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Primary central nervous system lymphoma in children and adolescents: Low relapse rate after treatment according to Non-Hodgkin-Lymphoma Berlin-Frankfurt-Münster protocols for systemic lymphoma

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Running heads: good outcome of childhood primary CNS lymphoma

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Primary CNS lymphoma (PCNSL) represent a rare subtype of Non-Hodgkin lymphoma (NHL) restricted to the CNS. In adults, PCNSL are associated with poor prognosis.(1) Patients with predisposing conditions such as immunodeficiency have an increased risk of PCNSL.(2) In children very little is known about PCNSL. The “International Primary CNS Lymphoma Collaborative Group” (IPCG) reported a retrospective collection of 29 PCNSL patients who had been treated with various treatment strategies.(3) Another retrospective review from North America identified 12 PCNSL patients.(4) And the recent retrospective mono-center experience of the Seoul Children Hospital summarized six patients treated achieving relapse free survival in five patients.(5) Taking these cases together with earlier case reports (2, 4, 6-10) far below hundred cases of PCNSL in children and adolescents were published until today.

In the current study of the population based NHL-BFM data (Berlin-Frankfurt-Muenster), the frequency, clinical characteristics, diagnostic difficulties, treatment and outcome of 17 pediatric PCNSL patients are discussed. All patients were uniformly diagnosed and treated according to NHL-BFM protocols. The study aims to add relevant information to the optimal treatment. And by describing the prolonged and difficult courses of diagnosis and differential diagnosis the current report might increase the attention for pediatric patients with PCNSL.

Children and adolescents diagnosed with any subtype of NHL were registered to the NHL-BFM-center after patients and/or guardians informed consent. Standard staging investigations included examination of cerebrospinal fluid (CSF), cranial computed tomography (CT) and/or cranial magnetic resonance imaging (MRI). CNS disease was diagnosed in patients with 1) intracerebral/intraspinal mass(es) (ICM) and/or 2) cranial nerve palsy (CNP) not caused by an extradural mass, and/or 3) blasts in the CSF. Epidural NHL was not considered as CNS disease. NHL were classified according to WHO Classification and centrally reviewed by NHL-BFM reference pathologists; except for cases 4 and 12. CSF slides were centrally reviewed (WW, AR, BB). Patients were treated according to the
protocols NHL-BFM90(11), NHL-BFM95(12), or B-NHL BFM04(13). Institutional review board approvals were obtained before the inclusion of patients.

For statistical analyses differences between subgroups were examined by chi$^2$ or Fisher exact test. Probability of survival (pOS) was calculated from diagnosis to first event (death, progression/relapse/nonresponse, second malignancy) or to last follow-up using the Kaplan and Meier method. Differences were compared using the log-rank test, and the standard error (SE) was calculated according to Greenwood. Statistical analysis was performed using the SAS program (SAS, version 9.13 SAS Institute Inc, Cary, NC).

Among 3,740 pediatric or adolescent NHL patients registered between 1990 and 2011, 17 patients with PCNSL were identified; 12 immunocompetent and five immunocompromised patients. Median age was 13.3 (1.3-17.9) years. The histological diagnosis was peripheral T-cell lymphoma (PTCL) in one patient, anaplastic large cell lymphoma (ALCL) in five patients and mature aggressive B-cell lymphoma (B-NHL) in eleven cases, characteristically shown in figure 1. EBER in situ hybridization to identify Epstein-Barr-Virus (EBV) antigens in the lymphoma tissue was performed in five cases (1, 5, 14, 15, and 16) and was positive in one (case 1) and negative in four samples.

In all but one patient (case 2), CT/MRI showed solid CNS lymphoma manifestation(s) including one patient (case 13) with one large intraspinal manifestation. Six patients (38%) had multiple intracerebral lesions. One patient was diagnosed with primary leptomeningeal disease with 1000 lymphoma cells/µl CSF and cranial nerve palsy (case 2).

