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Diagnosis of primary central nervous system lymphoma: a systematic review of the utility of CSF screening and the role of early brain biopsy

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Abstract

Background. Because less-invasive techniques can obviate the need for brain biopsy in the diagnosis of primary central nervous system lymphoma (PCNSL), it is common practice to wait for a thorough initial work-up, which may delay treatment. We conducted a systematic review and reviewed our own series of patients to define the role of LP and early brain biopsy in the diagnosis of PCNSL.

Methods. Our study was divided into 2 main sections: 1) systematic review assessing the sensitivity of cerebrospinal fluid (CSF) analysis on the diagnosis of PCNSL, and 2) a retrospective, single-center patient series assessing the diagnostic accuracy and safety of early biopsy in immunocompetent PCNSL patients treated at our institution from 2012 to 2018.

Results. Our systematic review identified 1481 patients with PCNSL. A preoperative LP obviated surgery in 7.4% of cases. Brain biopsy was the preferred method of diagnosis in 95% of patients followed by CSF (3.1%). In our institutional series, brain biopsy was diagnostic in 92.3% of cases (24/26) with 2 cases that required a second procedure for diagnosis. Perioperative morbidity was noted in 7.6% of cases (n = 2) due to hemorrhages after stereotactic brain biopsy that improved at follow-up.

Conclusions. The diagnostic yield of CSF analyses for PCNSL in immunocompetent patients remains exceedingly low. Our institutional series demonstrates that early biopsy for PCNSL is safe and accurate, and may avert protracted work-ups. We conclude that performing an early brain biopsy in a suspected case of PCNSL is a valid, safe option to minimize diagnostic delay.

Keywords

brain biopsy | lumbar puncture | primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal non-Hodgkin lymphoma that can involve the brain, eyes, meninges, or spinal cord without evidence of systemic disease, accounting for approximately 3% to 4% of all CNS tumors. The annual incidence of PCNSL is around 7 cases per 1 000 000 people in the United States, with a male predominance occurring mostly in the sixth decade of life.[1,2] Epidemiological studies have demonstrated a rise in the incidence of PCNSL over the last 40 years with higher overall rates in immunocompetent patients age 65 years or older.[3,4] Initial clinical symptoms can vary depending on lesion location and size; however, most patients present with focal

deficits (70%), neuropsychiatric symptoms (43%), increased intracranial pressure (33%), or seizures (14%), rather than systemic "B" signs (fever, night sweats, and unintentional weight loss).[5–7] When suspecting PCNSL, contrast MR is the diagnostic modality of choice; PCNSL is typically iso-hypointense on T1-weighted imaging and iso-hypointense to gray matter on T2-weighted imaging, with a strong homogeneous pattern of enhancement in 85% of patients because of its hypercellularity. However, radiographic imaging patterns are suggestive but not diagnostic of PCNSL, and definitive diagnosis must be achieved by histopathological confirmation by stereotactic (SBB) or open brain biopsy. Brain biopsy (open or SBB) is the preferred surgical procedure; although a positive cerebrospinal fluid (CSF) or vitreous biopsy for lymphoma can obviate the need for a surgical procedure.[8,9]

These adjuvant studies are typically recommended in the majority of cases; however, they may not be diagnostic and may delay prompt treatment. Here, we conducted a systematic review of the literature to characterize the diagnostic sensitivity of LP for the diagnosis of PCNSL. We also supplemented this discussion with a review of our patient series that advocates for an early biopsy, prior or simultaneously to the time of the LP. Our overarching goal is to characterize and elucidate the management paradigms to define the role of early brain biopsy in the diagnosis of PCNSL.

Materials and Methods

Our study was divided into 2 main sections: 1) systematic review assessing the sensitivity of CSF analysis on the diagnosis of PCNSL, and 2) a prospective, single-center patient series assessing the diagnostic accuracy and safety of early biopsy for patients with PCNSL.

