeated surgery was performed in 12 months' time due to tumour recurrence (no adjuvant treatment was conducted in-between). Notably, the first surgery consisted of GTR, however during the second one only STR was achieved because of brainstem involvement. A CSF-shunt was implanted in 2 patients before admission to our clinic and in one shortly after surgery. All but one patient received adjuvant treatment after surgery that consisted of combined chemoradiotherapy (n=10), chemotherapy alone (n=2) and radiotherapy alone (n=2). Median overall survival (OS) for 14 patients was 50 months with 4 patients surviving for more than 100 months, and being alive at the time of the preparation of this report. One patient dropped out of the follow-up because of moving to another country.

Comparison with supratentorial anaplastic astrocytomas

Characteristics of patients with cerebellar and supratentorial anaplastic astrocytomas are summarized in Table 2. Patients in the control group were matched in gender, age and IDH-1 mutation status with patients from the study group. Surprisingly, despite virtually ideal match, cAA had better outcome, than their supratentorial counterparts (OS: 50 months +/- 49.7 vs. 36.5 +/- 35.5 months). However, analysis of Kaplan-Meyer survival curves showed no difference in survival rates (log-rank two-tailed test p = 0.31).

Two survival curves show a crossing at the later time points which violates the assumption about proportional hazard rates underlying the log-rank test. However, restricting analysis to the segments of the curves before the crossing (e.g. taking time period limited to 150 months after the surgery) did not show significant difference between the two groups (p = 0.52) due to high variability in the estimates. We next turned to a more complex Cox regression model with group clustering (see Methods) which allowed to determine the role of different factors (such as age, gender, IDH-1 mutation status) across both groups while controlling for each group variance.

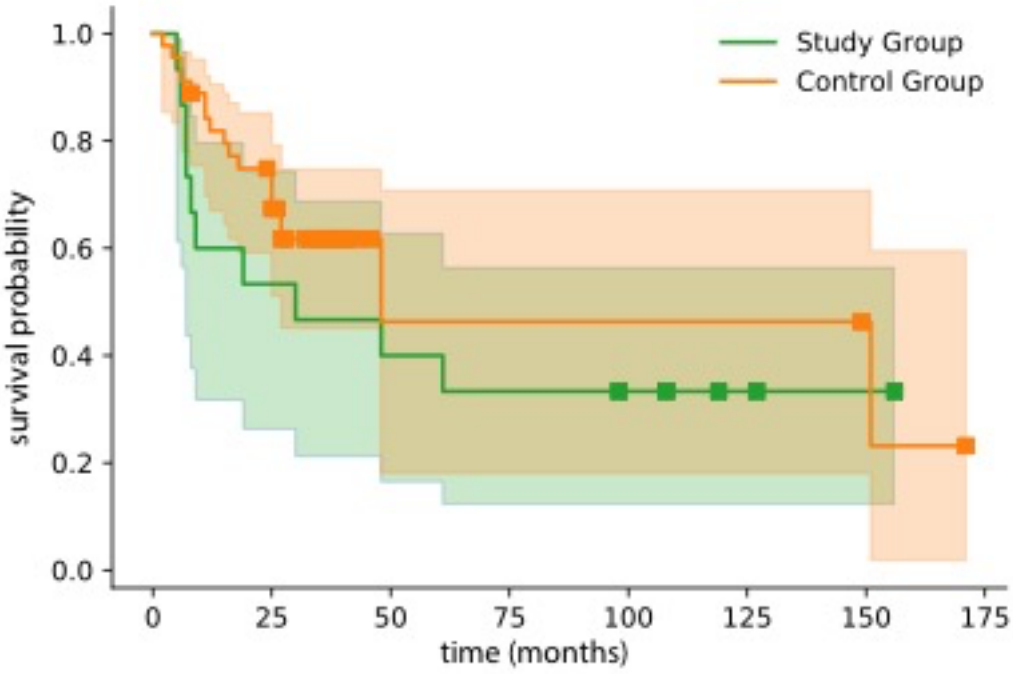


Figure 1. Kaplan-Meier survival curves for study group (green) and control group (orange). Shaded areas are 95% confidence intervals, squares show censored data.

