Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO).

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ABSTRACT

Central nervous system involvement by malignant cells is a rare complication of Waldenström macroglobulinemia, and this clinicopathological entity is referred to as the Bing-Neel syndrome. There is currently no consensus on the diagnostic criteria, therapeutic approaches and response evaluation for this syndrome. In this series, we retrospectively analyzed 44 French patients with Bing-Neel syndrome. Bing-Neel syndrome was the first manifestation of Waldenström macroglobulinemia in 36% of patients. When Waldenström macroglobulinemia was diagnosed prior to Bing-Neel syndrome, the median time interval between this diagnosis and the onset of Bing-Neel syndrome was 8.9 years. This study highlights the possibility of the occurrence of Bing-Neel syndrome without any other evidence of progression of Waldenström macroglobulinemia. The clinical presentation was heterogeneous without any specific signs or symptoms. Biologically, the median lymphocyte count in the cerebrospinal fluid was 31/mm^3. Magnetic resonance imaging revealed abnormalities in 78% of the cases. The overall response rate after first-line treatment was 70%, and the overall survival rate after the diagnosis of Bing-Neel syndrome was 71% at 5 years. Altogether, these results suggest that Bing-Neel syndrome should be considered in the context of any unexplained neurological symptoms associated with Waldenström macroglobulinemia. The diagnostic approach should be based on cerebrospinal fluid analysis and magnetic resonance imaging of the brain and spinal axis. It still remains difficult to establish treatment recommendations or prognostic factors in the absence of large-scale, prospective, observational studies.

Introduction

Waldenström macroglobulinemia (WM) is a rare, indolent B-cell lymphoproliferative disorder, classified as lymphoplasmacytic lymphoma in the 2008 World Health Organization classification. It has a wide spectrum of complications, mostly related to the monoclonal M-component (e.g. hyperviscosity syndrome, cryoglobulinemia, cold agglutinin hemolytic anemia, IgM-related neuropathies or tissue deposition). Neurological complications are dominated by IgM-related neuropathies (such as demyelinating peripheral neuropathy with IgM antibody activity against myelin-associated glycoprotein), but direct involvement of the central nervous system (CNS) by malignant lymphoid cells can occur. It was first described in 1936 by Jens Bing and Axel Neel, who reported two cases with hyperglobulinemia and CNS involvement,[1] 8 years before the first description of WM was reported by Jan Waldenström.[2]

Bing-Neel syndrome (BNS) is a rare and probably under-recognized complication of WM. Limited information is currently available in the literature, which is mostly based on case report descriptions. There is currently no consensus on the diagnostic criteria, treatment strategies and evaluation of response. BNS can present as either a diffuse or tumoral form. In the diffuse form, malignant cells infiltrate the leptomeningeal space, periventricular white matter or spinal cord. The tumoral form can be characterized by the presence of an intraparenchymal mass or nodular lesion. The distinction between these two forms is mainly based on imaging data.

We report the largest retrospective study to date in order to better characterize the clinical symptoms, biological features, radiological findings and clinical outcomes of patients with BNS.

Methods

Patients registered in the databases of 17 French centers were retro-

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spectively analyzed in this multicenter, observational study. Patients were included if they had non-ambiguous cytological or histopathological evidence of CNS involvement by a lymphoplasmacytic proliferation, concomitant with a diagnosis of systemic WM according to the Second International Workshop on WM.[3] We excluded all patients with a diagnosis of aggressive B-cell lymphoma resulting from the transformation of WM and patients presenting with neurological symptoms without clear cytological or histopathological evidence of CNS infiltration by lymphoplasmacytic cells. The study was approved by an independent ethics committee and was conducted in accordance with the Declaration of Helsinki.

The response criteria for BNS were defined as follows: complete remission when clinical symptoms disappeared with normalization of cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings; uncertain complete remission when clinical symptoms disappeared with either normalization of MRI but without CSF evaluation available at the end of the treatment, or normalization of CSF without MRI evaluation; and partial response when there was clinical, CSF or radiological partial improvement, including patients with neurological sequelae. Treatment failure was defined as no improvement or progression of clinical symptoms, CSF involvement or radiological findings.

