

# Primary central nervous system lymphomas: Indian experience, and review of literature

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## Abstract

Primary central nervous system lymphomas (PCNSLs) are a rare form of non-Hodgkin's lymphoma which arise within and remain confined primarily to the central nervous system (CNS). They generally account for 1-2% of all primary brain tumors and are reported to be on the rise due to the Acquired Immune Deficiency Syndrome (AIDS) epidemic. **AIMS AND OBJECTIVES:** To study the clinicopathological and immunophenotypic characteristics of PCNSLs and look for any differences in PCNSLs reported in India from those in other countries. **MATERIALS AND METHODS:** All cases of PCNSLs between January 1998 and December 2006 were reviewed. Presence of lymphadenopathy, organomegaly and bone marrow study was done to exclude the possibility of secondary involvement by lymphoma. The diagnosis was confirmed by histopathology with Hematoxylin and Eosin and reticulin stains. Immunohistochemistry (IHC) with leucocyte common antigen (LCA), CD 20 and CD 3 was performed on available blocks. The immune status was evaluated by clinical examination and human immunodeficiency virus (HIV) serology (since 1996). **RESULTS:** In a 19-year study period, there were 56 patients of PCNSLs, accounting for 1.07% of all intracranial neoplasms. The patients ranged from 10-75 years of age with a median age of 42 years. Barring one patient who was HIV positive, all the others were immunocompetent. All cases were diffuse large cell lymphomas on histopathology. IHC with LCA and CD 20 revealed positivity in 100% and 86.4% cases respectively. There was a single case of CD 3 positive T-cell lymphoma. In the present study, PCNSLs occurred in young immunocompetent patients and majority were diffuse large B cell lymphomas.

**Key words:** Diffuse lymphoma, immunohistochemistry, PCNSLs

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## Introduction

Primary central nervous system lymphomas (PCNSLs) are a rare form of extranodal non-Hodgkin's lymphoma, that typically remain confined primarily to the central nervous system and involve the brain, leptomeninges, spinal cord or eye.<sup>[1]</sup> Historically, the first reported PCNSL was by Bailey in 1929,<sup>[2]</sup> when he used the term 'perithelial sarcoma'. Other terms that have been used are perivascular sarcoma, adventitial sarcoma, malignant reticuloendotheliosis, reticulum cell sarcoma, microglioma. It was much later that PCNSLs were recognized as neoplasia distinct from glial tumors by immunophenotyping and the lymphoid nature of the lesion was established.

Reports from the west<sup>[3]</sup> indicated that there was a three-fold increase in incidence of PCNSLs between 1973 and 1984. The Human Immunodeficiency Virus (HIV) was the main factor responsible for the rise. However, there was also a rise of PCNSLs in the immunocompetent. This increasing incidence could have been due to improved investigative modalities (stereotactic brain biopsies of deep-seated lesions), greater clinical and neuropathological awareness, widespread availability of immunohistochemistry and increase in the number of immunosuppressed patients, who have an increased risk of developing PCNSLs. Later reports<sup>[4]</sup> suggested that the annual incidence of PCNSL appeared to be stabilizing or in fact declining slightly. Studies published from India<sup>[5,6]</sup> indicate that there has been no increase in the incidence of PCNSL

and that they tend to occur a decade earlier than the west.

The purpose of this study was to determine the clinico-pathological profile of patients diagnosed with PCNSLs at a tertiary care centre, to determine the hospital-based incidence and look for any differences in PCNSLs occurring in India from those in other countries.

## Materials and Methods

All cases of histologically proven PCNSLs, diagnosed at a tertiary care center from January 1988 to December 2006, were included in the study. The complete clinical and imageologic details were obtained from the patient records. Details about lymphadenopathy, organomegaly and bone marrow study were obtained to exclude the possibility of secondary involvement by a systemic lymphoma. The histopathology of each case was reviewed with Hematoxylin and Eosin and reticulin stain. Immunohistochemistry (IHC) with leucocyte common antigen (LCA), CD 20 (B cell marker), and CD 3 (T cell marker) was performed on available formalin-fixed, paraffin embedded blocks using the standard Avidin-Biotin Complex technique. The antibodies used were monoclonal mouse Anti Human leucocyte common antibody CD 45, monoclonal mouse Anti Human CD 20 cy and polyclonal rabbit Anti Human CD 3. These were supplied by DAKO / Dakocytomation company (the suppliers being J. Mitra and sons, Chennai, Tamil Nadu, India; imported from Denmark.) The immune status was evaluated by clinical examination and HIV serology reports were available in all patients after 1996.

