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Original Article

Pathology Section

# Histopathological Spectrum of Central Nervous System Tumours in Adolescent and Young Adults: A Cross-sectional Study from Punjab, Northern India

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## ABSTRACT

**Introduction:** Central Nervous System (CNS) tumours are a common cause of cancer-related deaths in adolescents and young adults. The challenges in diagnosing and treating CNS tumours in this age group are unique and require special attention.

**Aim:** To study the histopathological spectrum of CNS tumours in Adolescents and Young Adults (AYA).

**Materials and Methods:** Present five-year cross-sectional study was conducted on CNS biopsies received in the Department of Pathology at Dayanand Medical College and Hospital, Ludhiana, Punjab, India, from July 1, 2016, to June 30, 2021, to analyse the histopathological spectrum of CNS tumours in the AYA group based on the site of the lesion, age, gender, and Isocitrate Dehydrogenase (IDH) status.

**Results:** During the study period, a total of 215 cases of CNS tumours were identified, of which 52 (24.2%) belonged to the AYA group. Of these, 35 (67.3%) were males and 17 (32.7%) were females. The majority of the patients presented with complaints of headache (50/52, 96.1%), with the frontal lobe being the most common site of involvement (21/52, 40.4%). Diffuse astrocytic and oligodendroglial tumours were the most commonly observed (23/52, 44.2%).

**Conclusion:** CNS tumours are one of the most common cancer diagnosis among the AYA group, and awareness should be enhanced among histopathologists and oncologists regarding these tumours based on the updated classification.


**Keywords:** Astrocytoma, Brain tumour, Glioblastoma, Intracranial space occupying lesion, Meningioma, Neoplasm

## INTRODUCTION

The AYA population has recently been recognised as an epidemiologically, biologically, and psychosocially unique group of patients [1]. CNS tumours are among the leading causes of cancer-related death in the 15- to 39-year-old age group [2]. The AYA patient population, aged between 15 and 39, faces multifactorial challenges in cancer care, attributed to unique tumour biologies in this group, limited research focus, and unmet psychosocial needs. Brain tumours encountered in AYAs generally have a slightly better prognosis than those encountered in older adults [3]. Therefore, AYAs with CNS tumours are likely to experience survivorship issues that adult neuro-oncologists may not always be experienced in handling [4]. Additionally, potential behavioural symptoms attributed to tumour location in the CNS or to medications such as steroids or antiepileptics may complicate an already emotionally tumultuous phase in the patient's life and may lead to misdiagnosis [4]. The literature focusing on AYAs with CNS malignancies is scarce in India; therefore, an attempt was made to study the histological spectrum of tumours in this epidemiologically, biologically, and psychosocially unique group [3-5].

## MATERIALS AND METHODS

The present five-year cross-sectional study was conducted at the Department of Pathology, Dayanand Medical College and Hospital, Ludhiana,Punjab, India, from July 2016 to June 2021. All intracranial space-occupying tumours were analysed with respect to the demographic profile, clinical, radiological, and histological data obtained from the institutional database. This included the age at presentation, gender, site of tumour, histological diagnosis, and WHO grade of tumour according to the WHO Classification of Tumours of the CNS 2016. Ethical clearance for the study was obtained from the ethical committee via letter number BFUHS/2K21p-TH/5036.

**Inclusion criteria:** All CNS tumours in the age group 15-39 years were included in the study.

**Exclusion criteria:** Brain tumours in patients younger than 15 years and older than 39 years were excluded from the study.

According to this classification, the presence of certain mutations such as IDH in astrocytic tumours and co-deletion of 1p-19q in oligodendroglial tumours are considered the major deciding factors for grading and prognosis. Research shows that the presence of an IDH mutation is associated with a better prognosis, with evidence of increased overall and progression-free survival. This is because the IDH mutation increases the chemotherapeutic and radiotherapy sensitivity of gliomas [5].

AYA was defined according to various published literature as 15-39 years [1-3]. The histological spectrum was studied according to the WHO 2016 classification of tumours of the CNS [5]. The 2016 WHO Classification of Tumours of the CNS includes a grading system that assigns grades to various CNS tumours based on their histological features and aggressiveness. As per WHO 2016, further attempts were made to perform immunohistochemistry to subclassify the astrocytic tumours wherever possible. Further attempts were made in immunohistochemistry using IDH-1 to subclassify the astrocytomas as IDH wild-type and IDH mutant-type tumours wherever possible.