Progression-free survival and overall survival were plotted using the Kaplan-Meier method, and the curves were compared using the log-rank test.

Results

Patients' characteristics

Forty-four patients treated for BNS between 1995 and 2014 were identified at 17 French centers. At the time of BNS diagnosis, the median age was 63 years (range, 47-84 years) and 35 patients (80%) were male. In 16 cases (36%), BNS was the first manifestation of WM; five of these patients had a previous diagnosis of monoclonal gammopathy of undetermined significance and the median time between the diagnosis of this gammopathy and that of BNS was 48 months (range, 9 to 108 months). For the 28 (64%) patients previously diagnosed with WM, the median time interval between the diagnosis of WM and that of BNS was 8.9 years (range, 9 months to 24.7 years). For 20 (71%) of the 28 patients previously diagnosed with WM, BNS occurred independently of a systemic progression of WM. Thirteen patients (33%, 13/39 patients with available data) were reported to have a diagnosis of peripheral neuropathy before the onset of BNS, and anti-glycolipid antibodies were positive in six (46%) of them [5 patients with anti-myelin-associated glycoprotein (anti-MAG) antibodies and 1 patient with anti-ganglioside (anti-GM1) antibodies]. The patients' characteristics are summarized in Table 1.

Clinical presentation of Bing-Neel syndrome

The median time interval between the appearance of neurological symptoms and the diagnosis of BNS was 4 months, with an upper limit of 36 months. The interval was longer than 1 year in nine (20%) patients. The symptoms or signs that led to the diagnosis of BNS were extremely heterogeneous, the most common being a balance disorder or disturbed gait [21 patients (48%), with ataxia described in 15 patients and dizziness in 6 patients] and cranial nerve involvement [13 patients (36%), with a predominance of facial or oculomotor nerve palsy]. Others ocular symptoms were decreased visual acuity or blurred vision. Other signs were poor performance status (>2) (12/44, 27%), cognitive impairment with frontal syndrome, memory loss or dementia (12/44, 27%), sensory deficit with hypoesthesia, dysesthesia or paresthesia (11/44, 25%), headache (8/44, 18%), pain (mainly localized in the back, neck or limbs) (8/44, 18%), cauda equina syndrome (6/44, 14%), motor deficit (6/44, 14%) and dysarthria or aphasia. Four patients with a tumoral form presented with convulsions, hemiparesis or aphasia. No intraocular involvement was documented in this series.

Biological results

CSF analysis was performed for all patients. The median lymphocyte count in CSF was 31 cells/mm^3 (range, 1-3990). Monotypy, assessed by flow cytometry, could be confirmed in 31 (94%) of 33 cases with available data, with monotypic kappa light chain restriction in 84% and lambda restriction in 16% of the cases. The diagnosis of BNS for the 13 patients with no monotypy relied on the

Table 1. Patients' characteristics.

Median age (years)	63 (range 47-84)
≥60 years (n)	75% (33/44)
Sex male/female (ratio)	35/9 (3.9/1)
Previously diagnosed WM	64% (28/44)
IPSS score at WM diagnosis (n=17/28)	
1	70% (12/17)
2	24% (4/17)
3	6% (1/17)
Median number of prior regimens for WM	2 (range 0-8)
Progressive WM disease	29% (8/28)
Median time interval between the diagnoses of WM and BNS (months)	107 (9-297)
Not-previously diagnosed WM	36% (16/44)
IPSS score at WM diagnosis (n=12/16)	
1	33% (4/12)
2	50% (6/12)
3	17% (2/12)
Serum IgM level (g/L)	12,3 (range 0.35-60)
CSF analysis	
Lymphocyte count (per mm^3)	31 (range 1-3990)
Protein level (g/L)	1,83 (range 0.39-7.8)
Diffuse/ tumoral form	
Diffuse	93% (41/44)
Tumoral	9% (4/44)
Median time interval between the first neurological symptoms and BNS diagnosis (months)	4 (range 0-36)
MRI abnormalities	78%
First-line treatments	
Cytarabine or methotrexate-based high-dose regimens	52% (23/44)
Rituximab (alone or in combination)	45% (20/44)
Fludarabine-based regimens	14% (6/44)
Intrathecal chemotherapy (alone or in combination)	73% (32/44)
Autologous stem-cell transplantation	14% (6/44)
Radiotherapy	14% (6/44)
Response rates	
Overall response rate	70% (31/44)
Complete response/Uncertain complete response	29% (13/44)
Partial response	41% (18/44)
Stable or progressive disease	30% (13/44)