Presenting symptoms were often symptoms of increased intracranial pressure with headache (53%), nausea (53%), and vomiting (47%) or ataxia (41%) and symptoms of cranial nerve disorders (59%). Median interval between onset of symptoms and the diagnostic procedure which led to the diagnosis of PCNSL was eight (2-20) weeks. Seven patients were treated for meningitis/encephalitis and one patient was treated for multiple sclerosis. Nonresponse to this anti-infectious treatment resulted in the tumor biopsy which allowed PCNSL diagnosis in these eight patients. At the time of PCNSL diagnosis, seven patients presented with severe
neurological complications as hemiparesis (one), seizures (three), incomplete paraparesis (two), and somnolence requiring immediate trepanation (one). Five patients suffered from underlying immunodeficiency or immunomodulation (Table 1). Patients were treated according to NHL-BFM protocols with pre-phase followed by six 5-day courses of chemotherapy summarized in Figure 2a.(11-13) ALCL patients received cranial radiotherapy (CRT) of 24 Gy after chemotherapy.

With a median follow-up of 7.5 (2.4-12.1) years, the 3-year probability of survival (OS) of all 17 PCNSL patients was 63±12% and 92±8% for the 12 immunocompetent patients (Figure 2). All five patients with underlying diseases died 0, 1, 4, 16, and 31 months after start of treatment (Table 1). Among the 12 immunocompetent patients, one event was reported in an ALCL patient who suffered leptomeningeal relapse nine weeks after end of treatment and died of lymphoma progression (case 2).

Concerning neurological outcome and late effects, two patients suffered from reduced visual acuity due to atrophy of the optical nerve related to prolonged increased intracranial pressure (cases 6, 10). One patient suffered from epilepsy after end of treatment (case 6), and one patient suffered from panhypopituitarism after surgical lymphoma resection localized in the suprasellar midline (case 5). In the remaining eight patients alive, no relevant neurologic deficit was reported 6, 21, 29, 41, 48, 80, 84, and 84 months after start treatment of PCNSL.

PCNSL represent a rare NHL-subtype in adults and children associated with poor prognosis. The current PCNSL series of the NHL-BFM-group represents the largest series of uniformly diagnosed and treated pediatric PCNSL patients. Patient characteristics and histological diagnoses of the NHL-BFM cohort are similar to earlier reports except for the initial serum LDH levels, which are normal for the majority of NHL-BFM patients, which is in contrast to the IPCG cohort with elevated LDH levels 53% of 17 cases with available data.(3) The detailed chart review of the NHL-BFM PCNSL patients documents for the first time the complicated medical histories until definite diagnosis in pediatric PCNSL patients. The onset of seizures lead to the shortest intervals between first symptoms and definite diagnosis.
Especially in adolescents with non specific symptoms the diagnosis of PCNSL is complicated. Although a rare disease, PCNSL should be taken into account in healthy children and adolescents with non specific neurological symptoms.

The performance status (PS) at diagnosis has been reported as prognostic factor.(3) The current NHL-BFM data cannot support an in- or decrease of treatment intensity according to general condition at diagnosis. Any other evaluation of reported prognostic parameters like age, LDH, or cortical versus deep brain lesions could not be tested in the NH-BFM series as only one immunocompetent patients suffered relapse.

All five NHL-BFM patients with severe underlying diseases died due to toxicity or complications of the underlying disease (n=4) and lymphoma progression without PCNSL treatment (n=1). Abla reported four PCNSL with immunodeficiency of whom one died of infectious complications after treatment.(4) The IPCG cohort included three patients with immunodeficiency but outcome is not specified.(3) In addition, individual cases of pediatric PCNSL patients with immunodeficiency were reported.(2, 7) In conclusion, the number of pediatric PCNSL patients with immunodeficiency is limited and the individual medical course variable. However, the NHL-BFM-group will critically discuss treatment recommendations when consulted for PCNSL patients with immunodeficiency taking into account the experiences and guidelines for NHL-treatment in patients with chromosomal instability syndromes.(14)

In NHL-BFM series only one out of the 16 patients treated for the PCNSL suffered relapse. With the limitation of small numbers, the disease control of PCNSL treated according to NHL-BFM protocols for CNS positive NHL seems therefore comparable to that of systemic NHL with CNS involvement.(15) The relapse rate in the current NHL-BFM series is remarkably lower than in the IPCG cohort with ten relapses in 29 patients (34%), all suffering from isolated CNS relapse.(3) The 2-year progression-free survival of 61% and the 3-year OS of
82% for IPCG cohort might indicate insufficient frontline treatment at least for a subset of patients. In contrast, the intensive NHL-BFM treatment might reduce the rate of relapses but also select for resistant disease at relapse. This hypothesis is supported by a recently reported series of six pediatric PCNSL patients treated with intensive protocols LMB-FAB96 in five patients and CCG-106B in one patient and the observation of only one relapse but resistant disease at the time of relapse.(5)

