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Clinicopathological Spectrum of Ependymal Tumours with Relevant Immunohistochemistry as per CNS WHO 5

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Abstract

Background: Ependymal tumours are a heterogeneous group of CNS neoplasms accounting 3-5% of all CNS tumors and 6-12% of pediatric brain tumors. The WHO CNS 5th Edition (2021) has redefined their classification by incorporating molecular markers alongside histology, enabling integrated diagnosis with improved prognostic stratification.

Aim: To study the spectrum of ependymal tumours with their relevance to immunohistochemistry as per CNS WHO 5.

Materials and Methods: Hospital-based observational study including 41 cases with histopathological features suggestive of ependymal tumours were studied. Specimens fixed in 10% NBF, processed, H&E evaluated. IHC performed using H3K27Me3, H3K27M, RELA, L1CAM, YAP1, MIB-1 for integrated molecular diagnosis as per WHO CNS 5.

Results: Of 41 cases, 32 (78.04%) confirmed ependymal, 08 (19.51%) reclassified non-ependymal on IHC. M:F = 2.15:1. Bimodal age distribution (peaks 0–10 and 41–50 years). Spinal most common (46.34%). PF tumours predominantly paediatric (85.71%), spinal predominantly adult (83.33%). Spinal NOS most common subtype (39.02%), PFB 14.63%, ST-ZFTA 4.88%. No PFA identified.

Conclusion: IHC-based molecular subtyping as per WHO CNS 5 is essential for accurate ependymal tumour classification and directly guides the selection of targeted treatments and predicts patient survival. IHC resolved differential diagnoses in 19.51% of cases.

Keywords: Ependymoma; CNS WHO 5; Immunohistochemistry; H3K27Me3; RELA; ZFTA fusion; Posterior fossa; Molecular classification

Introduction

Ependymal tumours are a heterogeneous group of central nervous system (CNS) neoplasms arising from ependymal cells lining the ventricles and central canal of the spinal cord.[1,2] They account for approximately 3–5% of all CNS tumours and 6–12% of paediatric brain tumours.[3,4] They exhibit marked clinical heterogeneity with respect to age, anatomical location, histological grade, and biological behaviour.[5]

The WHO CNS 5th Edition (2021) has fundamentally redefined ependymal tumour classification by incorporating molecular features alongside traditional histopathological parameters.[6,7] Ependymomas are now classified based on anatomical location and molecular subtype. Supratentorial ependymomas are subtyped by ZFTA and YAP1 fusion status. Posterior fossa ependymomas are classified into PFA (H3K27Me3 loss) and PFB (H3K27Me3 retained).

Spinal ependymomas include conventional, myxopapillary, and MYCN-amplified subtypes.[7,8]

Immunohistochemistry (IHC) serves as a practical surrogate for molecular testing in resource-limited settings. Markers such as H3K27Me3 for posterior fossa subtyping, RELA/L1CAM for supratentorial ZFTA fusion detection, for spinal, MYCN is available only on genetic testing, no IHC is available and MIB-1 for proliferative index enable integrated diagnosis.[9,10] In the present study, 41 cases were evaluated using relevant IHC markers to achieve integrated molecular classification as per CNS WHO 5.

Aim

To study the spectrum of ependymal tumours with their relevance to immunohistochemistry as per CNS WHO 5.

Materials And Methods

Relevant clinical and radiological data was taken. A total of 41 cases with histopathological features suggestive of ependymal tumours were studied. All neuropathology specimens were fixed in 10% neutral buffered formalin and processed as per standard guidelines. H&E stained sections were evaluated. IHC was performed according to diagnostic need using: H3K27Me3, H3K27M, RELA, L1CAM, YAP1, MIB-1 labelling index, Olig-2, NF, and LIN-28. Integrated diagnosis was given as per WHO CNS 5th Edition. Of 41 cases, 32 (78.04%) were confirmed ependymal and 08 (19.51%) were reclassified as non-ependymal on IHC.