BNS: Bing-Neel syndrome; WM: Waldenström macroglobulinemia; IPSS: International Prognostic Scoring System; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

cytology of CSF or the histopathology of a CNS biopsy demonstrating the lymphoplasmacytic infiltration. The median protein level in CSF was 1.83 g/L (range, 0.39-7.8) and was increased (>0.4 g/L) in 39 (95%) cases. The diagnosis was assessed by the histopathology of a meningeal or a brain biopsy in eight cases. No data are available in this series regarding electrophoresis of CSF as this was not performed in routine practice.

At the time of the diagnosis of BNS, the median serum IgM level was 12.3 g/L (range, 0.35-60 g/L). Six patients had a concomitant immunophenotypic characterization of blood or bone marrow and CNS specimens, which was concordant in all cases.

Radiological findings

Magnetic resonance imaging was performed in 41 (93%) patients and was abnormal in 32 (78%) cases according to the local physicians' interpretation. Seventeen patients had a cerebral computed tomography scan, which was abnormal in six (35%). All three patients who did not have MRI imaging had a normal cerebral computed tomography scan.

Two neuroradiologists reviewed the available MRI analysis of ten patients (all 10 patients had brain MRI analysis, and 7 of them had concomitant spine MRI analysis) before or immediately after the diagnosis of BNS. Brain parenchymal involvement was present in the classical sequences (characterized by high signal in T2 and iso- or hypointensity in T1 sequences) in six patients (6/10) with a predilection for sub-cortical or peri-ventricular locations. Medullary parenchymal involvement was found in two out of seven patients with medullary MRI imaging. One patient (1/10) had evidence of optic nerve involvement. A brain diffusion study was available for six patients; the diffusion sequence was normal in four patients and abnormal in two patients who showed cerebral vasogenic edema. Gadolinium injection also revealed cerebral or medullary leptomeningeal involvement in eight out of ten patients. Six out of seven patients with medullary MRI available had cauda equina enhancement after gadolinium injection. Finally, dura matter involvement, better visible after gadolinium injection, was present in six patients (6/10).

Table 2. Chemotherapeutic regimens used.

	First-line (n=44)	Second-line for refractory patients (n=7)	Second-line for relapsed patients (n= 10)
Methotrexate HD			
Alone (+/- R)	14% (6)	29% (2)	
+ cytarabine HD	7% (3)		10% (1)
+ cytarabine HD + CVP	2% (1)		
+ CHOP (+/-R)	11% (5)		
+ vincristine-procarbazine	2% (1)		
+ BVP	2% (1)		
+ CAP	2% (1)		
Cytarabine HD			
+ DHAP/C + R	7% (3)		10% (1)
+ ifosfamide + R	5% (2)		10% (1)
Fludarabine (+/-R)	7% (3)	14% (1)	10% (1)
+ cyclophosphamide (+/-R)	7% (3)		
+ mitoxantrone		14% (1)	
Intrathecal chemotherapy			
Alone	5% (2)		
+ R	2% (1)		
+ ASCT	2% (1)		
Intrathecal rituximab		14% (1)	
Radiotherapy alone		14% (1)	10% (1)
Rituximab alone	2% (1)		10% (1)
CD (+/-R)	5% (2)		
Bendamustine +R	2% (1)		20% (2)
CHOP (+/-R)	5% (2)		
CVP	2% (1)		
Others			
Cladribine	2% (1)		10% (1)
Chlorambucil+R	2% (1)		
Chlorambucil + etoposide	2% (1)		
PAD	2% (1)		
ICE		14% (1)	
Alemtuzumab			10% (1)