In the current series only ALCL patients but not B-NHL patients received cranial radiotherapy per protocol. Interestingly, the only relapse occurred in one of the five ALCL patients but none in the B-NHL patients. This supports the conclusion of the above mentioned report which stated that PCNSL of B-NHL subtype can be successfully treated without irradiation.(5)

In adults, PCNSL are also rare and aggressive lymphoma subtypes with 32-77% five-year survival. Whether the differences in outcome between PCNSL in children and adults are related to treatment regimens or to differences in the lymphoma biology or differences in co-morbidities remains open.

In conclusion, the rare subtype of PCNSL in pediatric patients can be treated successfully with protocols designed for pediatric NHL patients suffering from CNS positive systemic NHL. However, the treatment of pediatric PCNSL patients with immunodeficiency or other severe underlying diseases remains challenging.
Conflict of Interest:

Authors declare no competing financial interests in relation to the work described.

Authorship Contributions:

HT, OM, PL, AvS, GF, JW, HJ, WW, AR and BB recruited the patients, provided clinical data and performed the analyses; MZ performed the statistical analysis; IO and WK performed reference pathology and EBER i. s. hybridization; WW, AR and BB performed central cytomorphological review of CSF cytospins; HT and BB coordinated the research; HT, MZ and BB wrote the paper. BB was the principal investigator and takes primary responsibility for the paper; all authors read and approved the paper.
References


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DOD: death of disease; DLBCL: diffuse large B-cell lymphoma, ALCL: anaplastic large cell lymphoma; PTCL: peripheral T-cell lymphoma; B-BHL nfc: B-cell lymphoma not further specified

* congenital variable immunodeficiency syndrome, parents refused any PCNSL directed treatment, died of lymphoma progression

§ heart transplantation fifteen months prior to the diagnosis of PCNSL and history of two episodes of severe acute graft rejection and modified immunosuppression, received by 50% reduced doses of cytostatic agents due to toxicity and died of graft failure after 5th course of chemotherapy

+ patient was admitted to hospital due to neurological symptoms, received anti-infectious and immunosuppressive treatment for five months until the diagnosis of PCNSL could be established At that time in vegetative state with PS <20% at PCNSL diagnosis. Due to persistent vegetative state and new radiological lesions in the brain the lymphoma treatment was modified and finally stopped after five courses. The patient died 27 months after the end of treatment due to pneumonia.

* suffered from a severe congenital retardation and colitis ulcerosa treated with glucocorticoid steroids and related Cushing syndrome, died of treatment related toxicity at day 13 after start of treatment

# lymphoma was completely resected, histological subtyping was complicated and time consuming and when reference diagnosis was available parents refused further treatment
Figure Legends:

Figure 1: Pathological and immunohistochemical findings of PCNSL of diffuse large B-cell subtype in patient No.16. At low magnification a diffuse infiltration of the CNS-tissue by mononuclear cells can be observed (Hematoxylin- Eosin x50), B: At high magnification large blastic lymphoid cells are seen in between glial cells and glial stroma (Hematoxylin- Eosin x400). The large cells express the B-cell marker CD20 (C and D, x200), areas with dense infiltration (C) and areas with only scattered blasts (D) are present within the same biopsy. The large cells express BCL2 (E, x200) and show a high proliferation index (F, KI67 x100). Provided by Ilske Oschlies, Kiel.

Figure 2: Outline of the treatment schema (figure 2a). Probability of survival for all 17 patients with primary central nervous system lymphoma registered in the NHL-BFM center between 1990 and 2011 (Figure 2b). And probability of survival for 12 immunocompetent patients with primary central nervous system lymphoma registered in the NHL-BFM center between 1990 and 2011 (Figure 2c).

P: Prephase; IT: intrathecal treatment; HD: high dose; RT: cranial radiotherapy; ALCL: anaplastic large cell lymphoma
immunocompetent PCNSL patients (N=12, 1 event)