## Results

### Incidence

During the study period, there were 5208 intracranial neoplasms, of which 56 were PCNSLs, giving a percentage of 1.07%. Table 1 shows the year-wise distribution of cases along with the incidence and confidence limits. There has been a fairly constant incidence of PCNSLs from 1988 to 2006.

### Clinical features

The age of the patients ranged from 11 to 75 years of age with a median age of 42 years and a male to female ratio of 1.5: 1. Of the 56 patients, only one was HIV positive and the rest were immunocompetent. The age /gender distribution is depicted in Table 2. The clinical features with which the patients presented with are shown in Table 3.

The most common presenting symptom was headache.

The site of involvement is shown in Table 4.

Majority of the lesions occurred in the supratentorial

**Table 1: Year-wise distribution of CNS tumors**

Year	CNS tumors	PCNSLs	Percentage	95% confidence limits*
1988	122	2	1.6	0.002 to 0.058
1989	148	1	0.6	0.000 to 0.037
1990	191	1	0.5	0.000 to 0.028
1991	274	1	0.3	0.000 to 0.020
1992	289	2	0.7	0.000 to 0.024
1993	230	Nil	0.0	0.000 to 0.016
1994	284	Nil	0.0	0.000 to 0.013
1995	121	Nil	0.0	0.000 to 0.030
1996	301	1	0.3	0.000 to 0.018
1997	283	2	0.7	0.000 to 0.025
1998	205	3	1.4	0.000 to 0.042
1999	398	8	2.0	0.008 to 0.039
2000	274	Nil	0.0	0.000 to 0.013
2001	197	2	1.0	0.001 to 0.036
2002	302	4	1.3	0.003 to 0.033
2003	230	6	2.5	0.009 to 0.055
2004	455	6	1.3	0.004 to 0.013
2005	423	9	2.1	0.009 to 0.040
2006	473	8	1.6	0.007 to 0.033
Total	5208	56	1.07	0.008 to 0.014

\*Lower and upper range of 95% confidence limits calculated by exact (Binomial) method, CNS: Central nervous system, PCNSLs: Primary central nervous system lymphomas

**Table 2: Age/gender distribution of patients with PCNSLs (n = 56)**

Age range in years	Male	Female
0 - 9	Nil	Nil
10 - 19	6	1
20 - 29	4	2
30 - 39	7	3
40 - 49	7	9
50 - 59	5	4
60 - 69	3	2
70 - 79	2	1

One patient was HIV positive, the rest were immunocompetent, PCNSLs: Primary central nervous system lymphomas

**Table 3: Clinical presentation of patients with PCNSLs (n = 56)**

Clinical features	Number of cases
Headache	40
Weakness/paresis	24
Vomiting	27
Seizures	11
Upper motor neuron palsy	7
Behavioral changes	7
Altered sensorium	5
Diminished vision	4
Gait disturbances	6
Speech defects	2
Deafness	2
Loss of smell	1
Loss of taste	1

PCNSLs: Primary central nervous system lymphomas

region, with multiple lesions being common and frontal lobe being most frequently involved.

Imageologic details were available in 36 of 50 patients. In 20 of these patients, CT scans were available and in another 16 cases, MRI scans were also available. The CT scans showed isodense to hyperdense lesions in majority of the patients and four patients had hypodense lesions. The MRIs revealed lesions which were hypointense on T<sub>1</sub> and hyperintense on T<sub>2</sub> with three patients having ring-enhancing lesions.

All the patients were assessed for evidence of a systemic lymphoma and the search did not yield a primary. Most of the patients had a bone marrow evaluation as part of a staging work-up, but these were normal.

After diagnosis, most of the patients were referred for chemotherapy and/or radiotherapy. They were subsequently lost to follow-up.