R: rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; BVP: carmustine, etoposide, prednisone; CAP: cyclophosphamide, doxorubicin, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DHAP/C: dexamethasone, cytarabine, cisplatin/carboplatin; CD: cyclophosphamide, dexamethasone; PAD: bortezomib, doxorubicin, dexamethasone; ICE: ifosfamide, carboplatin, etoposide; GEMOX: gemcitabine, oxaliplatin; HD: high-dose.

Table 3. Responses according to first-line regimens.

First-line regimens	Responses
Methotrexate HD	
Alone (+/- R)	1 CR (with radiotherapy), 3 PR, 2 PD
+ cytarabine HD	2 PR, 1 PD
+ cytarabine HD + CVP	1 PR
+ CHOP (+/-R)	2 CR, 3 PR (including 1 ASCT)
+ vincristine-procarbazine	1 PD
+ BVP	1 PD
+ CAP	1 PD
Cytarabine HD	
+ DHAP/C + R	2 CR (including 2 ASCT), 1 PR
+ ifosfamide + R	1 CR (including 1 ASCT), 1 PR
Fludarabine (+/-R)	2 CR, 1 PD
+ cyclophosphamide (+/-R)	2 PR, 1 PD
Intrathecal chemotherapy alone	1 PR, 1 PD
+ R	1 CR
+ ASCT	1 PR
Rituximab alone	1 PR
CD (+/-R)	2 PD
Bendamustine +R	1 PR (with radiotherapy)
CHOP (+/-R)	2 CR (including 1 ASCT)
CVP	1 PD
Others	
Cladribine	1 CR
Chlorambucil+R	1 PD
Chlorambucil + etoposide	1 CR
PAD	1 PR

R: rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; BVP: carmustine, etoposide, prednisone; CAP: cyclophosphamide, doxorubicin, prednisone; CVP: cyclophosphamide, vincristine, prednisone; DHAP/C: dexamethasone, cytarabine, cisplatin/carboplatin; CD: cyclophosphamide, dexamethasone; PAD: bortezomib, doxorubicin, dexamethasone; ICE: ifosfamide, carboplatin, etoposide; GEMOX: gemcitabine, oxaliplatin; HD: high-dose; CR: complete response; PR: partial response; PD: progressive disease; ASCT: autologous stem-cell transplantation.

Treatment and response rates

First-line treatment consisted of systemic chemotherapy in 40 (91%) cases and was based on high-dose chemotherapy in 52% of cases (methotrexate and/or cytarabine). Intrathecal chemotherapy was given to 32 (73%) patients. Fludarabine-based regimens were used in six patients (14%) (Table 2). Rituximab was part of the first-line treatment in 20 (45%) patients. Autologous stem-cell transplantation was performed as first-line therapy in six (14%) patients; conditioning regimens used were carmustine-etoposide-cytarabine-melphalan (BEAM) for two patients, bendamustine-etoposide-cytarabine-melphalan (Be-EAM), total body irradiation with melphalan, thiotepa-busulfan-cyclophosphamide and thiotepa-busulfan-melphalan. For six patients, the treatment was completed by whole-brain radiotherapy. Two patients received only intrathecal chemotherapy (only 1 patient responded). First-line treatments are detailed in Table 2 and responses according to first-line regimens are summarized in Table 3.

After first-line treatment, the overall response rate of patients with BNS was 70% [complete response, n=1 (2%); uncertain complete response, n=12 (27%); partial response, n=18 (41%)]. Stable disease or progression was observed in 13 (30%) patients. All six patients who underwent autologous stem-cell transplantation responded, with four complete responses and two partial responses. After first-line treatment, the median serum M immunoglobulin level had decreased to 3 g/L. Among the 31 patients who responded to the first-line treatment, ten (30%) relapsed after a median of 16.5 months (range, 2-68 months), and seven (70%) responded to a second line of therapy. Seven of the 13 refractory patients underwent salvage therapy; only three of them (43%) responded and six patients died before salvage therapy could be initiated. Salvage treatments are summarized in Table 2.

