PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA
Diagnostic path and significant delays

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ABSTRACT

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Primary central nervous system lymphoma (PCNSL) is a very aggressive non-Hodgkin lymphoma. It restricts to the central nervous system and has a low survival rate while responding well to radiation and chemotherapy. The immunohistochemical profile, mutation analysis, cytokines from cerebrospinal fluid (CSF) and oedema occurring might have diagnostic and prognostic value when suspecting PCNSL. PCNSL has a lower mass effect, leading to less oedema compared with same size other tumours such as gliomas or metastases.
PCNSL reacts favourably to glucocorticoids, such as dexamethasone, but they might also interfere with the diagnosis, leading to delay in the diagnostic path. This is something that requires assessment in the future. An oedema and its mass effect grading system could help with decision to refrain from dexamethasone usage if lymphoma is suspected. The longest delay causing factor in OYS and KYS was waiting for the biopsy. This problem could be dealt with the possibility to do on-call biopsy or with the CSF fluid analysis leading to diagnosis.

Keywords: primary central nervous system lymphoma, diagnostic path, delays

Tiivistelmä

Primaariaivolymfooma on aggressiivinen non-Hodginin lymfooma, joka rajoittuu keskushermostoon. Kuolleisuus on korkea huolimatta usein hyvästä alkuvaiheen säde- ja sytostaattihoitovasteesta. Diagnoosi perustuu immonohistokemiallisiin tutkimuksiin ja tarvittaessa mutaatioanalyyseihin. Aivolymfoomilla on yleensä pienempi massavaikutus ja vähemmän aivoturvotusta kuin glioomilla tai aivometastaaseilla. Primaariaivolymfooma reagoi hyvin glukokortikoideihin, kuten dexametasoniin, mutta ne voivat merkittävästi vaikeuttaa ja viivästyttää diagnostiikkaa. Tämä tarvitsee jatkotutkimuksia. Aivoturvotuksen ja sen massaefektin luokittelujärjestelmä voisi auttaa dexametasonin käytöstä pidättäytymisessä, mikäli epäillään aivolymfoomaa. Pisimmän viiveen aiheuttava tekijä OYS:ssä ja KYS:ssä oli biopsian odottaminen. Tämä ongelma voitaisiin välttää päivystysbiopsian mahdollisuudella tai likvorin analytiikan tehostamisella.

Avainsanat: primääri aivolymfooma, diagnostiikkapolku, viiveet

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ABBREVIATIONS

PCNSL	primary central nervous system lymphoma
CSF	cerebrospinal fluid
OUH	Oulu University Hospital
KUH	Kuopio University Hospital
CNS	central nervous system
DLBCL	diffuse large B-cell lymphoma
MRI	magnetic resonance imaging
CT	computed tomography
H&E	hematoxylin and Eosin
IHC	immunohistochemistry
CD	cluster of differentiation
BCL	B-cell lymphoma
MUM	multiple myeloma oncogene
OS	overall survival
PFS	progression free survival
TLR	toll-like receptor
BCR	b-cell receptor
ER	emergency room