## STATISTICAL ANALYSIS

The statistical analysis of the data involved using Statistical Package for Social Sciences (SPSS) Statistics 21.0 for Microsoft Windows (Chicago, USA). The data were described in terms of range, mean±Standard Deviation (SD), frequencies

(number of cases), and relative frequencies (percentage) as appropriate.

## RESULTS

During the study period, a total of 215 cases of CNS tumours were identified, of which 52 (24.2%) belonged to the AYA group, where males (35) outnumbered females (17) (M:F=2:1). The majority of the patients presented with complaints of headache (50/52, 96.1%), while right/left-sided weakness (18/52, 34.6%) and seizure disorder (12/52, 23.07%) were the other common presentations. The frontal lobe was the most common site of involvement (40.4%), followed by the temporal lobe (21.2%) [Table/Fig-1]. Astrocytomas were the most common histopathological diagnosis (13/52, 25%), followed by oligodendroglial tumours (10/52, 19.2%), tumours of sellar origin (8/52, 15.3%), and meningiomas (7/52, 13.4%). Metastatic tumours and tumours of haematopoietic origin were the least common, with two cases each. The age group 15-19 years had fewer cases (n=8), whereas 20-30 years (n=22) and 30-39 years (n=22) did not show any variations [Table/Fig-2,3]. Of the 52 cases, immunohistochemistry was done only in four cases in this group, as the majority of the patients moved to a higher tertiary care centre for further evaluation and treatment. In astrocytic tumours, an attempt was made to further subclassify, with one case each of Diffuse astrocytoma IDH mutant, Anaplastic astrocytoma IDH wild type, and two cases of metastasis showing CK 7 positive and CK 20 negative, and CDX 2 positive, thus indicating a primary site of pancreatobiliary origin. Histopathological features of all these lesions have been demarcated in [Table/Fig-4].

| S. no. | Site of involvement | AYA (n=52) |
|---|---|---|
| 1 | Frontal lobe | 21 |
| 2 | Parietal lobe | 5 |
| 3 | Temporal lobe | 11 |
| 4 | Occipital lobe | 1 |
| 5 | Cerebellum | 6 |
| 6 | Sellar region | 8 |

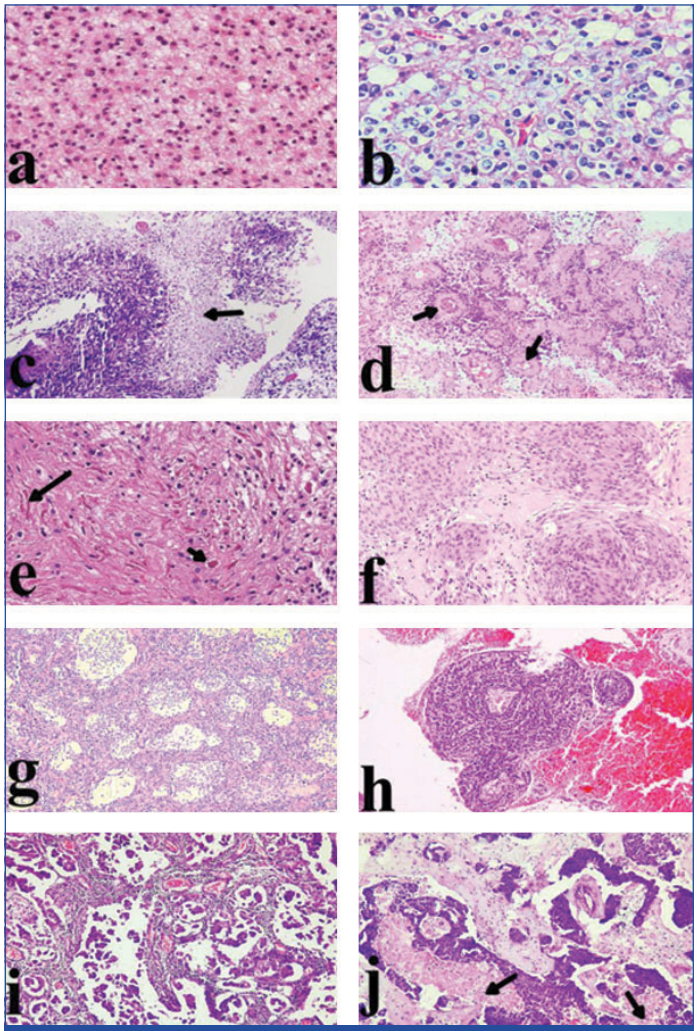
**[Table/Fig-1]:** Site wise distribution of CNS tumours in AYA group.