We could not identify any difference in the response rates according to the first-line chemotherapy regimens used. The responses were heterogeneous but no predictive marker for treatment response based on biological parameters or chemotherapeutic regimens used could be identified.

Survival

The median follow-up period of living patients was 4.6 years after the diagnosis of BNS and 11.4 years after the diagnosis of WM. The overall survival rate after BNS diagnosis was 71% at 5 years and 59% at 10 years (Figure 1). The median overall survival from the time of the diagnosis of WM was 17.1 years. The median progression-free survival after the first-line treatment of BNS was 26 months (Figure 2). Fourteen (32%) patients died, nine due to BNS, one of BNS-treatment-related causes, one due to WM progression and three due to other causes (myocardial infarction, infection secondary to chronic obstructive pulmonary disease and death of unknown cause for one patient).

Discussion

To our knowledge, this series of patients with BNS is the largest ever studied. We used stringent inclusion criteria for all patients who had to have well-documented CNS involvement as confirmed by cytological and immunophenotyping analysis of CSF, or histopathological analysis of a brain biopsy. BNS is generally considered to be a rare complication of WM, but some cases are probably under diagnosed. This could be explained by the lack of specificity of clinical symptoms. A diagnosis of BNS should be considered in patients with WM in the case of any unexplained and persistent neurological manifestations. The first symptoms appeared in this series at a median of 4 months before the BNS diagnosis, although the delay was longer than 1 year for 20% of the patients. Another critical point that could explain the under recognition of BNS is the frequent occurrence of BNS independently of any systemic progression of WM (70% of cases previously diagnosed with WM in this series). In one third of the cases, BNS was the first manifestation of WM, and this study also highlights the possibility of a very late occurrence of BNS (up to 25 years after the diagnosis of WM). In our series, the incidence of peripheral neuropathies among the patients was 33% (as expected in a global population of WM patients). This represents another major pitfall in the diagnosis of BNS as peripheral neu-

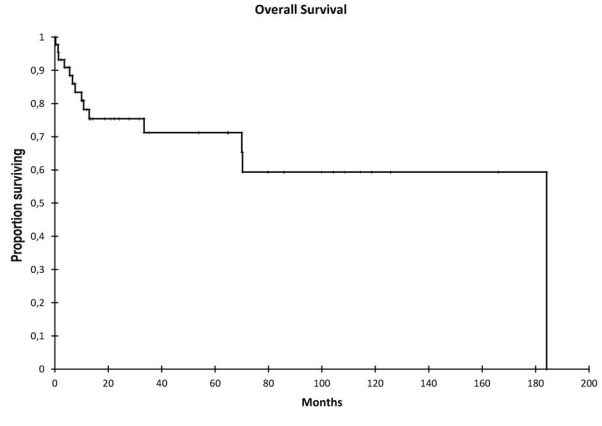

Figure 1. Overall survival of patients with BNS since their diagnosis.

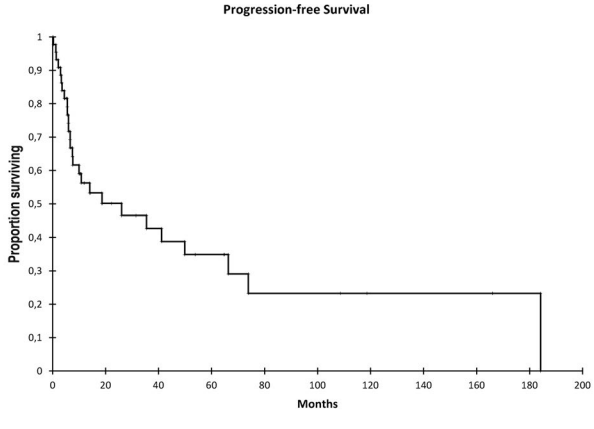

Figure 2. Progression-free survival of patients with BNS since their first-line treatment.