Results

A total of 41 cases were studied. Male predominance (28/41, 68.29%; M:F = 2.15:1). Bimodal age distribution with peaks at 0–10 years (26.83%) and 41–50 years (21.95%). Mean age 29.73 years, range 1–70 years.

Spinal location was the most common (46.34%), followed by supratentorial (38.02%) and posterior fossa (15.63%).

In paediatric population, posterior fossa (85.71%) was the most common location. In adult, spinal (83.33%) was the most common location. Mean age group: Spinal 38.21±16.43; Posterior fossa 08.24±06.96; Supratentorial 18.33±13.32 yrs.

Also, in pediatric age group, 6–12 years had the maximum number of cases (53.8%). M:F was 1.6:1.

Out of 41 histopathologically confirmed ependymal cases, 32 (78.04%) were diagnosed as ependymoma and 8 (19.51%) as non ependymal on IHC.

Of 07 supratentorial cases, 03 were identified as ZFTA- fusion positive (age 7-41 years), with no YAP1 fusions identified. The remaining 04 cases (57.1%) were negative for RELA and YAP1, thus classified as NOS and advised genetic testing.

06 out of 07 posterior fossa ependymomas were classified as Posterior Fossa B (PFB) with retained H3K27me3, while no Posterior Fossa A (PFA) cases were identified. One case showed negativity for both H3K27me3 and H3K27M and was placed under 'not otherwise specified' (NOS) and was advised genetic testing.

Spinal tumors were the most common location (18/41, 43.90%). Due to the lack of MYCN testing at our centre, 16 cases were classified as spinal ependymoma NOS and 02 as myxopapillary ependymoma.

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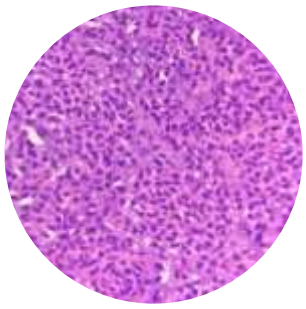
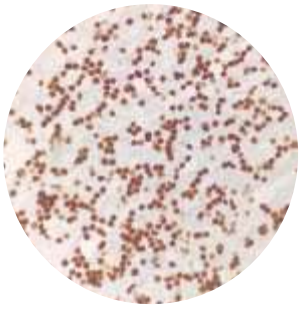
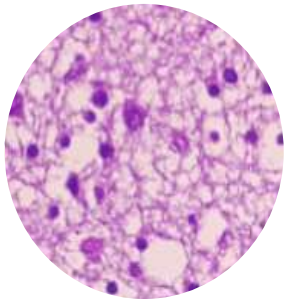


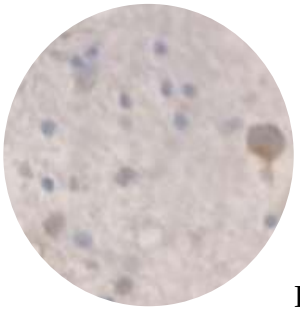
(A) Posterior fossa B ependymoma- CNS WHO Grade 3 (40x)



(B) Posterior fossa B ependymoma - H3K27Me3 retained (40x)



(C) Supratentorial ependymoma- CNS WHO Grade 02 (40x)



D) Supratentorial ependymoma- RELA fusion positive (40x)

Discussion

The present study analysed 41 cases with histopathological features suggestive of ependymal tumours. Using IHC markers as per WHO CNS 5th Edition, 32 cases (78.04%) were confirmed as ependymal tumours and 08 cases (19.51%) were reclassified as non-ependymal.

Gender Distribution

In our study, males predominated with M:F ratio of 2.15:1 (68.29% males). McGuire et al.11 (SEER data, M:F 1.3–1.4:1) and Villano et al.4 (US epidemiology, M:F 1.6:1) reported concordant male predominance. However, Chavali et al.15 from NIMHANS reported slight female predominance (M:F 1:1.16) in supratentorial ependymomas, not in concordance with our study.