| Classification | Histopathological subtypes | AYA (N=52) |
|---|---|---|
| Diffuse astrocytic and oligidendroglial tumours | Diffuse astrocytoma- IDH mutant | 01 |
| | Diffuse astrocytoma NOS | 05 |
| | Anaplastic astrocytoma IDH wild type | 01 |
| | Glioblastoma NOS | 04 |
| | Oligodendroglioma NOS | 10 |
| Other astrocytic tumours | Pilocytic astrocytoma | 02 |
| Ependymal tumours | Ependymoma | 02 |
| Embryonal tumours | Medulloblastoma histologically defined | 02 |
| | CNS neuroblastoma | 01 |
| Tumours of cranial and paraspinal nerves | Schwannoma | 05 |
| Meningiomas | Transitional | 03 |
| | Meningothelial | 01 |
| | Fibrous | 01 |
| | Atypical | 01 |
| | Anaplastic (malignant) | 01 |
| Lymphomas | Diffuse large B cell lymphoma of CNS | 02 |
| Tumours of sellar region | Craniopharyngioma | 01 |
| | Pituitary adenoma | 07 |
| Metastatic tumours | Metastatic carcinomatous deposits | 02 |

**[Table/Fig-2]:** Spectrum of various CNS tumours in AYA group.

| Histopathological subtypes | | 15-19 years (n=8) | 20-30 years (n=22) | 31-39 years (n=22) |
|---|---|---|---|---|
| Astrocytic tumours | Diffuse astrocytoma IDH mutant | 00 | 00 | 01 |
| | Diffuse astrocytoma NOS | 00 | 04 | 01 |
| | Anaplastic astrocytoma IDH wild type | 00 | 00 | 01 |
| | Glioblastoma NOS | 00 | 01 | 03 |
| | Pilocytic astrocytoma | 01 | 01 | 00 |
| Oligodendroglioma | | 00 | 05 | 05 |
| Ependymoma | | 01 | 01 | - |
| Meningioma | | 00 | 04 | 03 |
| Embryonal tumours | | 01 | 01 | 01 |
| Schwannoma | | 01 | 02 | 02 |
| Others | | 04 | 03 | 05 |

**[Table/Fig-3]:** Age-wise prevalence of CNS tumours in AYA group.




**[Table/Fig-4]:** a) Diffuse astrocytoma- Tumour cells exhibits moderate nuclear pleomorphism, prominent nucleoli and moderate amount of cytoplasm (H&E 400X); b) Oligodendroglioma- Tumour cells are round having vesicular nuclei, perinuclear halo and moderate amount of cytoplasm (H&E 400X); c) Glioblastoma -Tumour showing geographic necrosis (arrow) palisaded by tumour cells (H&E 100X); d) Ependymoma- Perivascular pseudorosettes (arrow) formed by tumour cells arranged around blood vessels forming an aneucleate zone (H&E 100X); e) Pilocytic astrocytoma- Tumour cells in sheets with presence of numerous Rosthenthal fibres (long arrow) and eosinophilic granular bodies (short arrow) (H&E 400X); f) Meningothelial meningioma- Tumour cells are packed in fascicles, whorls, and syncytia having delicate chromatin and ill-defined cytoplasmic boundaries (H&E 400X); g) Desmoplastic medulloblastoma- Micrograph showing pale nodular areas surrounded by densely packed hyperchromatic cells (H&E 100X); h) Lymphoma -Expansion of blood vessel wall and dense infiltration by polymorphic cell population. (H&E 400X); i) Metastatic carcinomatous deposits from breast-Cells arranged in nests and sheets along with focal areas of necrosis (H&E 100X); j) Metastatic carcinomatous deposits from lung-Tumour cells arranged in papillae, nests and focal glands (arrows) (H&E 100X).

## DISCUSSION

AYAs have recently been recognised as an epidemiologically, biologically, and psychosocially distinct patient group. The majority

of published literature defines AYAs as patients aged 15 to 39 years. Patients in this age group develop rare CNS tumours or, in rare cases, common tumours. The current study found that low-grade astrocytomas and oligodendrogliomas were more common in the AYA group [6-8].