Table 4. Review of the 33 cases of BNS published between 1995 and 2014.

Reference	Age (years)*, sex	Interval between WM diagnosis and BNS onset (months)	Clinical presentation	Form: infiltrative (I), tumoral (T)	CSF analysis Leukocytes (/mm³)	CSF analysis Proteins (g/L)	Treatments
Imai F *et al*. 1995	65, F	36	Confusion, memory loss, disorientation	T	NA	NA	Radiotherapy (40 Gy)
Richards AI *et al*. 1995	56, M	48	Sudden loss of consciousness, right facial palsy, seizure	I	NA	NA	Cladribine
Civit T *et al*. 1997	70, M	60	Partial epilepsy	T	NA	NA	Surgery, radiotherapy
Philipeau F *et al*. 1999	74, F	96	Cerebellar syndrome, dysarthria, nystagmus, hypoacusia	I	2	0.22	Cyclophosphamide
Abad X *et al.* 1999	66, M	84	Proximal weakness, areflexia	I	135	1.6	IVAM, intrathecal chemotherapy, dorsolumbar irradiation
	61, M	60	Proximal weakness, areflexia, paraesthesia	I	12	2.45	HD methotrexate/vepeside/ifosfamide, intrathecal chemotherapy, dorsolumbar irradiation
	68, F	6	Distal weakness, areflexia, abducens palsy	I	66	1.7	IVAM, intrathecal chemotherapy
	50, M	48	Paraparesis, areflexia	I	2	0.46	CHOP, intrathecal chemotherapy, radiotherapy
Welch D *et al.* 2002	82, M	180	Progressive cognitive decline, weakness in the arms and legs	I+T	NA	Slightly increased	Gammaglobulin infusions, rituximab
Delgado J *et al.* 2002	77, M	4	Left hemiparesis	T	NA	NA	Whole brain irradiation (45 Gy), cyclophosphamide/cladribine/prednisone
Massengo S *et al.* 2003	77, F	120	Cauda equina syndrome	I	39	9.4	Intrathecal chemotherapy, cyclophosphamide/vindesine/prednisone
Bhatti M *et al.* 2005	61, F	120	Hemiparesis, headache, diplopia, confusion, visual hallucinations	I	210 (Ly 77%)	1.89	Intrathecal chemotherapy
Garderet L *et al.* 2006	80, M	Concomitant	Dizziness, progressive muscle weakness, diffuse bone pain	I	460 (Ly 83%)	16	No treatment
Kim HD *et al.* 2007	51, F	36	Headache	I	43 (Ly 52%)	1.81	Whole brain irradiation, fludarabine
Sutter R *et al.* 2007	70, M	6	Headache, nuchal rigidity, double vision, dysphagia, dysarthria	I	106	3.1	Radiotherapy, steroid
Donix M *et al.* 2007	54, M	Concomitant	Aphasia	I	NA	0.45	NA
Drappatz J *et al.* 2008	64, M	NA	Headache, aphasia	I	2 (Ly 71%)	4.36	Temozolomide
Kolbaske S *et al.* 2009	60, M	168	Gait ataxia, seizure-like events, intention tremor of upper limbs	I+T	50 (Ly 80%)	3.5	Fludarabine/cyclophosphamide, intrathecal rituximab
Grewal JS *et al.* 2009	67, M	120	Confusion, slurred speech, ataxia	I	40 (Ly 78%)	1.12	Whole brain irradiation (30 Gy), fatigue, rituximab, intrathecal chemotherapy (liposomal cytarabine)
Kim HJ *et al.* 2009	75, M	36	Dysarthria, memory impairment, dizziness, ataxic gait	I	81 (Ly 50%)	0.49	Chlorambucil, methylprednisolone
Stacy RC *et al.* 2010	51, M	48	Decreased eye movements, vision loss	I+T	6 (Ly 30%)	2.55	Steroid, HD methotrexate, intrathecal chemotherapy, ASCT
Malkani RG *et al.* 2010	67, F	144	Headache, aphasia, facial paralysis	I	11 (no B cells)	1.36	R-MPV, fludarabine
Doshi RR *et al.* 2011	57, M	108	Bilateral visual loss	I	NA	NA	HD methotrexate, intrathecal chemotherapy, radiotherapy