1 INTRODUCTION

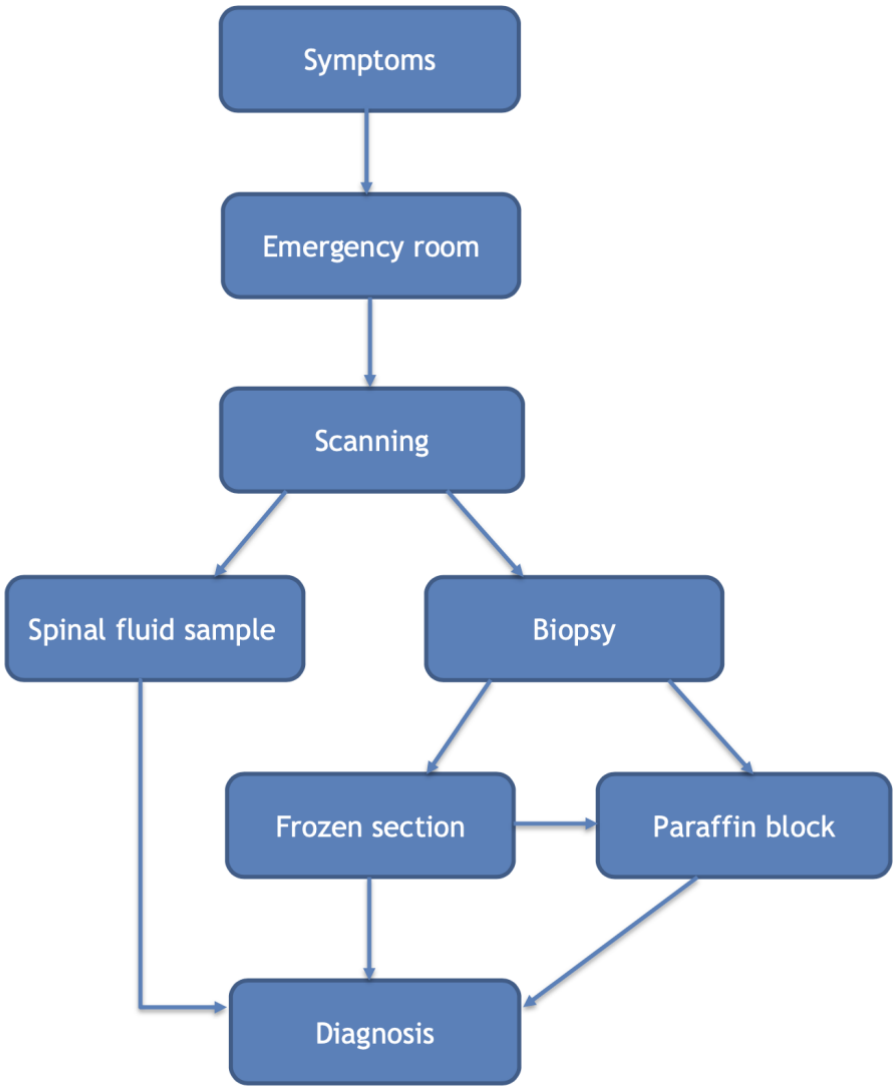
Primary central nervous system lymphoma (PCNSL) is an uncommon type of extranodal non-Hodgkin lymphoma, which means that it occurs outside of the lymph node area (Grommes & DeAngelis, 2017). It is extremely aggressive and restricted to the central nervous system (CNS). Apart from the brain and spine, it can also be found on cerebrospinal fluid (CSF) and eyes. While it has a favourable response to radiation and chemotherapy, survival is generally lower compared to systemic lymphomas. PCNSL can develop in both immunosuppressed and immunocompetent patients. Majority of PCNSLs are diffuse large B-cell lymphomas (DLBCL) (Grommes & DeAngelis, 2017).

The incidence rates of PCNSL are increasing, especially in patients older than 60 years, with a rate of 0.5 per 100 000 per year (Grommes & DeAngelis, 2017). In the United States, around 1 500 new patients are diagnosed every year. In the Oulu University Hospital, the rate is 0.44-0.87 per 100 000 per year which means around 24-47 new patients every year (Kuittinen & Kuitunen, 2017). A remarkable risk factor for the development of PCNSL is immunodeficiency, including iatrogenic immunosuppression, congenital disorders and especially HIV (Villano, Koshy, Shaikh, Dolecek, & McCarthy, 2011). Among immunocompetent patients, the mean age of occurrence is from 53 to 57 years, while in immunocompromised patients it is from 31 to 35 years (Bhagavathi & Wilson, 2008).

2 PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

2.1 Clinical presentation

Patients with PCNSL develop various neurologic signs such as notable neurologic deficits, changes in behavioural and mental status, seizures and symptoms that occur when intracranial pressure is increased, including headaches, nausea and vomiting (Grommes & DeAngelis, 2017). However, the symptoms depend on the part of the CNS involved. In most cases PCNSL is a single brain lesion located in the supratentorial area, involving frontoparietal lobes. Involvement of the spinal cord is rare and lesions in eyes and CSF are also less frequent. Spinal cord lymphoma mimics the symptoms of myelopathy which may include cauda equina and paresthesis (Flanagan et al., 2011). Symptoms vary depending on the segment involved.



Graph 1. Diagnostic path of the primary central nervous lymphoma.

2.2 Imaging

Usually, magnetic resonance imaging (MRI) exposes a homogeneously increasing mass lesion (Grommes & DeAngelis, 2017). The tumour is typically in contact with meningeal and ventricular surfaces with the involvement of the supratentorial brain (Mansour, Qandeel, Abdel-Razeq & Hussain, 2014).

Mansour et al. (2014) studied specific MRI findings in immune competent patients suffering from intracranial PCNSL. They discovered that T1- and T2-weighted images typically present a homogenous mass with high-cellular signal intensity due to hypercellularity and high nuclear/cytoplasmic ratio. Necrosis, internal calcification and haemorrhage are atypical and rare characteristics of PCNSL. When typical imaging findings are absent, new imaging techniques such as magnetic resonance spectroscopy (MRS), perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) have important role in the diagnosis of PCNSL.

Differential diagnosis of PCNSL from other tumours is important because as corticosteroids are effective in reducing the oedema caused by the tumour, they may also reduce the size of the PCNSL leading to significant delays in diagnosis. Supratentorial location in addition to contact with meningeal and ventricular surfaces, absence of haemorrhage, necrosis and internal calcification should raise suspicion of PCNSL.