### Pathology

Gross pathology: Most of the biopsy specimens were resected biopsy specimens, consisting of multiple grey-white, or grey-tan soft tissue bits, with few showing hemorrhagic and necrotic areas. A few cases had stereotactic biopsies.

### Histopathology

All the cases showed a non-Hodgkin's lymphoma arranged in a diffuse pattern. Of these, 55 cases were reported as diffuse large cell lymphoma [Figure 1] and

**Table 4: Sites of involvement by PCNSLs (n = 56)**

Site	Number of cases
Multiple	12
Frontal	18
Parietal	16
Temporal	8
Thalamus	8
Corpus callosum	4
Occipital	2
Cerebellum	2
Periventricular	2
Capsulo ganglionic segment	2
Cerebello pontine angle	1
Meningeal	1
Third ventricle	1

PCNSLs: Primary central nervous system lymphomas

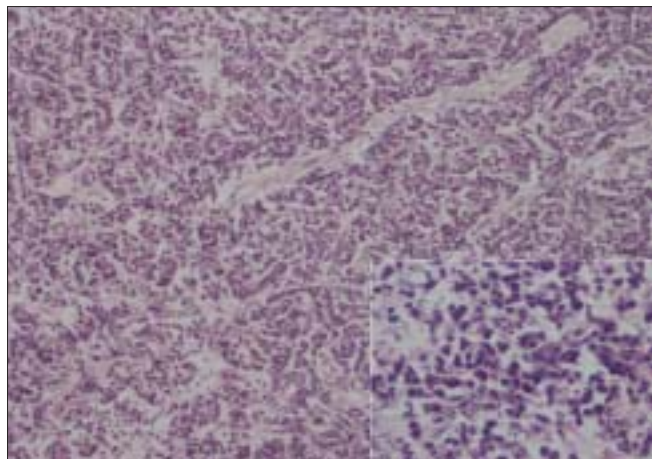
**Table 5: Immunohistochemistry results**

Immunohistochemistry marker	Result
Lymphoma panel	-
Leucocyte common antigen (LCA)	Done in 56 cases
Strongly positive	54/56 cases (96%)
Weakly positive	2/56cases (4%)
CD 20 (B - cell marker)	Done in 37 cases
Strongly positive	27/37 cases (72.9%)
Weakly positive	5/37 cases (13.5%)
Negative	5/37 cases (13.5%)
CD 3 (T - cell marker)	Done in 18 cases
Positive	1/18 cases
Negative	14/18 cases
Reactive T - cell + ve	3/18 cases

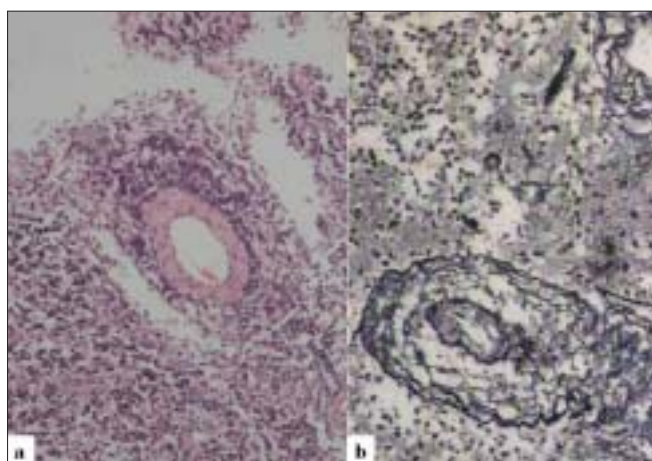
one as lymphoblastic lymphoma. Angiocentric pattern was noted in 48 cases [Figure 2]. Splaying of reticulin fibres around blood vessels was seen in 28 cases. Necrosis, reactive gliosis and brain infiltration was seen in 17, 16 and 13 cases respectively. The lesion was admixed with inflammatory cells and histiocytes in five cases. There were two cases of recurrent PCNSLs, which showed post-therapy changes in the form of stromal collagenization and calcification.