Study Selection

A systematic literature search was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines between the years 1985 and 2018 using the PubMed database for all articles containing the terms primary central nervous system lymphoma, and CSF or cerebrospinal fluid or study or trial: (((("primary"[All Fields] AND "central nervous system"[All Fields] AND "lymphoma"[MeSH Terms])) AND ((((trial) OR study) OR CSF) OR cerebrospinal fluid)).[10] The objective was to screen for articles containing series of patients with PCNSL and CSF assessment for lymphoma or leptomeningeal disease (LD), at any stage of the disease (diagnosis or follow-up). Inclusion criteria were as follows: 1) series with more than 20 patients with CSF assessment for lymphoma or LD, 2) diagnosis of PCNSL, and 3) HIV-negative patients.

The article search was limited to English with humans as the only study participants. All articles were specified as retrospective or prospective patient studies, clinical trials, randomized clinical trials, or post hoc analyses of clinical trials. Reviews, editorials, commentaries, and case reports were excluded.

Data Analysis

All articles included were reviewed for data available on number of patients in the study, number of patients with CSF screening for lymphoma or LD, method used to diagnose PCNSL, initial staging work-up, CSF screening method, number of patients with positive CSF at any stage of the disease, and steroid use before CSF or biopsy screening. The type of study and general characteristics of the population included were also mentioned.

The second part of our study included a retrospective, single-center patient series assessing the diagnostic accuracy and safety of early biopsy for patients with PCNSL. We conducted a retrospective review of all cases with histological confirmation of PCNSL in immunocompetent patients treated at our institution from 2012 to 2018. Patients were excluded if they had a prior diagnosis of lymphoma, history of immunodeficiency, and systemic disease as demonstrated by positive body imaging. All relevant demographic, epidemiologic, and clinical variables were collected.

Results

After applying the inclusion criteria, 23 studies were included for data analysis, 2 of which were excluded because of inadequate data description (Fig. 1). A final number of 21 studies with a total of 1481 patients with PCNSL were included in our analysis: retrospective series (11), followed by prospective clinical trials (6), prospective descriptive studies (2), a randomized clinical trial (1), and post hoc analysis of a randomized clinical trial study (1) (Table 1). A PRISMA flow sheet of the articles screened can be found in Fig. 1. Two articles were included with a minor percentage (2% to 4%) of patients who were diagnosed by radiological/clinical findings rather than histopathologic report of tumor tissue.

We found 35 patients in 6 studies[8,15,17,18,20,26] in which surgery was obviated because of positive CSF for lymphoma, with a total of 472 patients screened (7.4%, n = 35/472). CSF analysis during all stages of disease (diagnosis or staging) was positive in 14.9% of cases (222/1481). In 2 studies, different methods were used in addition to standard cytology (flow cytometry in 1 and polymerase chain reaction [PCR] analysis of immunoglobulin heavy chain in another). Brain biopsy was the preferred method of diagnosis in 95% of patients (n = 1029) followed by CSF (3.1%, n = 35)) and vitreous sampling (1%, n = 16). The initial assessment in most studies included a combination of HIV test, bone marrow biopsy, CT of the chest, abdomen, and pelvis, and ophthalmologic exam with slit lamp. The use of steroids at the time of diagnosis was described in only 2 studies and varied from 18.4% to 65% of cases.

Retrospective Series

From 2012 to 2018, 26 patients were newly diagnosed with PCNSL at our 2 major teaching hospitals (Table 2). All cases were confirmed by brain biopsy and were histologically confirmed by the pathology department. The surgical procedures were frameless SBB in 16 patients (61.5%), craniotomy for tumor resection in 8 cases (30.8%), and endoscopy-guided biopsy in 2 cases (7.7%). The most common regions affected were the frontal lobes (13), followed by temporal lobes (6), parietal (3), thalamic (2), occipital (1),

