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ASTROBLASTOMA: DOES IT REQUIRE DIFFERENT TREATMENT?

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Background- Astroblastoma is partially understood, poorly reported and rare in occurrence tumor with significant dilemma regarding cellular origin, diagnostic criteria, clinical behavior, and management protocol. *Material and method*- Thorough search of published English scientific literature was made with search word **Astroblastoma** through Google Search, PubMed, ResearchGate and Cochrane Library till June 2018. The reports thus collected were examined for data regarding age, gender, location and laterality of disease, pathological grade, treatment received, and outcome of treatment. *Results*- Data of 161 patients was retrieved from 72 publications. Median age at presentation was 18 years. Females were affected much more frequently than males. Most common site of involvement was the frontal lobe. Laterality data was inconsistent and sparingly reported. Most common presenting complaint was headache followed by history of seizure. Surgery was performed in majority of patients-79.6% of the patients underwent a gross total resection, 45% (44 out of 98 reported) had a high-grade tumor. Sixty patients received adjuvant radiation with a median dose of 54 Gy (Range 20-72), mostly for high grade, residual or recurrent disease. Adjuvant chemotherapy was used in 25 patients. Median follow-up was 43 months (range 1-238). Median overall survival was 138 months. Patients with a higher-grade tumor had significantly worse overall survival. *Conclusion*- Astroblastoma is rare but known to have two distinct grades, with higher-grade tumors bearing significantly poor survival. Maximal safe surgery is the standard. Though there is lack of consensus, adjuvant radiotherapy with or without Temozolamide should be considered in view of high rates of local recurrence.

INTRODUCTION

First description of Astroblastoma in English literature dates back to 1926 by Bailey and Cushing.[1] Since then, limited number of cases have been described, mostly as case reports. Owing to rarity of the disease and limited published information, significant dilemma exists regarding cellular origin, diagnostic criteria, clinical behavior, and

treatment protocol of this tumor. This work intends to review the available data on Astroblastoma to make our understanding better about it.

MATERIALS AND METHODS

Methodology

Thorough search of published English scientific literature was made with search word **Astroblastoma** through Google Search, PubMed, ResearchGate and Cochrane Library till June 2018. The reports thus collected were examined for data regarding age, gender, location and laterality of disease, pathological grade, treatment received, and outcome of treatment. References and cross references were carefully checked by arranging all published work in their order of publication year to rule outrepetition. Only the articles providing adequate information about demography, diagnosis, treatment and/ or outcome were considered. Available data were arranged in *excel* chart and analyzed.

Statistical analysis

Categorical variables were summarized by frequency (ratio and/ or percentage) and quantitative variables by median and/ or range. Overall survival (OS) was calculated from time of diagnosis. The Kaplan Meier method was used for survival analysis. Log rank test was used to find the impact of different prognostic variables and p value of ≤ 0.05 was taken as significant.

OBSERVATIONS

Patient Characteristics

Data of 161 patients with astroblastoma were retrieved from 72 publications, published over almost a century.[1-74] Most were case reports or small case series. Only four retrospective analyses had a sample size of more than hundred.[75-78] Patient's characteristics are shown in Table 1.

Characteristics			Number (%)
Age in years			
(n=149)	Range		0 to 73 years
	Mean		18 years
Gender			
(n=155)	Males		108 (69.7%)
	Females		47 (30.3%)
Location			
(n=136)	Supra-tentorial		109 (80.1%)
	Infra-tentorial		27(19.9%)
Site involved			
	Frontal lobe		49 (36%)
	Parietal lobe		23 (17%)
	Temporal lobe		21 (15%)
	Occipital lobe		13 (10%)
	Others		30 (22%)
Treatment taken			
	Surgery		98
		GTR	78 (79.6%)
		STR/ Bx/ Dcx	20 (20.4%)
	Radiotherapy		60
		Alone	14 (23.3%)
		Adjuvant	46 (76.7%)

Table 1

Median age for the entire cohort was 18 years (Range 0- 73 years). More than half of the patients were in the first two decades of life (86/149; 57.7%). This frequency gets almost halved after consecutive two decades i.e. a gradual decline in frequency was observed (Figure 1).

