Journal of the Neurological Sciences 398 (2019) 121–127

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Neurologic manifestations associated with cryoglobulinemia: A single center experience

Lauren Feldman, Megha Dhamne, Yuebing Li*

Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

ARTICLE INFO

Keywords:
Cryoglobulinemia
Peripheral nervous system
Central nervous system
Mononeuritis multiplex
Peripheral neuropathy
Immunotherapy

ABSTRACT

Introduction: Limited information is available describing the spectrum of neurological complications of cryoglobulinemia.
Methods: Single center retrospective review of patients with neurologic symptoms and elevated serum cryoglobulins, with their potential association being classified as definite, possible, or unlikely using defined criteria.
Results: Among 492 patients, 131 (87 classified as definite and 44 as possible) had neurologic symptoms associated with cryoglobulinemia. Common comorbidities included hepatitis C ($N = 43$), monoclonal gammopathy of undetermined significance ($N = 20$), Sjogren's syndrome ($N = 17$), membranoproliferative glomerulonephritis (N = 17), and systemic lupus erythematosus ($N = 10$). Features supporting an association between cryoglobulinemia and neurological symptoms were the presence of purpura ($p < .001$), positive rheumatoid factor ($p = .001$) and low C4 ($p = .002$). Common peripheral neurological diagnoses were symmetric polyneuropathy ($N = 84$), small fiber neuropathy ($N = 25$), and mononeuritis multiplex ($N = 16$). Central neurological manifestations were infrequent and included seizures ($N = 3$), posterior reversible encephalopathy syndrome ($N = 2$), intracerebral hemorrhage ($N = 1$), vasculitis (N = 1), rapidly progressive dementia ($N = 1$), lymphoma (N = 1), and myelitis/meningitis (N = 1). Treatments utilized included corticosteroids ($N = 74$), rituximab ($N = 42$), cyclophosphamide ($N = 27$), methotrexate, azathioprine, or mycophenolate mofetil ($N = 28$), anti-viral therapy ($N = 20$), plasmapheresis ($N = 16$), and intravenous immunoglobulin (N = 20). Neurologic symptoms associated with cryoglobulinemia remained stable or improved in 86% of patients.
Conclusion: This study describes a wide spectrum of patients with neurologic symptoms attributed to cryoglobulinemia and provides a framework to approach this challenging diagnosis.

1. Introduction

Cryoglobulinemia is defined as the detection of immunoglobulins (Ig) that precipitate in vitro at 4 °C and dissolve when heated to 37 °C. According to their molecular composition, cryoglobulins are classified into three types: isolated monoclonal Ig (type I) is associated with B cell lymphoproliferative disorders, while mixed cryoglobulinemia (MC), composed of either monoclonal and polyclonal Igs (type II) or polyclonal Igs (type III), is associated with chronic infections (most notably hepatitis C virus (HCV)) and connective tissue disorders [1].

The nervous system, skin, and kidneys are frequently affected by cryoglobulinemia [2,3]. Despite its prevalence, approach to diagnosis and treatment of cryoglobulinemic neurological complications is not standardized. The frequency of neurologic involvement is relatively unknown; small-scale studies and case reports estimate that neurological symptoms occur in 5% to 60% of cases [4,5]. However, literature focused on patients with HCV, which may have limited generalizability [4–6]. The primary goal of this study is to describe the neurologic manifestations associated with cryoglobulinemia in a diverse population evaluated at our tertiary care center. Identification of key features in the diagnosis and management through retrospective analyses may improve clinical care.

Abbreviations: MC, mixed cryoglobulinemia; HCV, hepatitis C virus; SFN, small fiber neuropathy; CNS, central nervous system; PNS, peripheral nervous system; SLE, systemic lupus erythematosus; OR, odds ratio; RF, rheumatoid factor; EDX, electrodiagnostic; PRES, posterior reversible encephalopathy syndrome; CI, confidence interval; IVIG, intravenous immunoglobulin; MRC, medical research council; IVMP, intravenous methylprednisolone; CK, creatine kinase

* Corresponding author at: Neuromuscular Center, Desk S90, Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH 44195, United States.
E-mail address: liy@ccf.org (Y. Li).