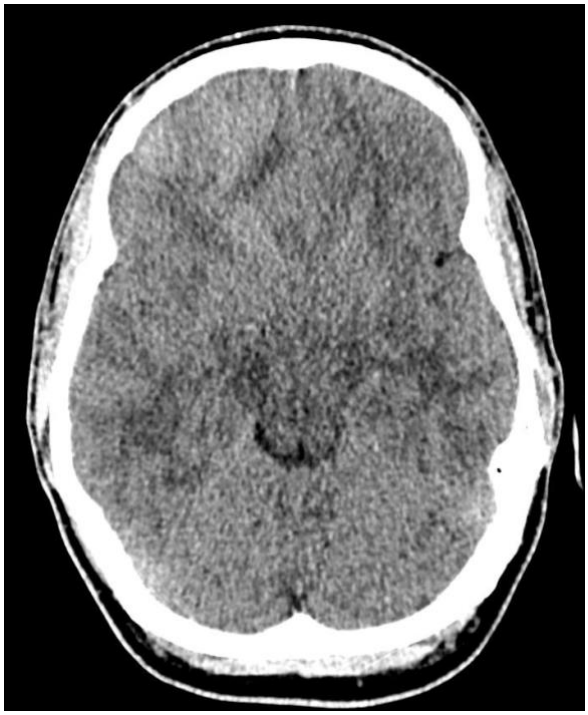


Image 1. CT finding of a patient with right frontal lobe PCNSL.

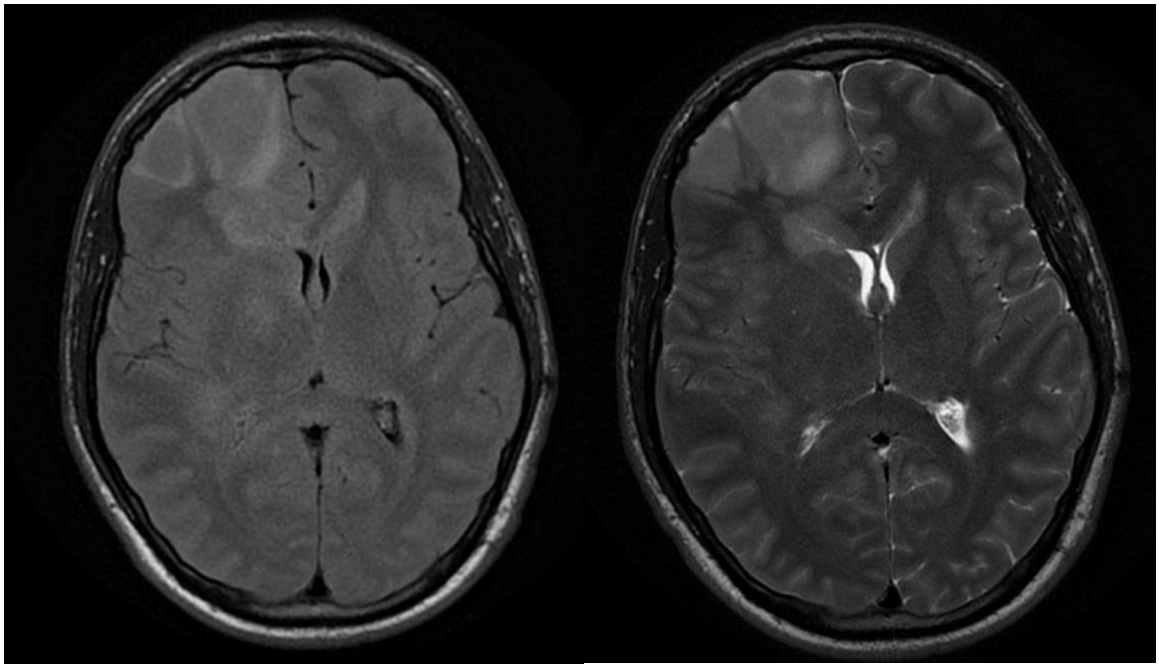


Image 2. T2-weighted MRI of the right frontal lobe PCNSL without (left) and with contrast agent (right).