### Immunohistochemistry

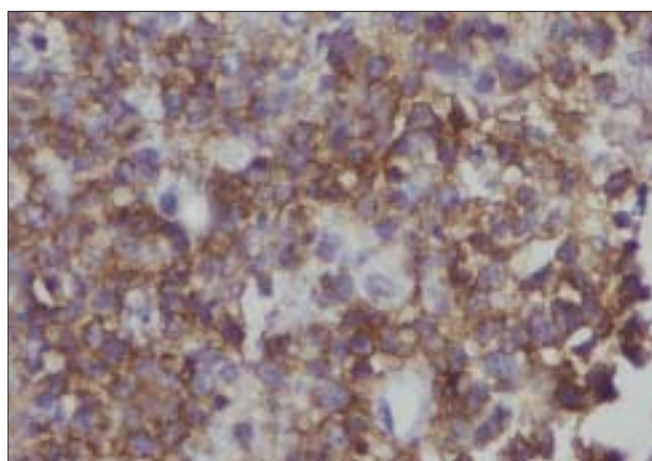
The immunohistochemical results are depicted in Table 5.



**Figure 1:** Non-Hodgkin's lymphoma showing monotonous population of lymphoid cells in diffuse sheets. H&E x100. Inset higher magnification of the same. H&E x200



**Figure 2:** a) Angiocentric pattern of the lymphoid cells. H&E x100. b) Splaying of the reticulin network around the vessel. Reticulin x100



**Figure 3:** CD 20 showing characteristic membrane positivity in the lymphoid cells. Strept ABC x200

IHC was performed, whenever the blocks were available. The panel used when lymphomas were suspected were

LCA, CD 3 and CD 20. Leucocyte common antigen (LCA) was strongly positive in 42 cases and weakly positive in 2 cases. The B-cell marker CD 20 was positive in 86% cases [Figure 3]. Due to non-availability of the markers, further typing with CD 79a or PAX 5 for B-cell origin was not done. Three cases of B-cell lymphoma showed reactive T- lymphocytes and one case was diagnosed as a T- cell lymphoma. This patient was a female, immunocompetent with a single lesion in the cerebellum.

IHC was performed with other markers when there was a differential diagnosis of lesions like metastasis, small cell glioblastoma and other round cell tumors. The other markers done which were negative, were epithelial membrane antigen (EMA)-3 cases, glial fibrillary acidic protein (GFAP) – 8 cases, and one case each of cytokeratin (CK), neuron specific enolase (NSE) and CD 99.

### Discussion

The results of our findings were compared to other studies - western, Indian and from the far east and are shown in Table 6.

The incidence of PCNSLs in India seems to be fairly constant through the years, as seen in previous series<sup>[5,6]</sup> as well as in the present study. In literature, the incidence varies in different time periods. One publication from Pakistan,<sup>[10]</sup> which included both cranial and spinal lymphomas, reported that lymphomas accounted for 4.6% of intra-cranial and spinal neoplasia. There have been two large case-studies from Japan<sup>[11,12]</sup> which reported that PCNSLs accounted for 2.4% of all intracranial neoplasms in Japan.

The male to female ratio is 1.5:1 in the present series, which is similar to most published series in immunocompetent patients. In patients with AIDS, the disease is much more common in males.

In the previous studies from India,<sup>[5,6]</sup> majority of the PCNSLs have been reported in the immunocompetent. The present study has only one patient who was HIV positive (35 year old male). Sarkar *et al.*<sup>[5]</sup> had one HIV positive patient and one patient of renal allograft. Powari *et al.*<sup>[6]</sup> had two patients with renal allografts. In spite of an increasing number of HIV positive patients in India, the incidence of PCNSLs in these patients is low. A possible explanation for this could be that AIDS patients die earlier in India due to opportunistic infections.<sup>[5]</sup> Though other lymphomas, including those at extranodal sites seem to occur in India in patients with AIDS, PCNSLs are still infrequently reported.