Over the last two decades, brain tumour research has clearly demonstrated that molecular assessment, rather than traditional histogenetic assessment using immunohistochemistry and electron microscopy, is more effective in characterising a tumour entity and evaluating the biological behaviour of brain tumours, particularly neuroepithelial tumours [5]. Many of the canonical genetic alterations had been identified by the time the WHO classification was published in 2007, but the majority view at the time was that such changes could not yet be used to define neoplasms. Instead, genetic status served as supplementary information within the framework of diagnostic categories established through standard histology-based means. Additionally, the 2016 classification added reliable molecular characteristics to the diffuse glioma classification [5]. The WHO CNS 5$^{th}$ edition recently restructured diffuse gliomas into adult-type and paediatric-type diffuse gliomas, with the latter further subdivided into low-grade and high-grade gliomas [9]. Despite paediatric-type diffuse gliomas sharing overlapping histology with adult-type gliomas, the biology and genetics are unique because they are generally indolent despite "anaplastic" histological features and lack IDH mutation and 1p/19q co-deletion, the genetic hallmarks of adult-type gliomas. However, they do have characteristic genetic profiling such as MAPK-pathway alteration [9]. This distinction is critical for distinguishing between these two prognostically and biologically distinct types of tumours, allowing for better care for both children and adults with CNS tumours. The age of the patient has no bearing on the definitions of paediatric-type and adult-type. Instead, they are classified based on common molecular changes, implying that paediatric-type gliomas can occur in adults and vice versa [10,11].

The spectrum and prevalence of CNS tumours in the AYA population differ by Indian region. Kakkar N et al., reported a similar histopathological spectrum in their study in North India, with astrocytoma being the most common (60/114), followed by oligodendrogliomas (21/114). In contrast to Kakkar N et al., present study found a higher prevalence of haematopoietic tumours and metastatic tumours, but no haemangiopericytoma or germinoma [12]. Singh R et al., reported a predominance of astrocytic tumours (11/22, 50%) in their study, but the prevalence of CNS tumours in AYA was 7.6% (22/287) [13]. In their study focusing on the AYA group, Kalyani R et al., found that the most common sites of malignancy in males were cancer of the mouth, stomach, testis, bone, and penis, and in females were cancer of the mouth, cervix uterus, breast, thyroid, and stomach [14]. AlMuhaisen GH et al., in their analysis of AYA CNS tumours, showed that gliomas comprised the most common histologic subtype (58.9%, n=218), followed by, in descending order, embryonal tumours (16.8%, n=62), ependymal tumours (7.8%, n=29), glioneuronal tumours (6.5%, n=24), and meningiomas (3.2%, n=12). The remaining 25% constituted a heterogeneous group composed of lymphomas, germ cell tumours, and vascular tumours, among others [15].

CNS tumours in AYAs are generally diagnosed late due to behavioural or psychiatric symptoms (frontal lobe syndrome). Other common symptoms include headaches, epileptic seizures, focal deficits, gait disturbances, and neurocognitive changes, in addition to behavioural changes [5,14]. Even after diagnosis, AYAs with CNS tumours present with unique endocrine and developmental issues, with therapeutic and survivor implications. Though data on the treatment of AYA patients with CNS tumours is limited at the institute, the standard protocol includes surgery as the mainstay of treatment. For high-grade tumours, postsurgery radiotherapy with concurrent Temozolomide is used [16].

Furthermore, the lack of dedicated teams and units results in dispersed treatment and a scarcity of clinical trials specifically targeting the AYA group. Understanding the unique needs of people who have a brain tumour during a developmentally sensitive period and are likely to live long enough to experience its aftereffects is a critical component of managing brain tumours in AYAs [8,12,13]. AYAs are distinguished from older people with brain malignancies by these two features [15,17]. The patients are approached as either children or adults, which generates the biggest challenges with this age group [18-20]. Multidisciplinary teams treating AYAs with brain tumours should include adult and paediatric neuro-oncologists as well as endocrinologists [19,20]. AYAs find the Cushingoid phenotype especially distressing, but steroid use also causes osteopenia and Addisonian symptoms upon withdrawal [9,13,15]. Chemotherapy might cause infertility; as a result, preparations, including sperm banking and ovarian protection, are necessary [13,15].

### Limitation(s)

The present study was limited by its small sample size and single-institute data.

## CONCLUSION(S)

Brain tumours are common in AYAs, and the majority of these tumours are uncommon disease entities. Molecular profiling of all AYA brain tumours should be performed, not only for the purpose of diagnosis but also to explore the biology of the tumour. More research in a larger cohort, along with treatment and follow-up data, is warranted to assess the outcomes.

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