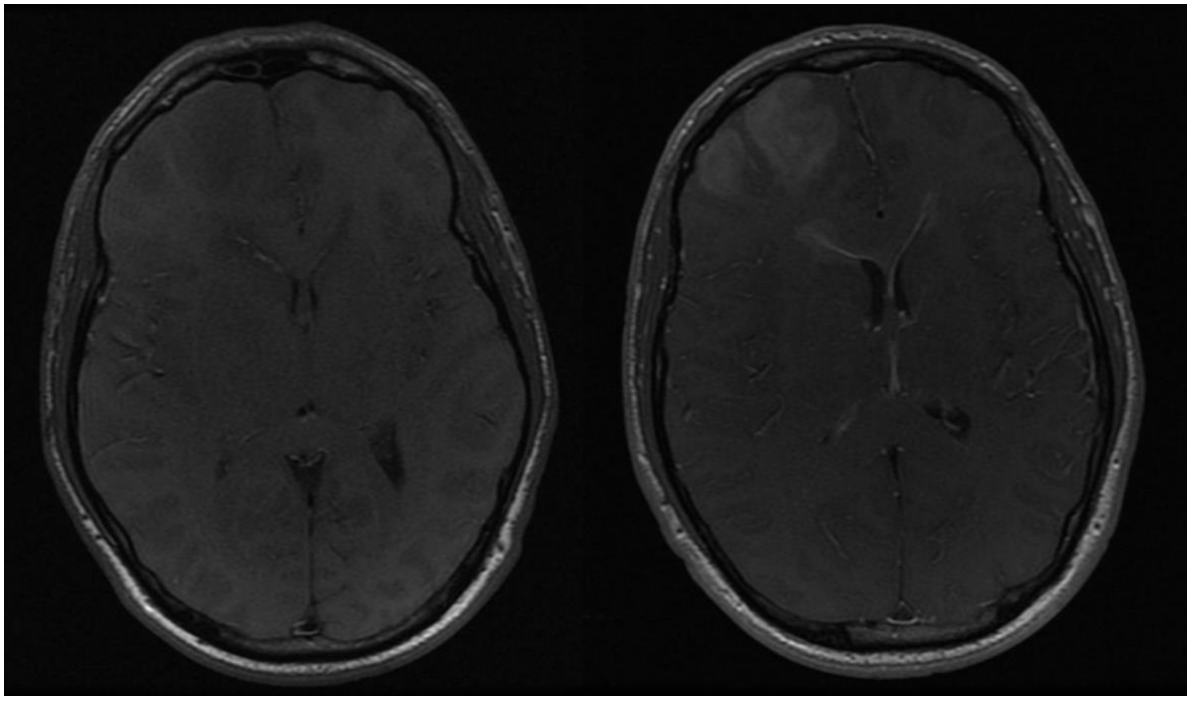


Image 3. T1-weighted MRI of the right frontal lobe PCNSL without (left) and with contrast agent (right).

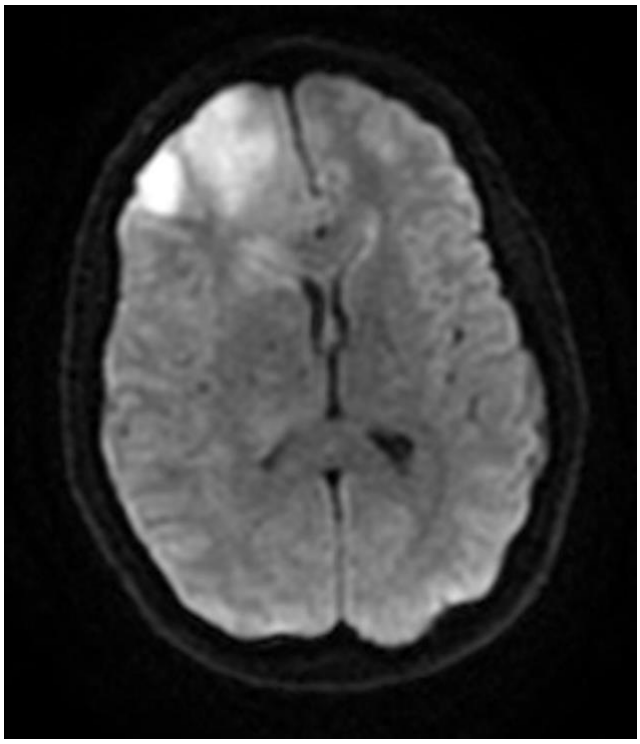


Image 4. Diffusion-weighted MRI shows increased signal intensity at the right frontal lobe.

2.3 Biopsy

In addition to MRI, diagnosing PCNSL requires ophthalmologic and CSF evaluation. The establishment of the diagnosis includes stereotactic biopsy, which is a golden standard of the PCNSL diagnosis. However, the availability of operating rooms cand of the on-call biopsy can cause delays in the diagnosis of PCNSL, as it is at present at the Oulu University Hospital (OUH). When there is eye or CSF manifestations of the PCNSL, only vitrectomy or CSF cytology might be enough (Grommes & DeAngelis, 2017).

2.4 Immunohistochemical staining/Histopathology

Histologically, PCNSL is a diffuse growing tumour with characteristic angiocentric infiltration pattern, where tumor cells form cuffs around blood vessels (Bhagavathi & Wilson, 2008). Tumour cells are large and atypical with distinct nucleoli, corresponding to centroblasts or immunoblasts, which are mature B-cells with CD20-positive phenotype. Expression of BCL-2 is typical and most tumours express BCL-6 and MUM-1 as well. CD10 is expressed in less than 10% of PCNSLs while the expression rate is much higher in systemic diffuse large B-cell

lymphomas (DLBCLs) (Deckert, Brunn, Montesinos-rongen, Terreni, & Ponzoni, 2014). The relevance of the immunohistochemical markers is discussed further.