**Table 6: Comparison between present study and previous studies on PCNSLs**

Study, year, reference, number of cases (n)	Percentage of IC SOLs	M:F	Immunocompetent	AIDS	Median age (in years) Immunocompetent	Immunosuppressed	Site and number of lesions	Histology, IHC profile
Fine et al, 1993 <sup>[7]</sup> n=1107	NA	1.3:1	NA	7.3:1	55.2	30.8	60% periventricular	Majority B cell
Miller et al, 1994 <sup>[9]</sup> n=104	6.6	NA	NA	NA	NA	NA	NA	Diffuse-100%, Majority B-cell, one T-cell
Hayabuchi et al, 1999 <sup>[11]</sup> n=466	2.4	1.45:1	NA	Nil	NA	Nil	NA	91% B-cell 8.5% T-cell
Muzaffar et al, 2000 <sup>[10]</sup> n=43	4.6	1:2	50	Nil	50	Nil	Cranial+spinal	Diffuse-100% 83% B-cell
Powari et al, 2002 <sup>[6]</sup> n=40	1.2	2:1	24-75 yrs	Nil	24-75 yrs	Two renal allografts	Parietal	Three cases T-cell 90.3% B-cell
Sarkar et al, 2005 <sup>[5]</sup> n=186	AIIMS - (n=116)	2.3:1	AIIMS- 44.4 yrs	One HIV	AIIMS- 44.4 yrs	One renal allograft,	Frontal	99% B-cell One case-T-cell
	0.95					One HIV		
	NIMHANS - (n=70)							
	0.92					39.5 yrs		
Fitzimmons et al, 2005 <sup>[8]</sup> n=NA	NA	1.2-1.7:1	53-57	7:1	53-57	31-35	60%	Majority B cell
Rubinstein et al, 2005 <sup>[16]</sup>	NA	2:1	56	NA	56	38	Periventricular	95% HG-DLBCL
Batchelor et al, 2006 <sup>[1]</sup>	2.7	1.2:1	53-57	NA	53-57	NA	Solitary-65%, Multiple-35%	90% DLBCL; 10%-LG-NHL or
n=NA							Hemisphere-38%	Burkitt's or Tcell
Present study, n=56	1.07	1.5:1	42	One HIV	42	One HIV	Frontal	86% B cell One case - T cell

NA: Details not available, IC SOL: Intracranial space occupying lesions, AIDS: Acquired immune deficiency syndrome, HIV: Human immunodeficiency virus, DLBCL: Diffuse large B cell Lymphoma, LGNHL: Low grade non Hodgkin's Lymphoma, AIIMS: All India Institute of Medical Sciences, NIMHANS: National Institute of Mental Health and Neurosciences, PCNSLs: Primary central nervous system lymphomas

The median age of presentation is 42 years in immunocompetent, which is similar to those observed from India like – AIIMS (44.4 years) and NIMHANS (39.5 years). This is a whole decade earlier than those reported in the west. This has been attributed to the demographic pattern of the Indian population.<sup>[5]</sup> The authors have also observed that other hematologic malignancies like multiple myeloma and chronic myeloid leukemia also present a decade or two earlier in India than in the west.

The most common presenting symptom was headache occurring in 57% patients. Seizures at presentation were seen in only 20% patients. This has been attributed to the fact that PCNSLs less often involve excitable cerebral cortex than other tumors do.<sup>[14]</sup>

In this study, majority of the lesions were in the supratentorial region with the frontal lobe being most commonly involved. This is similar to other studies.<sup>[5,13]</sup>

Of the 56 PCNSLs, 55 were diffuse large cell lymphomas and one was reported as lymphoblastic. Virtually all PCNSLs show a diffuse growth pattern. A follicular growth pattern has not been described in intraparenchymal lesions. There have been occasional case reports of follicular lymphomas of the dura.<sup>[15,16]</sup> These lesions have a less aggressive behavior and survive longer than the usual intraparenchymal PCNSLs.