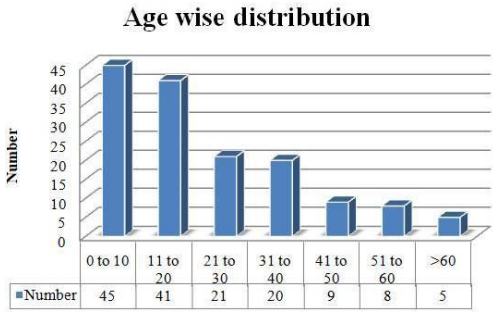

Figure 1

Astroblastoma was observed more than twice as frequent in femalesas in males (69.7% versus 30.3%; M:F = 3:7).

The tumors were almost intracranial, the only case reported to involve spinal cord.Frontal lobe was involved most commonly (36%) followed by parietal (17%), temporal (15%) and occipital (10%); in that order. Only one patient with spinal astroblastoma was reported. Supra-tentorial part was involved much more commonly thanthe infra-tentorial (4:1). Laterality (left versus right) data was inconsistent and sparingly reported.

Available data revealed headache to be themost common presenting complaint (61%) followed by history of seizure (26%). Others had weakness, focal neurological deficits and occasionally incidental observation for intracranial bleed.

Treatment

Surgical details could be retrieved for 98 patients: 79.6% of the patients underwent a gross total resection (GTR), and the remainder had a decompression (Dcx), biopsy (Bx) or subtotal resection (STR) only. Forty-four out of 98 (45%) had a high-grade tumor. Sixty patients received radiotherapy for high grade, residual or recurrent disease; with a median dose of 54 Gy (range 20-72 Gy). Chemotherapy was used in 25 patients, Temozolamide being used in over half of those. Combination chemotherapy with Cisplatin, Etoposide, Vincristine, or Ifosfamide was used in others but one case, where Bevacizumab was added.

Radiotherapy and chemotherapy was found to be used mainly in setting of sub-optimal resection, high grade or recurrent disease. Since, bias was observed in use of treatment modalities, a head on comparison of results of surgery versus other modality or a combination was not found logical.

Outcome

Median follow up duration was 43 months (Range 1-238 months). Median overall survival was 138 months. Patients with a high grade tumor had significantly poor overall survival compared to low grade counterparts (Median OS- 53 months for high-grade tumors versus not reached for low-grade tumors; p = 0.001). Patients who underwent GTR had a 5-year OS of 76.2% compared to 18% of the patients with a STR. Other factors like age, gender, tumor location, adjuvant treatment (radiotherapy and/or chemotherapy) were not found to have significant impact on survival.

DISCUSSION

Astroblastoma have a controversial claim as a distinct entity, with no established WHO grade. These lesions are characterized by the presence of the *perivascular pseudorosettes* composed of tumour cells with a prominent process extending to a central blood vessel and perivascular hyalinization.

In publication of first case of Astroblastoma in 1926, Bailey and Cushing described ‘Astroblasts’ to be the embryonic, destined to become astrocytes, intermediate stage cells during development from spongioblasts to astrocytes.[1]

The cell of origin was later described as a *Spongioblast.* Microscopic characteristics included- abundant thick blood vessels surrounded by plasma cells and lymphocytes. The perivascular tumor cells with broad footplates form a typical *pseudorosette* pattern as seen in ependymoma. Expression of glial

fibrillary acidic protein (GFAP) and vimentin points towards an origin from astrocytes, while expression of epithelial membrane antigen (EMA) and cytokeratin (CK) positivity indicates ependymal differentiation.[4]

Russel and Rubenstein suggested that dedifferentiation of mature astro-glial cells could lead to the development of astroblastoma. They subcategorized the tumor into well-differentiated and anaplastic variants depending upon cellularity, mitosis and anaplasia.[5]

Another theory relates to its origin from *Tanycyte*, a cell intermediate between astrocytes and ependymal cells.[15]

On histology, it may simulate an ependymoma, especially when well differentiated, and can be differentiated by the presence of rarified bodies in between pseudorosettes.[8, 53]

While WHO 2000 classification was being followed, Louis et al claimed that most glioma classifications were derived from the seminal system of Bailey and Cushing. Bailey and Cushing, rather presciently for the 1920s, drew parallels between the histological appearances of glial tumors and putative developmental stages of glia. Thus, they reasoned that the cells of Astrocytoma microscopically most closely resembled astrocytes and those of oligodendroglioma histologically most mimicked oligodendrocytes. As these tumors became more malignant, they resembled less differentiated (i.e. earlier) precursor cells; hence, malignant astrocytomas were dubbed "astroblastomas." Role of accurate classification of brain tumors, based on molecular and biological understanding and its importance in clinical decision making was also emphasized.[79]