2.5 Treatment

Treatment of PCNSL includes chemotherapy, high doses of methotrexate and radiotherapy (Bhagavathi & Wilson, 2008). It also responses dramatically to corticosteroids, but that is usually temporary. The genetic characterization of the lymphoma helps in individualization of the treatment (Hottinger, Alentorn, & Hoang-Xuan, 2015). In half of the patients, the results are durable, but late neurotoxicity can be associated with the treatment (Grommes & DeAngelis, 2017).

University hospital of Oulu is the only hospital in Finland which offers blood-brain barrier disruption treatment to PCNSL. Therefore, many patients from across the country are sent to OYS after diagnosis.

2.6 Prognosis

Age and the status of performance preoperatively are the most important prognostic factors apart from the therapy. There are also other factors that could be evaluated to predict the outcome of the treatment, including the level of lactate dehydrogenase, the concentration of CSF protein and the involvement of the deep brain. Molecular markers indicating phenotype and mutations might help in understanding the development and mechanisms of PCNSL and also have diagnostic and prognostic significance (Grommes & DeAngelis, 2017).

3 PCNSL AND DIAGNOSTIC MARKERS

3.1 Immunohistochemical profile

The expression of immunohistochemical (IHC) markers might have potential prognostic significance in PCNSL (Liu et al., 2017). In the analysis of 89 cases, the prognostic significance of various biological markers was evaluated with overall survival (OS) and progression-free survival (PFS). These markers were cluster of differentiation (CD)10, B-cell lymphoma (BCL)-6, multiple myeloma-1 (MUM-1), BCL-2, CD138, and Ki-67. The study suggests that high Ki-67 expression may be associated with poor prognosis in PCSNL because it was associated with shorter overall survival (OS) and progression free survival (PFS). Any other IHC markers listed were not significantly associated with either OS or PFS, suggesting that these markers might not have a prognostic value. However, this study was limited by the number of cases analysed and the short follow-up time.

Ki-67 and BCL-2 are proteins that are overexpressed in diffuse large B-cell lymphoma (DLBCL) and one study suggests that the BCL2/Ki-67 ratio is a very effective prognostic factor on patients with DLBCL (Tang, Zhou, Cheng, Su, & Wang, 2017). Ki-67 is used as an index to evaluate the lymphoma's proliferative activity because it synthesizes at the beginning of cell proliferation. BCL-2 functions in antiapoptotic signalling by inhibiting programmed cell death.

In OYS, pathologist performs intraoperative frozen section diagnostic with H&E and toluidine blue staining. If a quick immunohistochemical staining is needed, CD45 staining specially prepared for the frozen section analysis can be used to identify the lymphocytic cells. In final diagnosis, a routine immunohistochemical staining protocol including CD3, CD20, BCL-2, BCL-6, CD10, MUM-1 and Ki-67 is performed to the formalin fixed paraffin embedded tissue. No mutation analysis is performed. In some cases in this research, minor IHC staining protocol using only CD20 combined with Ki-67 or BCL-2 led to diagnosis.

Table 1. Immunohistochemical markers and their relevance

Marker	Value
BCL-6	Prognostic significance is controversial. Might predict favourable outcome in DLBCL because its positivity indicates an improved course of disease. (Liu et al., 2017)
MUM-1	Typical feature of PCNSL but doesn't have prognostic significance. (Liu et al., 2017)l
BCL-2	Important independent survival predictor in patients with DLBCL, although the association between BCL-2 and prognosis is inconclusive. (Liu et al., 2017)
Ki-67	Valuable IHC marker to differentiate indolent from aggressive lymphomas. (Liu et al., 2017)
MYC/BCL-2 co-expression	Significant prognostic value. Cases with MYC-BCL-2 co-expression has remarkably worse overall survival. (Shi et al., 2017)
IL-10	Might predict therapeutic response and severity of PCNSL. Combines reliable diagnostic biomarker together with increased IL-10/IL-6 level (Song et al., 2016)
IL-10/IL-6 ratio	Important parameter in differential diagnosis, especially for central nervous system infections. (Song et al., 2016)

3.2 Cerebrospinal fluid

Biomarkers in the cerebrospinal fluid (CSF) for PCNSL and liquid biopsies from the CSF could be used in the diagnosis of PCNSL. Cytokine interleukin-10 (IL-10) inhibits apoptosis and promotes proliferation of B lymphoma cells, and thereby it has a role in the development of lymphoma (Song et al., 2016). One study used electrochemiluminescence immunoassay (ECLIA) to determine the cytokine levels and the results demonstrate identically increased IL-10 levels in all patients with PCNSL. Moreover, in some cases the post-chemotherapy CSF IL-10 levels decreased, accompanied by disease remission. This suggests that IL-10 levels could be used in defining the state of the disease.