Of the cases where immunohistochemistry was performed, 86% were classified as B-cell lymphomas. This is similar to reports,<sup>[11]</sup> where 90% of the PCNSLs are diffuse large B-cell lymphomas. There was one case of T-cell lymphoma, which occurred in a 51-year-old female in the cerebellum. As per literature,<sup>[17]</sup> T-cell lymphomas constitute only 2% of all PCNSLs, occur mainly in the immunocompetent, have a higher male to female ratio, are more frequent in the posterior fossa, mainly cerebellum, with a propensity to arise in the meninges. Studies from the east<sup>[11,18]</sup> indicate that the incidence of T-cell lymphomas were high in Japan (8.5%) as well as Korea (16.7%). T-cell lymphomas have to be differentiated from T-cell rich B-cell lymphomas. There were three cases of B-cell lymphomas which had reactive T lymphocytes, admixed with the tumor cells.

Majority of the patients were further evaluated for lymphadenopathy, organomegaly, and had a bone marrow evaluation to rule out secondary involvement by a systemic lymphoma. None of the patients had marrow involvement at diagnosis. Following the diagnosis of PCNSL, the extent of staging required to evaluate for a systemic lymphoma is controversial.<sup>[1,8,19]</sup> There are

those who advocate that it is sufficient to perform a thorough clinical examination, complete blood counts, routine biochemical tests, serum LDH levels and chest radiographs; but there are others who recommend that the patients have contrast-enhanced CT scans of the chest, abdomen, pelvis as well as a bone marrow biopsy, given that 3.9-12.5% of patients with PCNSLs are found to have occult extra neural disease on additional evaluation.

Regarding prognosis,<sup>[20]</sup> it is suggested that an age more than 60 years, performance status more than one, elevated LDH levels, high CSF proteins and involvement of deeper regions of the brain (periventricular, basal ganglia, brain stem and cerebellum) were significantly and independently associated with a worse survival.

The exact pathogenesis of PCNSLs in the immunocompetent is still not clear. Various theories of origin have been put forward.<sup>[7,17]</sup>

- 1) A polyclonal intracerebral inflammatory lesion may expand clonally in the brain and progress to a monoclonal neoplastic state. However, infection or inflammatory diseases have only exceptionally been described to antedate the development of PCNSL.
- 2) Lymphoma cells may be systematically eradicated by an intact immune system, but may be protected in an immunologically protected site like the brain. However, there is no evidence of concomitant lymphoma at other immunologically privileged sites like the testis.
- 3) B-cells may be transformed at a site elsewhere in the body and then develop adhesion molecules specific for cerebral endothelia. However, a study by Paulus *et al.*,<sup>[21]</sup> showed that the expression pattern of a number of integrins and immunoglobulin adhesion molecules by tumor cells did not differ between cytologically similar PCNSLs and nodal lymphomas. It is possible that the responsible adhesion molecules were missed in the study or were down regulated by lymphoma cells, once they entered the brain.

Studies have shown a consistent association of tumors occurring in immunocompromised individuals with Epstein Barr virus (EBV), suggesting an important role for the virus in the pathogenesis of these tumors. An infrequent association of the virus with PCNSL in the immunocompetent has also been noted. A study from India<sup>[22]</sup> showed that immunocompetent individuals in developing countries are infrequently EBV associated and possibly a different pathogenetic mechanism is operational in the evolution of these tumors.

Systemic diffuse large B cell lymphomas (DLBCLs)

are known to be clinically and morphologically heterogeneous. They have recently been sub-classified as germinal centre B-cell origin (GCB) and non-germinal centre B-cell types using microarray. The germinal centre B-cell DLBCL is associated with a better prognosis compared to non-germinal centre B cell type. PCNSLs have a poorer prognosis when compared to other DLBCLs. Two studies<sup>[23,24]</sup> using an extensive immunohistochemical panel including CD 10, BCL – 6, BCL – 2, MUM 1, etc have shown that PCNSLs are more homogenous than systemic DLBCLs and predominantly express the activated B-cell line (ABC) phenotype. This activated B-cell phenotype is thought to be responsible for the biologic aggressiveness and poor prognosis of PCNSL.

### Conclusion

The present study, like other Indian studies,<sup>[5,6]</sup> concludes that there has not been an increase in PCNSLs in India. The PCNSLs tended to occur in young patients, and majority were diffuse large B cell lymphomas. Though there is an epidemic of HIV/AIDS in India, association of PCNSLs with HIV/AIDS is still low.

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Source of Support: Nil, Conflict of Interest: None declared.