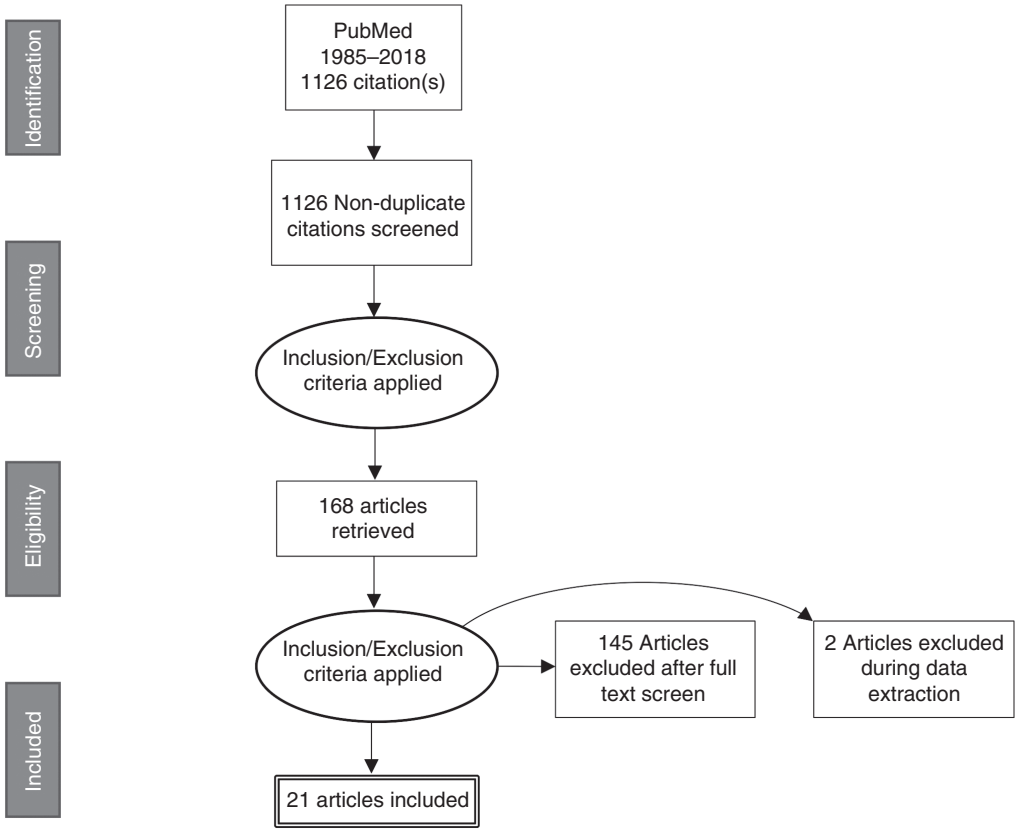

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines and How They Were Used for Our Assessment of the Literature.

and brainstem (1). Owing to our institutional bias for early biopsy, only 7 patients (26.9%) were screened prior to surgery with LP for CSF analysis for cytology and flow cytometry. CSF analysis was negative for all cases. Initial brain biopsy was diagnostic in 92.3% of cases (24/26), with 2 cases that required a second procedure for diagnosis. In both cases, the patients were on preoperative steroids, and the pathology reports were not conclusive. A second procedure (SBB) was performed in each case after the patients were completely off steroids, permitting a definitive diagnosis of PCNSL. Although 42.3% (n = 11) of patients were on steroids preoperatively, a brain biopsy was still diagnostic in the majority of these patients (n = 9, 81.8%). Perioperative morbidity was noted in 7.6% of cases (n = 2) due to hemorrhages after SBB that improved at follow-up. The first patient developed mild dysarthria in the first 12 hours of the procedure that resolved entirely in 2 weeks with conservative treatment. The second patient had an event 24 hours after the surgery, becoming lethargic and showing a new motor deficit (hemiparesis) that slightly improved at last follow-up. No perioperative mortality was noted in our series.

Discussion

Appropriate management of PCNSL comprises an adequate use of diagnostic and therapeutic tools. Traditionally, less-invasive modalities (LP, vitreous sample, steroid trial) have been suggested to preclude brain biopsies for the diagnosis of PCNSL. However, the utility of these diagnostic procedures was previously undefined. Our study remains the first systematic review that helps define the diagnostic yield of CSF studies for PCNSL.