Over 70 abnormal genes have been reported in PCNSL, including CD79B and MYD88, which are clinically useful because those can be directly targeted in the therapy (Hiemcke-Jiwa et al., 2018). MYD88 affects the Toll-like receptor (TLR) pathway and CD79B affects the B-cell receptor (BCR) pathway. Together these combine on the NFκB pathway. As a result, IL-6 and IL-10 are produced, leading to cell proliferation. Mutations in the MYD88 lead to incorrect activation of TLRs, including TLR4, TLR5, and TLR9 (Akhter et al., 2015). In this study, 85% of DLBCL cases expressed high amounts of TLR9 compared with normal B-lymphocytes. It is suggested that high expression of TLR9 in normal B-cell lymphomas promotes malignant

transformation, tumor cell maintenance, and progression. These pathways could be targeted in future therapies.

When PCNSL is suspected, the patient is admitted to the neurosurgery unit and a CSF sample is collected if it is not contraindicated (Graph 1). Flow cytometry analysis is performed to the CSF sample and if positive, the tissue biopsy is not needed. CSF diagnosis is expected to indicate correct diagnosis up to 25% of the patients with PCNSL and in this case unnecessary tumour biopsy can be avoided. If CSF flow cytometry analysis is negative it is necessary to continue to the stereotactic biopsy.

Table 2. Mutations and their effect on outcome in PCNSL (Hiemcke-Jiqa et al., 2018)

Gene	**Function**	**Number of patients with aberration** (Hattori et al., 2017)	**Genetic deviation**
CD79B	BCR complex, NFκB pathway activation	22/42	Mutation
MYD88	TLR, NFκB pathway activation	33/42	Mutation
CARD11	BCM complex, NFκB pathway activation	8/42	Mutation
TBL1XR1	Co-factor in transcription, Regulation of ETV6 activity, negative modulation of TLR/MYD88 signalling	10/42	Mutation
TNFAIP3 (A20)	Tumour necrosis factor (TNF) mediated apoptosis, inhibition of NFκB pathway	5/42	Mutation
CDKN2A (TP16)	Essential in genomic stability, tumour suppressor, control of cell-cycle phase G1	10/18 (Braggio et al., 2015)	Loss of function mutation
ETV6	Transcriptional repressor, need for development of vascular network and haematopoiesis, role in malignant transformation	1/18 (Braggio et al., 2015)	Mutation
PIM1	Protein kinase, which is involved in survival and proliferation of cells, a target of somatic hypermutation	29/42	Mutation
PRDM1	Tumour suppressor, B-cells terminal differentiation	10/42	Mutation, homozygous deletion, chromosomal loss
TOX	Regulation of T-cell development, differentiation of B-cells	5/42	Homozygous deletion
NFKBIZ	May serve as additional and/or alternative modulator of the MYD88/TLR signalling pathway, increased TLR activity	24/41 (Chapuy et al., 2016)	Copy number gain (Chapuy et al., 2016)

3.3 Oedema

Perilesional oedema is a common characteristic of PCNSL, occurring in more than 90% of cases. PCNSL still has a lower mass effect when compared with same size metastases or malignant gliomas (Mansour, Qandeel, Abdel-razeq, Ali, & Ali, 2014). This information might have diagnostic value when PCNSL is suspected.

4 OYS AND KYS DIAGNOSTIC PATHS WITH DELAYS IN EACH PHASE

4.1 Materials and methods

The aim of this study was to analyse the efficiency of the diagnosis and treatment path of the primary nervous system lymphoma (PCNSL) and to identify delay causing factors in the diagnostic path and in the starting of the cytostatic treatment. Research data consists of patients who were diagnosed with PCNSL in Oulu University Hospital (OUH) or Kuopio University Hospital (KUH) in the period between years 2000-2019. The data was collected from patient records. The efficiency of the diagnostic path was estimated with mean delays between each phase of the diagnostic path (Table 3). The phases are emergency room visit, imaging, biopsy, diagnosis and the beginning of the cytostatic treatment.

The patient dependent delay was not taken into account in these delays because of the lack of ability to detect when the symptoms had started if the emergency room visit was not needed due to the situation being rather chronic than acute. The number of cases vary in the delay analysis due to the missing date in the patient records or because every patient didn't undergo every phase. Almost every patient needed on-call imaging because of the symptoms, except those whose symptoms had developed during a longer period of time and were not rapidly progressive.

4.2 Results

The mean delays from the first emergency room visit to the confirmed diagnosis were 48.52 days in OUH and 22.67 in KUH. The longest delay in diagnostic path in OUH was the delay from first emergency room (ER) visit to imaging and the second longest was from the imaging to biopsy. The reason why the latency from ER visit to imaging is so long is because this n number included those whose lymphoma presented only as eye symptoms, so it took longer time to realize that the cause of eye symptoms was lymphoma. After excluding those patients, the mean delay from ER visit to imaging in OUH was only 2.36 days.

Table 4 shows diagnostic delays after removing rare delaying factors such as non-diagnostic biopsy, eye symptoms treated as something else than lymphoma, tumour not seen in CT imaging and shrank tumour possible due to the preoperative dexamethasone. This shows

standard diagnostic delays, which is 18.20 days in OUH and 18.45 days in KUH. Long delays and their causes are discussed later.