https://doi.org/10.1016/j.jns.2019.01.041
Received 22 July 2018; Received in revised form 17 January 2019; Accepted 24 January 2019
Available online 25 January 2019
0022-510X/

2. Methods

2.1. Study sample

This retrospective study was approved by the Cleveland Clinic Institutional Review Board. We included adult patients (age ≥ 18 years) with neurologic symptoms and elevated serum cryoglobulins (≥50 μg/mL) detected between 10/1999 and 2/2017. The association between neurologic symptoms and cryoglobulinemia was classified as definite, possible, or unlikely using the following criteria: Definite - clinical evidence of unexplained polyneuropathy, small fiber neuropathy (SFN), mononeuritis multiplex, or unexplained central nervous system (CNS) involvement plus elevated cryoglobulins on two determinations. If cryoglobulin level was only checked once, additional criteria were required: at least one supporting factor (purpura) [6] or presence of an associated condition (HCV, autoimmune disorder, lymphoproliferative disorder) [3], or response to empiric treatment. Possible - The above-mentioned criteria were fulfilled in the presence of a comorbidity that could cause similar symptoms such as alcohol abuse, diabetes mellitus, chemotherapy, critical illness neuropathy, or thyroid disease. Unlikely- neurologic symptoms were clearly associated with another etiology, such as isolated mononeuropathy, postherpetic neuralgia, or migraine, or cryoglobulins were only minimally elevated once (52–64 μg/mL).

Neurologic symptoms were classified as predominantly affecting the peripheral nervous system (PNS) or CNS. The diagnosis of neurological disorders was made based on the patient's symptoms and signs, electrophysiological, radiological or pathological findings. Diagnoses of polyneuropathy were made based on the presence of distal predominant sensorimotor deficits on history and physical examination, supplemented by electrophysiological study and/or results of nerve or skin biopsy. All major associated conditions (e.g. hepatitis C, Sjogren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, lymphoproliferative disorders and membranoproliferative glomerulonephritis) were diagnosed by specialists in our institution based on clinical, laboratory, radiological and pathological findings.

2.2. Data collection

Demographic and outcome variables were obtained by review of the medical record. Key variables recorded were associated conditions (infection, connective tissue disorders, lymphoproliferative disorders), maximal cryoglobulin level, systemic signs (purpura, arthralgia, myalgia), constitutional signs (fatigue, weight loss), associated laboratory findings, and response to treatment.

2.3. Statistical analysis

Patient characteristics were compared across groups using chi-square or Fisher exact test for categorical variables. Continuous variables were recorded as means with standard deviations or medians with interquartile ranges and compared across groups using Mann-Whitney test or Kruskal-Wallis test. Odds ratios (OR) were calculated to assess the effect of associated factors on the clinical outcome of patients with cryoglobulinemia. All factors were binary and OR was calculated by the proportion of improved outcome of a specified condition (e.g., mononeuritis multiplex) over the other condition (e.g., other neurological conditions) for key variables. Statistics were performed using the program R.

3. Results

Of the 492 patients with cryoglobulinemia, 271 (55%) had neurologic diagnoses. The association between neurological symptoms and cryoglobulinemia was classified as being definite in 87 patients, possible in 44, and unlikely in 140 (Fig. 1). Table 1 summarizes baseline characteristics of the 271 patients. Among 131 patients in the associated (definite and possible) groups, the most commonly related conditions were HCV (43 patients, 33%), monoclonal gammopathy of undetermined significance (20 patients, 15%), Sjogren's syndrome (17 patients, 13%), membranoproliferative glomerulonephritis (17 patients, 13%), and SLE (10 patients, 8%). Eighteen (14%) patients had no clearly known associated condition thus being idiopathic. In 98 of 271 (36%) patients, cryoglobulins were subtyped. Incidence of associated neurologic disorders were higher in patients with type I cryoglobulinemia (24/29, 83%) than MC (46/69, 67%, $p = .009$).

Patients in the definite group had a higher median cryoglobulin level than the possible group (524 and 385 μg/mL respectively, $p < .001$). Further subdivision of cryoglobulin values among the definite, possible and unlikely subgroups are reported in Table 2. A trend of higher cryoglobulin level in the associated group was seen ($p < .001$).