Age ad IDH-1 status came out significant predictors. While age has a negative effect on survival (increasing age by 1 year raises the hazard rate by 10.4% ($p<0.001$) while presence of the positive IDH-1 mutation decreases the hazard rate by 32.1% ($p<0.001$).

Table 4 Statistical results for the Cox regression analysis

	coef.	exp(coef)	se(coef)	robust se	z	p
Age	0.0426	1.0435	0.0139	0.0124	3.42	0.00062
IDH1	-0.3864	0.6795	0.4001	0.0907	-4.26	0.0001
Gender	-0.3082	0.7347	0.3857	0.2975	-1.04	0.30021

We also looked at the effects of the MGMT-status in cAA group of patients only (since MGMT data were not available in the control group). MGMT-status had a marginal ($p = 0.0916$) significant negative effect on hazard rates when accounting for gender, age and IDH-1 status but more data are needed to conclude whether positive MGMT mutation might improve survival outcomes.

Discussion

A thorough literature review revealed just a few articles where "cerebellar anaplastic astrocytoma" term was mentioned, most of them published between 1990 to1998. Because of its' very limited number, we found it essential to considerate each of them.

Chamberlain et al. [4], described 18 "poorly differentiated gliomas of the cerebellum", but the sample included a series of glioblastomas (28%), anaplastic astrocytomas (50%) and "mixed gliomas" (22%). Six patients were younger than eighteen years old at diagnosis. Median survival rate for 9 cerebellar anaplastic astrocytomas (including 1 pediatric case) was 44 months. Interestingly, 5 out of 18 patients demonstrated tumour relapse: 3 leptomeningeal and 2 parenchymal extracerebellar (parietal lobe and upper cervical cord, respectively). Unfortunately, no information is given regarding the histological type of tumour with extracerebellar relapse.

Rizk et al. [22], also presented a mixed series of cerebellar glioblastomas (n=2) and cerebellar anaplastic astrocytomas (n=8). This study was conducted in late 1970s - early 1990s and based on CT scan tumour appearances. Seventy percent of tumours developed within cerebellar vermis, thirty percent in hemispheres. Authors did not state median OS for either cGB or cAA, but 4 out of 8 cerebellar anaplastic astrocytomas were still alive by the time of article submitting without any signs of recurrence with a median follow-up of 7 years.

Paper of the most interest published by Djalilian et al. [7] presented an analytic review of malignant gliomas of the cerebellum and was based on 78 cases (37 cAA and 41 cGB), although only 7 of them were of authors' clinical experience. Median survival for patients with cAA was

32 months. Obvious conclusion is made that patients undergoing surgical resection and receiving radiation therapy demonstrated better survival rate. Despite the fact that the article combined both pediatric and adult cases, it provided a systematic review of malignant astrocytomas of the cerebellum presenting in particular 19 adult cAA patients.

Since all those papers were published decades ago, no information regarding genetic profile of malignant cerebellar gliomas was reported.

In this study we presented a series of 15 consecutive adult patients with cerebellar anaplastic astrocytomas treated in a single institution for over 20-year period. Survival analyses was performed with respect to patients age and IDH-1 mutational status, as well as MGMT methylation profile. We used control group of supratentorial AA as a "perfect match" with no difference in age, sex and IDH-1 mutation status.

Our results are aligned with previous studies demonstrating relatively prolonged survival in a group of cAA patients comparing to their supratentorial counterparts: in our group of cAA patients' OS was 50 months vs. 36.5 months in control group of supratentorial AA patients, but this difference did not reach statistical significance due to high variability in our sample.

OS in our control group was similar to the data published before: Strowd et al. [26] demonstrated OS for AA in the temozolomide era as 36,7 months. For this comparison, it is noteworthy that both patients harboring additional supratentorial tumour (in case 1 – anaplastic astrocytoma, in case 11 – tumour of unknown histology) had very short overall survival – 9 and 9.3 months, respectively. Interestingly, the eldest patient in the group demonstrated 20-months OS despite the absence of any adjuvant treatment; he underwent repeated surgery after 12 months, but then deteriorated due to brainstem involvement by the tumour.