Table 3. Diagnostic delays in different parts of the diagnostic path without excluding.

	All		OUH		KUH	
	N	Mean (Days)	N	Mean (Days)	N	Mean (Days)
Delay from first emergency room visit to imaging	76	17.75	55	22.87	21	4.33
Delay from imaging to biopsy	81	20.70	58	23.55	23	13.52
Delay from biopsy to diagnosis	86	3.37	63	2.83	23	4.87
Delay from first emergency room visit to diagnosis	77	41.47	56	48.52	21	22.67
Delay from diagnosis to the beginning of cytostatic treatment	78	8.50	56	7.56	21	11.67

Table 4. Delays in different parts of the diagnostic path after excluding patients with massive delays in diagnostic path.

	All		OUH		KUH	
	N	Mean (Days)	N	Mean (Days)	N	Mean (Days)
Delay from first emergency room visit to imaging	64	2.52	44	2.36	20	2.85
Delay from imaging to biopsy	68	13.16	47	14.11	21	11.05
Delay from biopsy to diagnosis	73	3.23	52	2.63	21	4.71
Delay from first emergency room visit to diagnosis	65	18.28	45	18.20	20	18.45
Delay from diagnosis to the beginning of cytostatic treatment	64	8.67	45	7.36	19	11.79

The main delay causing factor in OUH is waiting for the biopsy, being 14.11 days (Table 4, *Delay from imaging to biopsy*). Also, unpleasant delay causing factor may be preoperative dexamethasone. In cases discussed below there are examples, where dexamethasone caused improve in the symptoms after the tumor was detected on the CT. Unfortunately, in these cases it could have shrunk the tumour so that there was not a target big enough for the biopsy to be taken. In the future, it would be important to make a list of PCNSL imaging characteristics in order to avoid prescribing dexamethasone if lymphoma is suspected, which could make the diagnosis established faster. Also, it would be essential to define dexamethasone dosage which would help with the perilesional oedema, but it wouldn't shrink the tumour neither clean up the CSF from tumour cells, and thus wouldn't interfere with the diagnosis. This would decrease inconvenience caused by the lack of on-call biopsy.

Among the study patients there was one case in which the delay from symptoms to diagnosis was only two days because it was possible to make the diagnosis from the CSF analysis. There was no dexamethasone administered prior to the lumbar puncture. This patient had the cytostatic treatment started in six days after the symptoms occurred, which was an extraordinary short time delay.

In KUH the overall time from symptoms to diagnosis was significantly lower than in OUH, but after excluding 13 patients with massive delaying factors the mean delay was similar, being 18.20 days in OUH and 18.45 days in KUH. Also, in KUH on-call biopsy was available, which shortened the time from imaging to biopsy in some patients. In OUH, the intraoperative frozen section of the tumour was analysed by the pathologist during the surgery, which shortened the delay of the diagnosis. At the beginning of the study period there was no intraoperative frozen section diagnostics done in KUH, but later it started to be used.

The mean delay from diagnosis to the beginning of the cytostatic treatment was 7.36 days in OUH and 11.79 days in KUH. Usually, treatments required Rickham reservoir, which is a catheter inserted into the cerebral ventricles with injection reservoir for percutaneous punctures. This was sometimes inserted during the same anesthesy after the frozen section diagnosis confirmed the tumour to be lymphoma.

5 CASES WITH SIGNIFICANT DELAYS IN DIAGNOSIS AND WHAT CAUSED THEM

Table 5 lists cases of extreme delays in diagnosis. In group 1, the main factor causing the delay was a failed biopsy. Among these patients only one out of five didn't use dexamethasone. In group 2, CT imaging didn't reveal the tumour but fortunately, MRI did. In group 3, the lesion disappeared and reappeared later. In this group, all patients were using preoperative dexamethasone. In group 4, first PCNSL symptoms were eye symptoms, the patients were treated as having vitritis first. In group 4, the treatment time varied from few months to years. In this group, it was unclear whether there was an infection first which predisposed to the genesis of lymphoma, or if the cause of the symptoms was a lymphoma from the beginning, with misdiagnosis and wrong treatment. However, it caused distort to the diagnostic times, so it was considered better to analyse these cases separately.

The delay from imaging to biopsy in group 1 and 2 shows, that if lesion disappears or the biopsy is nondiagnostic, it leads to extremely long delays in establishing of correct diagnosis. Even though the number of cases in these groups is limited (n=13), it is something to consider whether to take a risk with dexamethasone usage and possibly longer diagnostic delay, when it comes to such an aggressive disease as primary central nervous system lymphoma.

Table 5. The reasons for long delays.