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Jennane S *et al*. 2012	57, M	72	Isolated left ptosis	I+T	60	2	R-DHAOx, HD methotrexate, intrathecal chemotherapy, ASCT
Ritzenhalter T *et al*. 2013	55, F	Concomitant	Headache, diplopia, meningitis, nystagmus, mood disorders	I	230 (Ly 95%)	1.4	MPV, intrathecal chemotherapy, R-DHAP
Rigual D *et al*. 2013	53, M	24	Dizziness, nausea, vomiting	T	NA	NA	Surgery, radiotherapy
Morita K *et al*. 2013	63, M	30	Recurrent light aversion (left optic neuritis)	I	NA	NA	R-MPV
Abdallah AO *et al*. 2013	50, M	84	Headaches, blurred vision, transient amnesia, nausea, vomiting	I	113 (Ly 92%)	2.17	DT-PACE, intrathecal chemotherapy, ASCT
Gupta N *et al*. 2014	67, F	29	Cognitive decline, fatigue	I	NA	NA	R-DHAC, intrathecal chemotherapy, ASCT
Rigamonti A *et al*. 2014	72, M	108	Spinal cord compression between C2 and C4 level	I+T	96 (Ly 90%) with no evidence of malignant cells	12.88	Dexamethasone before surgery, R-methotrexate/ cytarabine/thiotepa, intrathecal chemotherapy, ASCT
Nagaharu K *et al*. 2014	74, M	Concomitant	Cognitive impairment	I	NA	NA	intrathecal chemotherapy, cyclophosphamide, R-fludarabine
Hughes MS *et al*. 2014	56, M	24	Headaches, blurred vision, visual field loss, visual acuity loss	I	10 (Ly 95%)	NA	Dexamethasone, intrathecal chemotherapy, R-CHOP
	67, F	144	Blurred vision, visual field defect	I	0	NA	Dexamethasone, R-HD methotrexate, R-bendamustine

+ Age is indicated at the time of the BNS diagnosis. M: male; F: female; CSF: cerebrospinal fluid; Ly: lymphocytes; HD: high-dose; ASCT: autologous stem-cell transplantation; R: rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; IVAM: ifosfamide, vepeside, aracytine, methotrexate; DHAP/C/Ox: dexamethasone, cytarabine, cisplatin/carboplatin/oxaliplatin; MPV: methotrexate, procarbazine, vincristine; DT-PACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; NA: not available.

ropathy can mimic the symptoms of BNS (ataxia, sensory or motor deficit, pain), and an initial attribution of symptoms to peripheral neuropathy could delay the diagnosis of BNS. Thus BNS should be considered even in patients with a previously diagnosed peripheral neuropathy who complain of worsening symptoms or who are not responsive to treatment. A differential diagnosis to consider is another rare syndrome: the CANOMAD syndrome, characterized by the association of a chronic ataxic neuropathy, ophthalmoplegia, the presence of IgM monoclonal protein and anti-diasialosyl antibodies.

The diagnostic approach to BNS should be based on the findings of a lumbar puncture and MRI imaging of the brain and spinal cord. The CSF must be analyzed promptly after its collection. The cytological examination should be associated with immunophenotyping by flow cytometry in order to confirm the monotypy and the B-cell origin of the malignant cells and to demonstrate an immunophenotypic profile compatible with a WM proliferation. Electrophoresis performed on the CSF could show the M-component, but this examination is not always performed in routine practice; it is not sufficient alone and not specific enough to formally assess the CNS infiltration by tumor cells. The imaging protocol for the brain study of a suspected or known BNS should include T1-based images before and after gadolinium enhancement, T2 and T2* sequences, diffusion sequences, as well as delayed FLAIR images after gadolinium enhancement. The assessment should be completed with the study of the medulla, covering the whole spine, including T1 images before and after gadolinium enhancement, as well as T2 images. These analyses should be repeated in the case of suspected BNS if the initial results are negative, as illustrated by two patients in this series for whom the diagnosis of BNS could only be made after a second CSF analysis, and following previous examples reported in the literature.[4–6] The diagnosis of BNS in the absence of radiological abnormalities should be made with caution and assessed after a multidisciplinary discussion before starting the treatment. The evaluation of the response at the end of treatment needs to carefully re-evaluate brain and spinal MRI, as well as CSF clearance.