Age Distribution

Our study showed bimodal age distribution with peaks in 0–10 years (26.83%) and 41–50 years (21.95%), with mean age 29.73 years. Villano et al.4 (18% in 0–10 yrs, 13% in 41–50 yrs) and Karsonovich et al.16 (CBTRUS/SEER data, bimodal peaks at 0–4 yrs and 40–60 yrs, ~40% paediatric) reported concordant bimodal distribution. However, Elsamadicy et al.3 demonstrated approximately 7-fold higher incidence in adults compared to the paediatric population, discordant with our relatively higher paediatric proportion of 26.83%.

Anatomical Location

Spinal location predominated in our study (19/41, 46.34%), followed by supratentorial (14/41, 38.02%) and posterior fossa (08/41, 15.63%). Ostrom et al.17 (CBTRUS data, spinal 50–60%) and Lim et al.18 (141 cases, spinal 47%) reported concordant spinal predominance. However, Pajtler et al.5 in their landmark molecular classification study reported posterior fossa as the most common location (45–50%), discordant with our spinal predominance, likely reflecting different referral patterns.

Location-Age Correlation

Ependymoma in posterior fossa was found mostly in paediatric population (06/07, 85.71%) and spinal

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showed adult predominance (15/18, 83.33%) in our study. McGuire et al.11 (PF 70–80% paediatric, spinal 75–85% adult) and Ritzmann et al.19 (PF 75–80% paediatric, spinal 80–85% adult) reported closely concordant findings.

Paediatric Distribution

Among 13 paediatric cases, M:F was 1.6:1, the 6–12 year group was most common (53.8%), and posterior fossa was the predominant location (06/13, 46%). Jünger et al.2 (60–70% PF, 30% ST, <10% spinal) and Merchant et al.22 (CBTRUS: 54.4% PF, 32.5% ST, 13.1% spinal) reported concordant posterior fossa predominance.

Integrated Molecular Diagnosis

Spinal ependymoma NOS was the most common subtype (16/41, 39.02%). Among posterior fossa cases, all 06 confirmed cases were PFB (H3K27Me3 retained, 14.63%), with no PFA identified. One case was classified as PF-NOS (02.44%). Among supratentorial cases, 03 (4.88%) showed ZFTA fusion positivity. Chinnam et al.12 at PGIMER (200 cases) reported concordant spinal NOS predominance (20%) but found PFA as the most common posterior fossa subtype (30%), discordant with our exclusive PFB finding. Pajtler et al.5 (500 cases) similarly reported PFA predominance in posterior fossa, discordant with our study. The absence of PFA is attributable to the limited number of patients under 6 years of age, which is the primary age group where PFA tumors are most prevalent. Importantly, 08 cases (19.51%) were reclassified as non-ependymal on IHC, underscoring the indispensable role of immunohistochemistry in resolving histological mimics.

Supratentorial Subtype

In this study, 03 of 07 supratentorial cases were ZFTA-fusion positive (age 7-41 years), with no YAP1 fusions identified. The remaining 04 cases (57.1%) were negative for RELA and YAP1, thus classified as NOS and advised genetic testing. Consistent with CNS WHO 5, ZFTA fusions represent the majority of supratentorial subtypes in our study. Compared to Pajtler et al. (2022)5 and Jungler et al. (2021)2, who reported 65-75% ZFTA predominance, our data also showed ZFTA cases (42.8%) were more common than YAP1. Our higher proportion of NOS cases (57.1%) likely reflects the limitations of IHC in detecting variant fusions, which may require molecular techniques for identification.

Posterior Fossa Subtype

In the present study, 06 out of 07 posterior fossa ependymomas were classified as Posterior Fossa B (PFB) with retained H3K27me3, while no Posterior Fossa A (PFA) cases were identified. One case showed negativity for both H3K27me3 and H3K27M and was placed under 'not otherwise specified' (NOS) and was advised genetic testing. Our study included 3 cases <5 years, 3 cases between 5 to 18 years, and 1 case >18 years. As stated in literature, Posterior fossa A tumor though are more common but occurs >95% in <6yrs. PFB frequency is closely related to age, being most common in adults (90%) and rare in infants (<5%).