Clinical features suggestive of an association between cryoglobulinemia and neurological manifestations were analyzed. Significant features were the presence of purpura ($p < .001$), elevated rheumatoid factor (RF, $p = .001$) and low C4 ($p = .002$). There was no difference in rates of fatigue, weight loss, myalgia, or arthralgia between the definite, possible and unlikely subgroups.

Table 3 lists the PNS and CNS disorders encountered in the associated group. The most common PNS diagnosis was polyneuropathy, affecting 120 (92%) patients. Among them, 84 (70%) patients had symmetrical large-fiber polyneuropathy, 25 (19%) SFN, and 16 (12%) mononeuritis multiplex. The underlying etiology (HCV, lymphoproliferative disorder, or connective tissue disorder) was not statistically related to the type of neuropathy ($p = .973$). The most common presenting feature was painful dysesthesia, seen in 66 (55%) patients. Electrodiagnostic study (EDX) completed in 64 patients most frequently detected an axonal sensorimotor polyneuropathy. EDX was normal in 18 patients carrying a diagnosis of SFN supported by clinical exam, skin biopsy or quantitative sudomotor axon reflex test. The median cryoglobulin level for patients with SFN was lower than patients with symmetrical large-fiber polyneuropathy and mononeuritis multiplex (202 μg/mL vs 635 μg/mL, $p = .025$). Less common PNS diagnoses included facial nerve palsy ($N = 4$), myopathy ($N = 2$, polymyositis and non-irritative myopathy), and myasthenia gravis ($N = 1$).

In 8 patients, CNS complications of cryoglobulinemia were present (Table 3). These included 2 cases of posterior reversible encephalopathy syndrome (PRES).

Multiple immunosuppressive treatments were utilized in the associated groups, with corticosteroids being the most commonly administered (74 patients, 56%), followed by rituximab (42 patients, 32%), cyclophosphamide (27 patients, 21%), methotrexate or azathioprine or mycophenolate mofetil (28 patients, 21%), plasmapheresis (16 patients, 12%), and intravenous immunoglobulin (IVIG, 5 patients, 4%). Twenty patients with HCV were treated with anti-viral therapy. Specific treatments and responses are reported in Table 4. Clinically, neurologic manifestations remained stable in 72 (55%) patients and improved in 30 (23%). Cryoglobulin levels improved or normalized in 80 of 103 (78%) patients. Of 18 with definite cryoglobulinemia who improved (Table 5), all received immunotherapy, with 13 of 18 (72%) patients requiring 2 or more treatment modalities.

The efficacy of immunotherapy was assessed for the definite group. A trend of positive association exists between the use of immunotherapy and clinical improvement but it does not reach statistical significance (OR = 16.4; 95% confidence interval (CI) = 0.94 to 284.9; $p = .055$). Further analyses to search for individual predictors of improved clinical outcome were performed for the subgroup of 81 patients with polyneuropathy in the definite group. A positive association exists between clinical improvement and corticosteroid usage (OR = 6.0; 95% CI = 1.26 to 28.5; $p = .024$). A trend of positive association occurs between clinical improvement and the following factors: male sex (OR = 2.89; 95% CI = 0.75 to 11.1; $p = .124$), cyclophosphamide

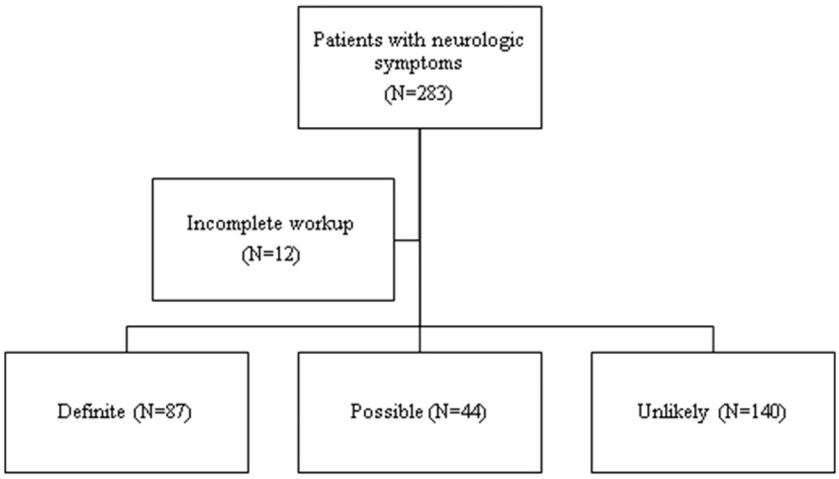

Fig. 1. Flow chart of patients with neurologic symptoms.