If there is suspicion of primary CNS lymphoma, initial work-up typically includes at least 1 HIV blood test, an LP (if there are no signs of possible contraindications), and ophthalmological assessment including slit-lamp examination. Also, systemic staging should include testicular ultrasonography (mostly in older patients) and either PET/CT or CT scan of the chest, abdomen, and pelvis.[9,31] Cytomorphology of the CSF is the most common technique for diagnosing leptomeningeal spread, but cellular immunophenotyping by flow cytometry or PCR analysis of immunoglobulin heavy and light chain genes may help when the cytological examination is negative.[32,33] It is important to acknowledge that many earlier studies on PCNSL predated the adoption of sophisticated molecular and cytometric tests.

In 1995, Balmaceda et al[8] proposed a diagnostic algorithm for patients with possible PCNSL that suggested that when a CT/MRI is suspicious for PCNSL, you should withhold corticosteroids and perform a slit-lamp exam and LP, postponing brain biopsy. In this series, they were able to diagnose only 14.5% of the patients by CSF analysis, avoiding the need to perform a brain biopsy in those cases. They also stated that most of the samples were

Table 1 Results of the Systematic Review: CSF Analysis in PCNSL

	Author and Year	No. of Pts with CSF Screening	Population	Diagnostic Method	Type of Study	Initial Staging Work-Up	CSF Screening Method	CTC	Positive CSF
1	Balmaceda et al 1995[8]	86	Consecutive PCNSL	BB: 78,1% Vitrectomy: 5.2% CSF: 14.5% Radiologic and clinical features: 2.1%	PS	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology	Yes: 65.1% No: 15.1% NA: 19.7%	26%
2	Schlegel et al 2001[11]	20	Consecutive PCNSL	BB:100%	PCT	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		0%
3	DeAngelis et al 2002[12]	81	PCNSL, including brain, eye, and meninges	Stereotactic or open biopsy, vitrectomy or CSF	PS	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		21%
4	Ferreri et al 2002[13]	241	PCNSL	BB: 95% CSF cytology: 4% Vitrectomy: 0.27% Autopsy: 0.27%	RS	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		16%
5	Pels et al 2003[14]	58	PCNSL, including brain, eyes, and meninges	BB: 100%	PCT	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		12%
6	Jahnke et al 2006[15]	25	Low-grade PCNSL	BB: 98% CSF cytology: 2.5%	RS	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		16%
7	Shenkier et al 2005[16]	32	PCNSL (T-cell)	BB: 95.5% CSF cytology: 2.2% Autopsy: 2.2%	RS	Ophthalmological exam HIV test	Cytology		19%
8	Quek et al 2006[17]	23	PCNSL	BB: 100%	RS	CT Scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		21.7%
9	Kiewe et al 2008[18]	34	Consecutive PCNSL	BB: 90.2% Vitrectomy: 2.7% CSF cytology: 2.7% Radiologic and clinical features: 4.1%	RS	CT scan Bone marrow biopsy Ophthalmological exam (only in patients with ocular symptoms) HIV test	Cytology		18%