	Group 1: Biopsy not diagnostic		Group 2: Imaging didn't reveal tumour		Group 3: Lesion disappeared		Group 4: Only eye symptoms	
	N	Mean (days)	N	Mean (days)	N	Mean (days)	N	Mean (days)
Delay from first emergency room visit to imaging	5	6.80	1	6.00	3	7.00	3	375.67
Delay from imaging to biopsy	5	94.40	2	27.50	3	72.67	3	12.33
Delay from biopsy to diagnosis	5	6.60	2	3.00	3	1.67	3	3.33
Delay from first emergency room visit to diagnosis	5	107.80	1	48.00	3	81.33	3	391.33

Delay from diagnosis to the beginning of cytostatic treatment	5	6.80	2	6.00	3	6.00	3	14.67

6 DISCUSSION

Since PCNSL is a very aggressive disease (Grommes & DeAngelis, 2017), thus it is important to optimize the diagnostic path. As seen in Table 4, the longest delay was caused by waiting for the biopsy. The CSF analysis could make biopsy unnecessary (Hiemcke-Jiwa et al., 2018), but it may require refraining from dexamethasone even though it has negative effect on the patient's symptoms. Hiemcke-Jiwa et al. also suggests, that in the absence of malignant cells or cells being too lytic for flow cytometry analysis, it could be beneficial to do the cytokine analysis of CSF or search for miRNA. The CSF samples of patients in our research undergone only flow cytometry analysis.

The PCNSL requires CT and MRI grading system, so it would be easier to make a decision to refrain from the dexamethasone and other glucocorticoids when lymphoma is suspected. The effect of the corticosteroids on the diagnosis of the PCNSL is a wildly discussed matter. In the analysis of 54 cases (Bullis et al., 2019), 18 patients had preoperative dexamethasone and only one patient had nondiagnostic tissue biopsy. These results suggest that short course of preoperative corticosteroids would not interfere with tissue biopsy diagnosis. They suggest that a second preoperative MRI could confirm the size and presence of the tumour when corticosteroids are used. This research was limited by the number of the cases included. Another study (Deckert et al., 2014) suggests that preoperative corticosteroids are a substantial clinical problem, and that they have been shown to prevent diagnosis in up to 50% patients. However, further research is needed whether the positive CSF fluid analysis remains positive after the corticosteroid usage, since the CSF has a lower cell count than the tumour from the beginning.

Among this research's patient group, nearly everyone's cytostatic treatment started with Bonn protocol. Starting cytostatic treatment already in the operative room as soon as positive frozen section result has arrived, could be considered in orher to shorten the delay from the diagnosis to the initiating of the treatment. In addition, the starting of the cytostatic treatment could also be faster by installation of Rickham reservoir simultaneously with stereotactic biopsy in cases of positive intraoperative frozen section. Since waiting for the biopsy already causes delay to the diagnosis, it would be essential to minimalize the delay from the diagnosis to the starting of the treatment.

Patients with persistent eye problems, such as vitritis, could benefit from early performed vitrectomy, so that possible lymphoma is differentiated from other eye diseases at as early stage as possible and the prognosis could be better without unnecessary delay in the diagnosis. Another option could be to perform MRI to detect possible asymptomatic brain lesion as soon as suspicion of lymphoma arises.

This research identified delays in the diagnostic path. The latest studies in this field have also been focused in making the diagnosis faster and safer for the patient. Many researchers are interested in the possibilities of the CSF analysis and have been discussing the benefits of the liquid CSF biopsy compared with the tissue biopsy, which is the golden standard of the diagnosis. While the CSF diagnosis holds promising research possibilities for the future, it still has relatively low diagnostic sensitivity (Hiemcke-Jiwa, 2018).

7 CONCLUSION

The most significant delay in the diagnostic path of the PCNSL was waiting for the biopsy. This could be avoided by the CSF analysis which could make biopsy unnecessary. However, further research on the CSF diagnostic is needed due to the fact that right now its sensitivity is relatively low. In the Table 6 below is listed delay causing factors and possible solutions which could minimize them.

Table 6. Possible delay causing factors identified in this research and solutions to their minimalization.

Possible delay causing factor	Possible solution
Waiting for the biopsy	On-call biopsy possibility CSF analysis leading to diagnosis
Negative CSF fluid analysis	Refraining from dexamethasone usage because it might clean the CSF from lymphoma cells. Cytokine analysis of CSF.
Nondiagnostic biopsy	Second preoperative MRI
Dexamethasone usage possibly leading to a delay in the diagnosis	Better identification of lymphoma. An oedema and its mass effect grading system which could help identify lymphoma.
Waiting for cytostatic treatment	Installation of Rickham reservoir simultaneously with stereotactic biopsy in case of positive intraoperative biopsy. A standardized starting dose of the cytostatic treatment and first dosage given in the operating room

A CT-negative tumour	Simultaneous magnetic resonance imaging in case of normal CT and severe or long lasted clinical symptoms
Eye manifestation of lymphoma treated as eye infection	Definition of criteria in collaboration with ophthalmologists on when to perform vitrectomy to exclude possible lymphoma if eye symptoms persist. Definition of criteria when to perform MRI to detect possible asymptomatic brain lesion.

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