treatment (OR = 2.83; 95% CI = 0.90 to 8.96; $p = .076$) and mononeuritis multiplex presentation (OR = 2.82; 95% CI = 0.79 to 10.1; $p = .109$). No significant association was detected between clinical improvement and young age (< 60 years old), rituximab or plasmapheresis treatment.

3.1. Illustrative case 1 – treatment responsive polyneuropathy

A 73 year-old female presented with a 4-week history of fever, weight loss, weakness, and neuropathic pain in her feet and left hand. Erythematous macules were present on the foot dorsum. Strength examination revealed the following (Medical Research Council (MRC) scale): flexor digitorum profundus 4 right and 3 left, first dorsal interosseous 3 bilaterally, hip flexors 4 bilaterally, knee flexors 4 right and 5

Table 2
Difference in the distribution of highest cryoglobulin level between groups of patients with neurologic symptoms associated with cryoglobulinemia and the unlikely group.

Cryoglobulin (μg/mL)	Total $N = 271$	Definite + Possible $N = 131$	Unlikely $N = 140$
≤100	81	21	60
101–400	91	42	49
401–800	26	14	12
801–1200	22	12	10
> 1200	51	42	9

Table 1
Demographics and baseline characteristics of all patients.

Characteristic	Total	Definite	Possible	Unlikely
	N	N	N	N
Total number of patients	271	87	44	140
Female Sex (%)	61	62	57	62
Age (Years), Mean ± SD	57 ± 13.8	58 ± 13.7	61 ± 11.4	54 ± 14.2
Cryoglobulin, Median (Q1, Q3)	207 (89,856)	524 (204,2310)	385 (141,1724)	118 (75,307)
HCV positive	77	28	15	34
RF positive[a]	96	44	14	38
Purpura[a]	84	48	15	21
Low C4[a]	68	30	15	23
Connective tissue disorder				
SS	27	13	4	10
SLE	12	10	0	2
RA	11	4	3	4
SSc	3	0	2	1
DM	1	1	0	0
Undifferentiated	2	1	0	1
Lymphoproliferative disease				
MGUS	30	13	7	10
NHL	25	5	7	13
MM	5	2	3	0
WM	2	1	0	1
CLL	1	0	1	0
Primary amyloidosis	1	1	0	0
MPGN	32	13	4	15
HIV positive	7	2	2	3

Abbreviations: HCV, hepatitis C virus, RF, rheumatoid factor, ANA, antinuclear antibody, RF, rheumatoid factor, C4, complement component 4, HIV, human immunodeficiency virus, SS, Sjogren's syndrome, SLE, systemic lupus erythematosus, RA, rheumatoid arthritis, SSc, systemic sclerosis, DM, dermatomyositis, MGUS, monoclonal gammopathy of undetermined significance, NHL, non-Hodgkin's lymphoma, MM, multiple myeloma, WM, Waldenstrom macroglobulinemia, CLL, chronic lymphocytic leukemia, MPGN, membranoproliferative glomerulonephritis.

[a] Statistically significant characteristics.

Table 3
A list of nervous system disorders associated with cryoglobulinemia.

	Definite N = 87 (%)	Possible N = 44 (%)
Peripheral nervous system		
Polyneuropathy[a]	81 (93)	39 (87)
Symmetrical polyneuropathy	57 (70)	27 (69)
Small fiber neuropathy	14 (16)	11 (25)
Mononeuritis multiplex	14 (17)	2 (5)
Painful polyneuropathy	45 (56)	21 (54)
Facial nerve palsy	3 (3)	1 (2)
Myasthenia gravis	1 (1)	0
Myopathy	0	2 (5)
Central Nervous System		
Seizures including PRES	3	0
Rapidly progressive dementia	1	0
Intracerebral hemorrhage	1	0
CNS vasculitis	1	0
CNS lymphoma	1	0
Myelitis/meningitis	1	0

Abbreviations: PRES posterior reversible encephalopathy syndrome.
[a] Patients may have more than one type of neuropathy.