Table 1 Continued

	Author and Year	No. of Pts with CSF Screening	Population	Diagnostic Method	Type of Study	Initial Staging Work-Up	CSF Screening Method	CTC	Positive CSF
10	Agarwal et al 2009[19]	20	Consecutive PCNSL	Stereotactic brain biopsy: 20 (100%)	RS	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		0%
11	Korfel et al 2012[20]	361 for CSF Cytology 152 for PCR	PCNSL	NA	PHCT	NA	CSF cytology IgH PCR (only in B-cell lymphoma)		12,2% in CSF cytology 10.5% in IgH PCR
12	Pasricha et al 2011[21]	48	Consecutive PCNSL	BB: 100%	RS	Bone marrow biopsy Lymphadenopathy and organomegaly screening	Cytology		2.08%
13	Kim et al 2014[22]	32	PCNSL, including brain, eyes, cranial nerves, meninges, and spinal cord.	NA	RS	CT scan PET scan Bone marrow biopsy Ophthalmologic exam HIV test	Cytology		28.1%
14	Rubenstein et al 2013[23]	41	PCNSL, including brain, and spine	NA	PCT	CT scan Bone marrow biopsy Ophthalmological exam HIV test	Cytology		24%
15	Xie et al 2015[24]	54	>60 years with PCNSL	BB: 98% Slit-lamp examination of the eye: 7.4% Vitrectomy: 5.6% CSF cytology: 3.7% CSF flow cytometry: 1.9%	RS	NA	Cytology		5.6%
16	Ferreri et al 2014[25]	29	PCNSL, including brain, eyes, and meninges	BB: 97.6% Vitrectomy: 2.4%	PCT	HIV	Cytology		10.3%
17	Wang et al 2014[26]	41	PCNSL, including brain, eyes, and meninges	NA	PCT	HIV test	Cytology		4.8%
18	Pulczynski et al 2015[27]	44	PCNSL	BB: 100%	PCT	CT scan Bone marrow biopsy Ophthalmologic exam HIV test US of the testes inage >60 years	Cytology flow cytometry		Cytology: 18% Flow cytometry: 6.6%
19	Omuro et al 2015[28]	78	Age >60 years with PCNSL	NA	RCT	NA	Cytology		29.4%
20	Patel et al 2015[29]	76	Consecutive PCNSL Brain only, not eyes or meninges	Stereotactic or open biopsy: 100%	RS	CT scan Bone marrow biopsy Ophthalmologic exam HIV test	Cytology	Yes: 18.4%	2.6%
21	Houillier et al 2017[30]	57	Age >60 years with PCNSL	NA	RS	NA	Cytology		21%

Abbreviations: BB, brain biopsy; CSF, cerebrospinal fluid; CTC, corticosteroids; PCNSL, primary central nervous system lymphoma; PCR, polymerase chain reaction; PCT, prospective clinical trial; PHCT, post hoc analysis of a randomized clinical trial; PS, prospective descriptive study; RCT, randomized controlled trial; RS, retrospective series; US, ultrasound.

Table 2 PCNSL Treated Between 2012 and 2018

Patient	Age	Procedure	Localization	Anesthesia	Preoperative Work-Up	Preoperative LP Result	Preoperative Steroids	Postoperative Complications
1	74	Craniotomy	Brainstem	General	Preoperative CT-CAP	Yes, negative	Yes	No
2	80	SBB	Frontal	General	No	No	No	No
3	67	SBB	Frontal	General	No	No	No	No
4	86	SBB	Frontal	MAC sedation	No	No	No	No
5	72	Craniotomy	Frontal	General	No	No	Yes	No
6	88	SBB	Frontal	General	No	No	Yes	No
7	80	Craniotomy	Frontal	Awake	No	No	No	No
8	71	SBB	Frontal	General	No	No	No	No
9	79	SBB	Frontal	General	No	Yes, negative	No	Second biopsy
10	79	Endoscopy	Frontal	General	No	No	Yes	No
11	66	SBB	Frontal	General	No	Yes, negative	No	No
12	84	SBB	Frontal	General	Preoperative CT-CAP	No	No	Mild dysarthria
13	84	SBB	Frontal	General	No	No	Yes	Small hemorrhage
14	68	SBB	Frontal	General	Preoperative CT-CAP	Yes, negative	Yes	No
15	60	SBB	Parietal	General	No	No	No	No
16	64	SBB	Parietal	General	Preoperative CT-CAP	No	Yes	No
17	62	SBB	Parietal	General	Preoperative CT-CAP	No	Yes	No
18	80	Craniotomy	Occipital	General	No	No	No	No
19	69	Craniotomy	Temporal	General	No	Yes, negative	No	Second biopsy
20	36	Craniotomy	Temporal	General	No	No	Yes	No
21	60	Craniotomy	Temporal	Awake	No	No	No	No
22	60	SBB	Temporal	General	Preoperative CT-CAP	Yes, negative	Yes	No
23	52	SBB	Parietal	General	No	No	No	No
24	45	Craniotomy	Parietal	General	No	No	Yes	No
25	45	SBB	Thalamic	General	No	Yes, negative	No	No
26	80	Endoscopy	Thalamic	General	No	No	No	No

Abbreviations: CT-CAP, CT scan chest, abdomen and pelvis; MAC, monitored anesthesia care; PCNSL, primary central nervous system lymphoma; SBB, stereotactic frameless brain biopsy.

obtained after corticosteroids were started, with a possible underestimation of the real value of performing an LP before a brain biopsy. Although a reasonable and less-invasive approach, available data from recent studies suggest that only a minor fraction of patients can be diagnosed by CSF analysis, ranging from 0% to 4% of the total cases (Table 1).