In comparison, Panwalkar et al. (2017) and Bouffet et al. (2019) reported a higher prevalence of PFA (89% in the latter) in pediatric groups with lower median ages. These studies were not concordant with our findings, likely due to the limitation of our sample size. However, the predominance of PFB in our cases aligns with the literature's age-related frequency for this molecular subgroup.

Spinal Subtype

In the present study, spinal tumors were the most common location (18/41, 43.90%). Due to the lack of MYCN testing at our centre, 16 cases were classified as spinal ependymoma NOS and 02 as myxopapillary ependymoma. The majority were adults (mean age 38.17 ± 16.02 years) with a M:F ratio of 2.00:1, which is in concordance with WHO CNS 5 literature.

Our findings also align with Elsamadicy et al. (2020), who reported a higher percentage of spinal cases in adults (88.9% in our study). Similarly, Pajtler et al. (2023) studied >2000 cases and found 70-75% were spinal and 15-20% were myxopapillary, which is in concordance with our data. Overall, our results reflect the established literature regarding the adult predominance and distribution of spinal ependymal subtypes.

Conclusion

IHC-based integrated molecular classification as per WHO CNS 5 is essential for accurate diagnosis and subtyping of ependymal tumours. IHC confirmed ependymal tumours in 80.49% and reclassified 19.51% as non-ependymal. H3K27Me3,

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RELA/YAP1, H3K27M and MIB-1 are valuable IHC markers. Spinal location predominated (46.34%) with significant age-location correlation. Molecular subgrouping should be integrated into routine neuropathology reporting. IHC facilitates precise diagnosis and risk stratification of ependymal tumors by identifying molecular subtypes, which directly guides the selection of targeted treatments and predicts patient survival.

Limitations

1. MYCN testing unavailable.
2. Limited number of infants <3 years may explain absence of PFA.

Declarations

Ethics: Approved by ethical committee, MGUMST, Jaipur.

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Table 1: Distribution According to Anatomical Location (n=41)

Location	Total Cases	Percentage (%)
Supratentorial	14	38.02
Posterior Fossa	08	15.63
Spinal	19	46.34
Total	41	100.00

Table 2: Distribution According to Location and Age Group (n=32 Ependymal)

Location	Paediatric (≤18)	Adult (>18)	Total
Spinal	03 (16.67%)	15 (83.33%)	18
Posterior Fossa	06 (85.71%)	01 (14.28%)	07
Supratentorial	04 (57.14%)	03 (42.85%)	07
Total	13 (40.62%)	20 (59.37%)	32

Table 3: Paediatric Ependymal Tumour Distribution (n=13)

Age Group	Male	Female	Total	Location	Subtotal
0–1 month	0	0	0	—	0
1 mon–1 yr	01	0	01	PF	1 (7.6%)
1–3 yr	01	0	01	PF	1 (7.6%)
3–5 yr	0	01	01	PF	1 (7.6%)
6–12 yr	04	03	07	PF, ST, Sp	7 (53.8%)
13–18 yr	02	01	03	PF, Sp	3 (23.0%)
Sub Total	08	05	13	PF 6; ST 4; Sp 3	13 (100%)

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Table 4: Integrated Molecular Diagnosis (WHO 2021) (n=41)

Location	WHO 2021 Subtype	Cases	%
PF Ependymoma	PFA (H3K27Me3 Loss)	0	00.00
	PFB (H3K27Me3 Retained)	06	14.63
	PF—NOS	01	02.44
ST Ependymoma	ST–ZFTA (RELA)	03	04.88
	ST–YAP1 Fusion	00	00.00
	ST–NOS	04	09.76
Spinal Ependymoma	Myxopapillary	02	04.88
	MYCN	0	Not done
	Spinal NOS	16	39.02
Subependymoma	Grade 1	01	02.44
Non-Ependymal	Glioma/SFT/Medulloblastoma	08	17.07
Total		41	100.00

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