Table 4
The use of immunotherapy and treatment response in cryoglobulinemic patients with associated neurological disorders.

	Definite	Possible
	N = 87 (%)	*N* = 44 (%)
Treatment[a]		
Corticosteroids	54 (62)	20 (45)
Rituximab	28 (32)	14 (32)
Cyclophosphamide	23 (27)	4 (9)
Methotrexate/azathioprine/mycophenolate mofetil	20 (26)	8 (18)
Plasmapheresis	15 (17)	1 (2)
IVIG	4 (5)	1 (2)
No immunotherapy	11 (13)	12 (27)
anti-HCV treatment[b]	15 (17)	5 (11)
Clinical response documented	79	39
Improved	18 (23)	12 (31)
Stable	52 (66)	20 (51)
Progressive/relapse	9 (11)	7 (18)
Change in cryoglobulin level	68	35
Normalized	20 (29)	12 (34)
Improved but not normalized	31 (46)	17 (49)
Worse	12 (18)	4 (11)
Stable	5 (7)	2 (6)

[a] Patients may have received more than one modality.
[b] Interferon alpha, ledipasvir, ribavirin, simeprevir, sofosbuvir.

left, dorsiflexors 0 bilaterally and plantar flexors 0 bilaterally. Serum cryoglobulin level was 320 μg/mL. EDX study demonstrated a severe subacute sensorimotor axonal polyneuropathy. Left sural nerve biopsy revealed findings of focal fibrinoid necrosis with vessel wall inflammation constituting a necrotizing vasculitis. Treatment with intravenous methylprednisolone (IVMP) at 1 g per day for 5 days was initiated, followed by prednisone 60 mg daily and oral cyclophosphamide 125 mg daily. In 2 months, significant improvement was observed in symptoms, physical examination findings and cryoglobulin level. After month 3, cyclophosphamide was stopped, prednisone was tapered and methotrexate 20 mg per week was initiated. At month 5, strength was normalized in her bilateral upper and proximal lower extremities except plantar flexors (left 4 and right 3) and dorsiflexors (0 bilaterally). Immunotherapy was tapered off at 1 year and she was stable for additional 2 years.

3.2. Illustrative case 2 – treatment responsive myelitis

A 54 year-old male presented with subacute onset of headache, confusion, urinary retention and paraplegia. Cerebrospinal fluid was notable for lymphocytic pleocytosis (WBC 219/μL, 94% lymphocytes) and protein 97 mg/dL. MRI brain and spine revealed intracranial and spinal leptomeningeal enhancement with subtle parenchymal signal changes suggestive of meningitis/myelitis (Fig. 2). Serum analysis was positive for HCV with a viral load of 3,830,000 IU/mL and cryoglobulin level of 288 μg/mL. Treatment with IVMP at 1 g daily for 3 days was initiated, followed by IVIG of 2 g per kilogram of body weight, and prednisone 50 mg daily. Within 2 weeks, improvement was seen on leg strength and on MRI of the brain and spine. Prednisone was slowly tapered off in 5 months. At month 4, his lower extremity strength improved to 3 to 4 (MRC scale), and at month 7 he regained urinary continence. Antiviral therapy (sofosbuvir and ledipasvir) was initiated at month 5. Cryoglobulin level significantly improved at month 4 and normalized at month 7. At month 18 he was able to ambulate without assistance.

4. Discussion

The occurrence of neurologic complications has been reported in both type I and MC with conflicting results. Early studies suggested a higher rate in MC [1] while more recent analyses reported equal occurrence in both groups [7]. We report a large case series of patients with neurologic symptoms and cryoglobulinemia. Overall, 27% of patients in our population had neurologic complications associated with cryoglobulinemia. While rates of neurologic symptoms were higher in patients with type I than MC, the majority of the patients in our study were not immunotyped.