However, positive CSF analysis during any stage of PCNSL (diagnosis or follow-up screening) tends to be more common, with an average of 14.9% (0% to 28%) of all patients with PCNSL. Although these numbers seem to show a higher sensitivity, we must understand that multiple LPs are performed in some centers as part of the follow-up of these patients at a more advanced disease, leading to a higher percentage of positive results. Most articles suggesting a less-invasive and more staged approach support recommendations for CSF analysis in the postdiagnostic stage of the PCNSL. This discrepancy (7.1% at diagnosis and 14.9% at follow-up) helps define the role of early biopsy for PCNSL.

Early brain biopsy has also been recommended in the literature because of the low rates of complications, high diagnostic rates, and to prevent the diagnostic delay that patients with PCNSL present.[34–38] In our series, definitive diagnosis was achieved in the first surgical intervention (regardless of preoperative LP) in 92.3% of the cases, similar to other publications.[39–42] Additionally, brain biopsies in our modern series remained relatively safe with low permanent morbidity (3.8%, hemiparesis in 1 patient). Overall, these data help advocate for early biopsies in immunocompetent patients with suspected PCNSL regardless of CSF analyses to help prevent diagnostic delays and start earlier treatment.

As previously reported, diagnostic delays in patients with PCNSL can occur frequently. In a study published by Cerqua and colleagues,[35] the authors compared time spans from clinical onset to final diagnosis in 28 patients with glioblastoma multiforme and 28 patients with PCNSL. They found that mean time span from first neuroimaging examination to final histologic diagnosis was much longer in PCNSL

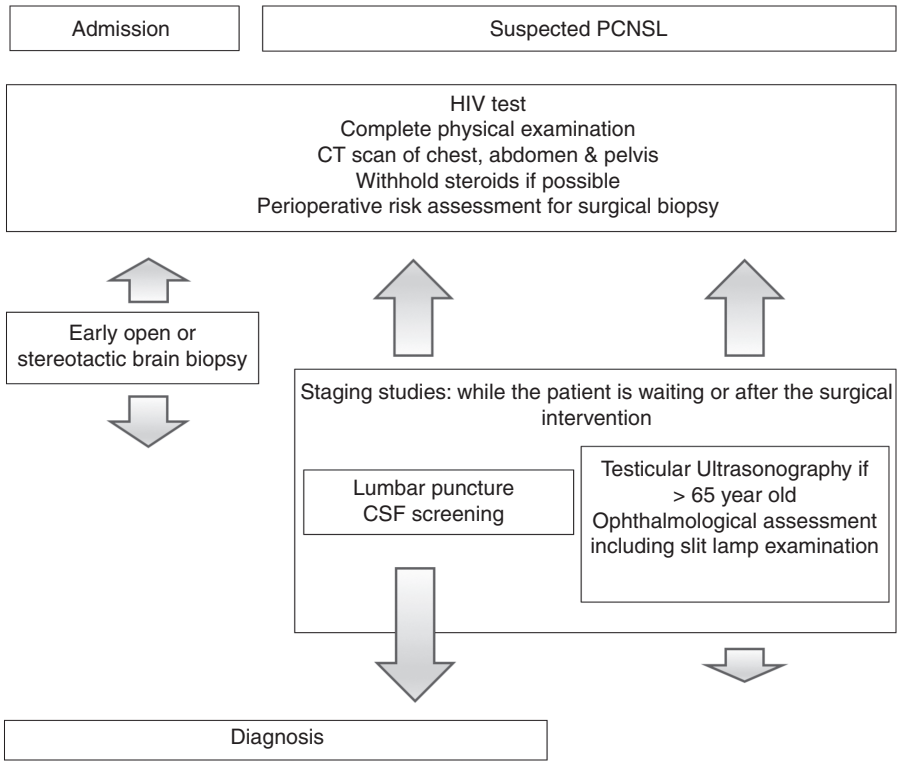

Fig. 2 Management Paradigm for Primary Central Nervous System Lymphoma. CSF indicates cerebrospinal fluid.