Navarro et al mentioned microscopic findings suggesting that anaplastic astroblasts have a tendency to evolve toward, or be associated with less differentiated cells, either neuro-epithelial or sarcomatous.[21]

In the WHO 2007 classification no formal grade was recommended, although well differentiated and malignant variants were recognized, possibly with clinical consequences. Astroblastoma was described to be positive for GFAP, S100 and Vimentin by IHC and frequently with focal expression of EMA. In the lack of consensus, Astroblastoma was classified as 'other neuroepithelial tumours'.[80]

WHO 2016 Classification of Tumors of Central Nervous System describes malignant astroblastoma as having focal or multiple foci of high cellularity, anaplasia, increased mitotic activity (>5 mitoses per HPF), elevated proliferative index (typically >10%), microvascular proliferation and necrosis.[81]

Brat et al suggested that Astroblastoma may have a characteristic cytogenetic profile in addition to their distinctive clinical, radiographic, and histopathologic features.[12]

Molecular studies are being carried to make understanding more clear. Recently, they have been described to overlap with a newly-discovered group of tumours described as 'high grade neuroepithelialtumour with MN1 alteration' (CNS HGNET-MN1), defined by global methylation patterns and strongly associated with gene fusions targeting MN1, so providing opportunity to understand the evolutionary history and provide novel therapeutic targets for astroblastoma/ CNS HGNET-MN1.[71]

So far reported as rare brain tumors, Astroblastoma predominates in children and young adults, with incidence range 0.45% to 2.8% of all glioma.[8]Though cases have been reported in adults, overall incidence has not been commented upon. Only 11 cases have been reported from India, so far.

Demographics are helpful in differentiating Astroblastoma from other tumors. From this analysis, it seems that Astroblastoma tends to occur early in life (childhood and teenage), with gradual decline in frequency over the ages. This is in contrast to glioblastomamultiforme (GBM), meningioma, and oligodendroglioma, which affect older adults, while ependymoma and atypical teratoidrhabdoid tumor (ATRT) are often found in younger children. While most large studies endorse similar pattern, [76-78] a bimodal

distribution was reported by Shugrue et al.[75]But, if we examine data of latter as well, a gradual decline of frequency with every decade of age group is found which is compliant with our observation.

In the present analysis, incidence in female was much more than in males (M:F = 3:7). Female predominance, with M:F ranging from1:3 to 1:11, has been reportedby reviews.[31,66,72] Unlike majority of reports showing a female preponderance, SEER data analysis reported equal incidence in males and females.[76]

We found the disease located in supra-tentorial area more than infra-tentorial area (4:1). This ratio has been found to range from 4.4:1 to as high as 11:1in earlier published reports.[75-78]

Present analysis found the tumorinvolving the frontal lobe most commonly, in nearly one third of the cases. Parietal and temporal lobe cases almost equaled to rank next, followed by occipital lobe. This finding corresponds to most reviews except slight change in middle order.[75-78]

Headache is themost common presenting complaint (61%) followed by history of seizure (26%) in this study, others being weakness, focal neurological deficits and incidental intracranial bleed. Most other studies found headache to be the commonest presentation instead of focal neurological deficits.

Because of rarity, Astroblastoma presents a challenge as to its diagnosis and treatment. No level I-III clinical evidence exists to guide treatment, so the optimal therapy remains disputed and possibly extrapolation of principles of astrocytoma management is applied.

Imaging may support early diagnosis and good prognosis. Astroblastoma often demonstrate T1 and T2-prolongation relative to white matter, with well-demarcated boundaries and heterogeneous contrast enhancement; different from meningioma, which tends to exhibit a homogeneous enhancement. Supra-tentorial location differentiates it from ependymoma, which usually occupies the posterior fossa. Calcifications are a consistent imaging finding, and would be unusual for GBM and ATRT. Astroblastoma tend to be peripherally oriented and may involve or arise primarily from the ventricular system. Although rim enhancement seen around its cystic components may resemble that of a necrotic GBM, Astroblastoma usually have minimal peri-tumor white matter T2-prolongation. The extent of peri-tumor edema is considered an unfavorable radiological feature that suggests early recurrence or progression in Astroblastoma.[31, 53]

Cunningham et al reviewed radiological features of Astroblastoma and observed that imaging often shows a supra-tentorial, superficial, well-defined, cystic-solid enhancing mass. On CT, most are hyper-attenuated, have calcifications, and may remodel adjacent bone if superficial. MRI characteristically reveals a hypointense mass on T1-W and T2-W sequences with restricted diffusion. MR spectroscopy, PET and catheter angiography findings are nonspecific.[77]

TREATMENT

The clinical behavior of Astroblastoma is unpredictable and prognosis has been described as intermediate between that of low grade astrocytoma and glioblastoma.