4.1. PNS complication of cryoglobulinemia

Peripheral polyneuropathy was described in 17% to 60% of patients with cryoglobulinemia [3]. Sensory symptoms, especially painful polyneuropathy, accounted for 50.4% of the patients in our series. In most patients, a distal symmetric sensory or sensorimotor polyneuropathy was encountered while mononeuritis multiplex accounted for 12% of patients. SFN was seen in 19% of patients, consistent with the recently described high incidence in this population [3]. Peripheral neuropathy often represents an early manifestation of MC [8]. In particular, SFN tends to occur early in the course of cryoglobulinemia and in those with mild systemic disease [6].

The development of a neuropathy is likely related to vasculitis of the vasa nervorum, consequent to the deposition of cryoprecipitate along the vessel walls which may compress the endoneural vessels leading to ischemic damage, cause epineural vasculitis or result in humoral mediated microangiopathy [6,9,10]. Nerve biopsy typically demonstrates axonal degeneration with loss of myelinated axons [9]. Consistent with the literature, most cases of cryoglobulin related polyneuropathy were axonal in this series. One case of demyelinating neuropathy was encountered based on EDX findings in the setting of autoimmune hepatitis, Sjogren's syndrome, and Hashimoto's thyroiditis. A few cases of demyelinating polyneuropathy in MC were previously described, supported by EDX and sural nerve biopsies [11–13]. Rarely, a clinical presentation of chronic inflammatory demyelinating polyneuropathy was encountered, responding to either antiviral therapy or corticosteroids [11–13].

Several reports suggested that cryoglobulinemia may be more common than previously thought, as a cause of peripheral neuropathy. In a prospective study of 100 patients with polyneuropathy or mononeuritis multiplex of unknown etiology after initial workup, 11 were eventually diagnosed with cryoglobulinemic neuropathy [14]. In another study of 100 patients with distal symmetric painful SFN with previously negative workup, 16% of patients had elevated cryoglobulins [15]. Results from these two publications suggest cryoglobulinemia, even in the absence of purpura, may account for a substantial number of “idiopathic” neuropathies. Other distinctive features of

Table 5
Characteristic of the definite group of patients who improved with immunotherapy.

Patient	Neurological diagnosis	Systemic condition	Treatment
1	Symmetrical polyneuropathy	MPGN	Corticosteroids, Mycophenolate Mofetil
2	Symmetrical polyneuropathy	MM	Corticosteroids, Cyclophosphamide
3	Symmetrical polyneuropathy	MPGN	Corticosteroids, Cyclophosphamide, Rituximab,
4	Symmetrical polyneuropathy	MPGN, HCV	Corticosteroids, Rituximab, plasmapheresis, anti-HCV
5	Symmetrical polyneuropathy	None	Corticosteroids
6	Symmetrical polyneuropathy	SS, autoimmune hepatitis	Corticosteroids, Cyclophosphamide
7	Symmetrical polyneuropathy	None	Corticosteroids, IVIG
8	Symmetrical polyneuropathy	ITP, SS, MGUS	Corticosteroids, Cyclophosphamide, IVIG, Rituximab
9	Mononeuritis multiplex	None	Corticosteroids, Cyclophosphamide, Methotrexate
10	Mononeuritis multiplex	None	Corticosteroids
11	Mononeuritis multiplex	None	Corticosteroids, anti-HCV
12	Mononeuritis multiplex	None	Corticosteroids, Cyclophosphamide, Methotrexate
13	Mononeuritis multiplex	None	Corticosteroids, Rituximab
14	Small fiber neuropathy	None	Mycophenolate Mofetil
15	Small fiber neuropathy	IgG MGUS	Corticosteroids, Methotrexate, Cyclophosphamide
16	Small fiber neuropathy	SS	Hydroxychloroquine
17	Thoracic myelitis	HCV	Corticosteroids, IVIG, anti-HCV
18	CNS vasculitis	MPGN	Corticosteroids, Cyclophosphamide, Mycophenolate Mofetil

Abbreviations: MPGN, membranoproliferative glomerulonephritis, MM, multiple myeloma, HCV, hepatitis C virus, SS, Sjogren's syndrome, ITP, idiopathic thrombocytopenic purpura, MGUS, monoclonal gammopathy of undetermined significance.