The treatments observed in this retrospective study were based on local physicians' choice and their heterogeneity precludes definite conclusions regarding the best treatment strategy to use. Most of the patients received systemic chemotherapy, notably when BNS was associated with WM progression. We did not observe any impact on overall

and progression-free survival related to the use of high-dose chemotherapy (including cytarabine or methotrexate). Only a few patients were treated with fludarabine-based regimens in this series. However, several previous reports have suggested that purine analogs are effective treatment for BNS,[7] and recent work confirmed the usefulness of fludarabine in the therapeutic armamentarium.[8] Despite lack of evidence that rituximab penetrates the CNS, we observed that this drug was used in nearly half of the cases but without any impact on the survival or response rate. Intrathecal chemotherapy was frequently administered with systemic chemotherapy and was the only specific treatment in two patients. Autologous stem-cell transplantation was performed in six cases as first-line treatment. All patients responded to transplantation, are without relapse and are still alive. One patient underwent autologous stem-cell transplantation as second-line therapy and initially responded, but this patient died due to toxicity of the transplant (septic shock during aplasia). Autologous stem-cell transplantation has also been previously reported in the literature,[9–13] but toxic deaths are described so that transplantation should be considered only for suitable patients.

The overall survival after the diagnosis of BNS in this series compares favorably with previously published data.[14] The onset of BNS did not appear to be associated with a more aggressive clinical course of WM in this series (70% of patients had an International Prognostic Staging System score of 1 at the time of WM diagnosis with a median overall survival from the time of WM diagnosis of 17.1 years).

We found 33 cases published in the literature during the same period (1995-2014),[4–7,9–13,15–35] which are some of the 56 cases described since the first description of BNS in 1936 (Table 4). The patients' characteristics were similar: the median age at the time of BNS diagnosis was 65.5 years (range, 50-84), and the majority of patients were male (71%). Diffuse forms are predominant (74%), and the association of diffuse and tumoral forms was described in five cases. The median white blood cell count in CSF was 46.5/mm^3 (range, 2-460) and the median protein level was 1.85 g/L (range, 0.22-16). As observed in our series, this review of the literature illustrates the possibility of a late onset of BNS, up to 25 years after the diagnosis of WM.

The pathophysiology of BNS remains unexplained, but the role of hyperviscosity has been raised to explain the disruption of the blood-brain barrier. However, in our cohort, the median serum IgM level was rather low, and no patient experienced hyperviscosity before or at the time of BNS occurrence.

In summary, BNS is a rare and probably under recognized condition that should be considered early in the context of unexplained neurological signs in patients with WM. It can occur in patients with indolent and stable WM, leading to delays and potential pitfalls in establishing a prompt diagnosis. The treatment remains challenging, but it could be interesting to investigate the potential efficacy of ibrutinib in BNS patients as this kinase inhibitor has recently been demonstrated to produce a high response rate in relapsed or refractory WM.[36] It was recently suggested that ibrutinib can penetrate the CNS on the basis of a recent study about mantle-cell lymphoma with CNS involvement.[37] The diagnostic accuracy of BNS could be improved by the detection of the L265P mutation in the *MYD88* gene in CSF specimens, as recently published.[38] This test could be an interesting tool that will need further investigation to assess its potential utility for the diagnosis and evaluation of response to treatment in patients with BNS.

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Authorship and Disclosures

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