Merfeld et al observed overall survival at 5 years to be 79.5% and emphasized that Astroblastoma be treated with curative intent.[72]

Surgery and extent

Sughrue et al observedsurvival trends in a cohort (n=116), and found statistically significantdifference (p=0.011) in 5-year progression-free survival for patients treated with GTR as compared to STR (83% versus 55%).[75]

Ahmed et al in review ofSEER data also revealed similar patterns of survival; patients treated with surgery alone compared to radiation therapy alone showed improved 5-year overall survival (62.2% versus 27.3%; p<0.001) and cause-specific survival (67.3% versus 31.9%;

p< 0.003). But the possibility of treatment bias can't be ruled out.[76]

In analysis by Mallick et al, patients treated with GTR were found to have better survival, with a trend to statistical significance (p = 0.0649) compared to those treated with a STR.[78]

Radiotherapy

No report could be found with radiotherapy given in neo-adjuvant setting.

The role of adjuvant radiotherapy to the tumor bed has been debatable. Adjuvant radiotherapy may not be necessary in low-grade astroblastoma tumors, particularly after radical surgery (i.e., GTR).

Bonnin et al reviewed and found two distinct histological types: low-grade and high-grade. In low-grade tumors, survival from 3 to 20 years after treatment was reported whereas in high grade, it was an exception beyond 3 years. Best clinical results were obtained after total or subtotal resection of the tumor, followed by radiotherapy.[74]

Janz et al presented a case in which there was early recurrence of a low-grade variant that warranted postoperative radiotherapy with no further recurrence.[53]

Lau et al, Yao et al and Samples et al have described low-grade Astroblastoma treated with GTR that recurred early, warranting another operation and adjuvant radiotherapy; thus advocating implementation of adjuvant radiotherapy even for low grade neoplasm.[22,57,66]

Mangano et al analyzed outcomes and treatment strategies in low and high grade Astroblastoma.Among the patients with high-grade tumors, those who received surgery and radiotherapy, had the highest survival rate.[27]

Ahmed suggested that surgery was superior to radiation alone and the combination of both did not improve survival.[76]

Mallick et al pointed that 65% of the patients required a salvage surgery and 50% underwentsalvage radiation. Ultimately, 68% of the patients received radiation either as adjuvant or in salvage therapy. Observations justified the addition ofadjuvant radiation to optimize the treatment outcome.[78]

Focal radiotherapy has been suggested largely in patients with high-grade tumors, tumors with STR, or in the setting of tumor recurrence.[8, 12,37,68,72]

Chemotherapy

Though, isolated reports have used chemotherapy and shown its benefit in adjuvant setting, no large review has ever endorsed its benefit. Few studies have advocated the use of Temozolamide, but that seems to be extrapolation of experience with GBM.[36, 44]

Combination of Cisplatin, Etoposide, Vincristine, or Ifosfamide was used in some. Bevacizumab has also been tried.

Words of caution come from Merfeld et al, who reported no benefit of chemotherapy.Rather hazard ratio of 2.516 was reported with use of adjuvant chemotherapy.[72]

PROGNOSIS

Prognosis of Astroblastoma appears to directly correlate with its histological grade. In general patients with high grade disease survive poor than those with low grade.[17, 27, 64, 78]

Extent of surgery is another factor. Astroblastoma, as stated above, treated with GTR have relatively better prognosis.[75-78]

Tumor site has also been associated with clinical outcome. The 5-year OS for tumors located at infra and supra-tentorial has been estimated to be 75% and 44.9% (p<0.001), respectively.[76]

The age and gender of the patient also seems to be of prognostic significance.[37, 68] A strong correlation between age and OS- the worse OS correlated with older age- has been reported.[76,78]

CONCLUSION

Astroblastoma is a rare tumor and hence not amenable to study in a prospective setting. In absence of clinical guidelines, patient's treatment should be customized. This review should help in clinical decision making. Maximal safe resection is the standard and

adjuvant radiotherapy is worth considering, in view of high local recurrence rate. Temozolamide may be considered in high grade Astroblastoma, proven otherwise.

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