Rizk et al. [22], reported that 4 out of 8 cAA patients presented with more than 7 years of follow-up without sings of recurrent disease.

This higher survival rate of patients with cAA when comparing to supratentorial AA remains a puzzling phenomenon: malignant cerebellar tumors hypothetically should be associated with a heavier burden due to their fast expansion and building-up mass-effect in a small compartment of posterior fossa, containing critical life-supporting structures of the brainstem. Moreover, tumour may involve brainstem itself with catastrophic consequences. Despite those well-recognized facts, cAA cases pertain to a better prognosis than supratentorial tumours of the same histological type. Interestingly, the same correlation was absent for cerebellar glioblastomas: in a series of 202 cGB collected from SEER database and presented by Babu et al. [2], OS for both cGB group and supratentorial GB (sGB) group was similar (7 months). Although Yang et al. [34] presented a series of 28 cGB patients with much longer OS (14.3 months), their results must be taken with caution due to small-size sample. Multicenter study of cerebellar GBM conducted by Weber et al.

[32] and based upon 45 cGB cases also suggested that prognosis of infratentorial GB was not different from supratentorial tumours with median OS of approximately 10 months. However, in all abovementioned series cGB groups were younger than sGB and that could have possibly affected OS rates. In our group age factor was carefully controlled by strict matching. No clear clarification of this phenomenon has been proposed so far.

One of the promising explanations – as well as for the rarity of malignant gliomas in the cerebellar - may be a substance P deficit in the cerebellar tissue. This amino acid peptide neurotransmitter is active throughout the cerebrum and brainstem, but not in the cerebellum. Substance P signaling has been shown to play a contributory role in glioblastoma development. [11]

Quite an unexpected result of the present study is a very high incidence of IDH-1 mutations in the study cohort (40%). In a similar study with 17 cerebellar GB conducted by Picart et al. [19] none of the reported tumours demonstrated IDH-1 positive status. It is a well-known fact that for supratentorial gliomas IDH-1 mutation pertains better prognosis [6,13]. Overall, our results confirm this tendency for the whole cohort (study + control groups). Unfortunately, we failed to demonstrate it separately for cAA patients due to the group small sample size and it will need further investigation. The frequency of the IDH-1 mutation in the study group could be explained by the secondary origin of the majority of the anaplastic astrocytomas as they result from a malignant transformation of low-grade astrocytomas. In contrast, the majority of the glioblastomas are de novo tumours and are not associated with the IDH-1 mutation [33].

Our results also pointed towards a potentially promising role of methylated MGMT promoter status in influencing prolonged survival in cAA patients, but the effect remains marginal and will require future replications.

Finally, patients in the study group had more frequent multifocal presentation (13% vs. 4.4% in the control group). Nevertheless, these results should be taken with caution since our control group was pre-selected to match the study group based on age, gender and IDH-1 mutation status and this selection bias might limit the interpretation.

Our study has several limitations. First, study's retrospective design limits the uniformity of clinical reporting and follow-up. Second, due to the rarity of cAA cases in the population, our study group has a small sample size which reduced our statistical power to detect possible differences between study and control groups. Lastly, large-scale molecular analysis could have significantly enriched the reported analyses and further contributed to tumour research.

Conclusions

To our knowledge this is the largest, single-institution series of cAA reported to date. Despite the location of the tumor in the restricted posterior fossa compartment containing critical life-supporting structures, cAA group did not demonstrate worse prognosis than their supratentorial counterparts. In fact, overall survival rate was even higher in the group of cAA patients, but the difference did not reach statistical significance. Furthermore, cerebellar anaplastic astrocytomas presented a relatively high rate of IDH-1 mutation when compared with cGB. The present study suggests that cAA does not represent a homogeneous entity but rather constitutes a heterogeneous subgroup of anaplastic gliomas. We believe further accumulation of data for cAA with subsequent meta-analysis might shed light on cAA characteristics and refine classification of these tumors.

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