patients (41.7 vs 16.2 days, $P = .008$). Other studies also confirm considerable delays in PCNSL diagnoses, ranging up to 124 days in certain patient populations.[37] In many hospitals, part of the delay includes lengthy cytology or flow cytometry analysis that may take up to 1-2 weeks in some hospitals. As a result, early, safe diagnostic options may be offered to patients to mitigate these diagnostic delays and reduce costs associated with extended hospitalizations. In our series, the diagnostic yield of CSF screening (n = 7/26) was 0%, and the time to diagnosis from first consultation was considerably higher in patients who underwent preoperative/diagnostic LP compared with those in the early biopsy strategy (21 vs. 11 days, respectively).

Some critics suggest that LPs should always be performed prior to brain biopsy because the benefits of noninvasive diagnosis outweigh the undue risks of brain biopsies. Previous literature suggests that brain biopsies may have a nontrivial risk of procedural complications including hemorrhage, nondiagnosis, and infection. However, many of these studies (premillennial) predate the invention of neuronavigation and intraoperative imaging (CT/MRI) that have intrinsically advanced the accuracy of SBBs. Nevertheless, LP has some utility in cases in which there is some equivocality on the diagnosis, especially in immunocompromised patients or patients with multifocal/LD. Lastly, we maintain that early brain biopsies do not preclude LPs if they are needed but should be offered simultaneously under anesthesia for appropriate staging at the time of diagnosis.

As has been reported, the use of steroids preoperatively can compromise the efficacy of brain biopsy and LPs in cases of PCNSL.[43,44] As such, the classic rationale recommends withholding steroid treatment for at least 14 days prior to a brain biopsy. Our data suggest that the diagnostic yield of brain biopsies is only slightly affected (~80%) when patients remain on steroids prior to surgery. This is comparable with other retrospective studies[45] that found no difference in the rate of definitive diagnosis in the first biopsy in patients on or off corticosteroids (88% vs 87%). However, the length of steroid treatment before the biopsy may remain important; another study by Manoj et al[45] reported a high incidence of false-negative results in the first biopsy when the treatment was longer than 1 week, compared with less than 1 week with no steroid treatment at all (44% vs 5.8% vs 0%, respectively). Therefore, withholding initial treatment or tapering corticosteroids is recommended until histologic confirmation has been obtained if the patient can tolerate the steroid wean. In those patients in whom steroid treatment is mandatory, performing an early biopsy may still remain effective (Fig. 2).

Establishing a minimally invasive approach in the diagnosis of brain tumors has always been a goal. In recent years, the detection of circulating tumor DNA in serum, plasma, or CSF has become a field of major interest in neuro-oncology. The molecular analysis of these fragments of tumor DNA or microRNA can identify genetic hallmark mutations of PCNSL, being remarkably useful

in the diagnosis of these types of tumors.[46–48] However, further studies are needed for these promising minimally invasive techniques to be included in the standard diagnostic paradigm.

Our study provides an updated framework that advocates for an earlier surgical biopsy when a PCNSL is suspected. However, in our systematic review we could find data only from retrospective studies that were not designed to assess the sensitivity of CSF screening, and many of them were multicenter studies with heterogeneous or incomplete data (ie, use of corticosteroids). In the future, we expect to see prospective studies about the efficacy of new minimally invasive techniques such as molecular analysis in the diagnosis of PCNSL.

Conclusions

The diagnostic yield of CSF analyses for PCNSL in immunocompetent patients remains exceedingly low (7.4%), although follow-up CSF screening may be positive in up to 14.9% of cases. Our institutional series demonstrates that early biopsy for PCNSL is safe and accurate, and may avert lengthy extensive work-ups. We conclude that performing an early brain biopsy in a suspected case of PCNSL is a valid option to minimize diagnostic delay, with a high rate of definitive diagnosis, and a low rate of complications.

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Conflict of interest statement. None declared.

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