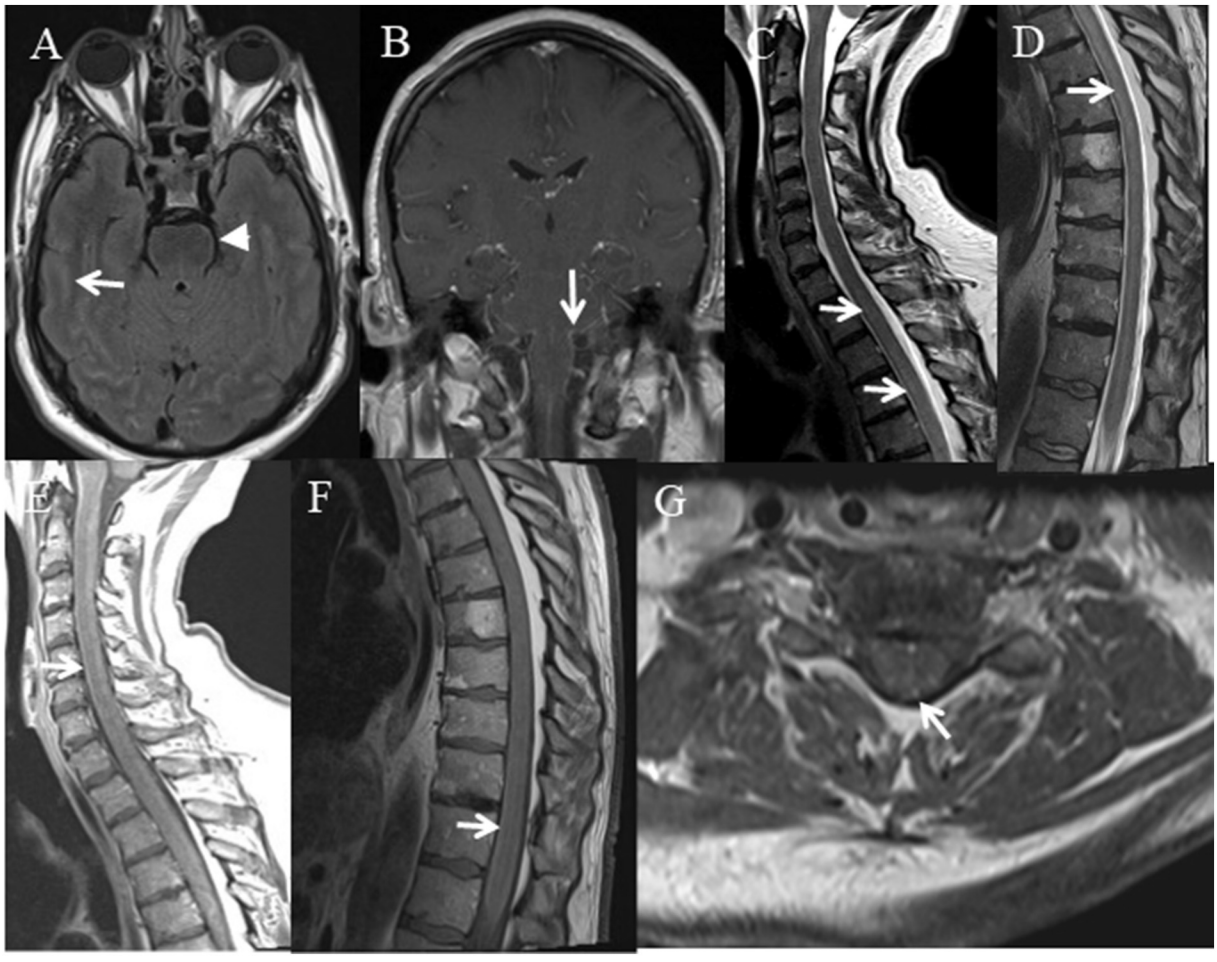

Fig. 2. Findings of MRI in a patient with diffuse meningitis and myelitis.
At presentation, MRI brain revealed hyperintensity along the sulci (arrow) and on the surface of brainstem (arrowhead) on axial FLAIR image (A) and leptomeningeal enhancement on coronal T1, mostly prominently in the brainstem (B). Sagittal T2 images of the cervical (C) and thoracic spine (D) revealed diffuse cord edema and subtle hyperintensity in the anterior portion of the lower cervical and thoracic spinal cord (arrows). Post contrast administration, predominantly pial enhancement (arrows) was visualized in the sagittal image of cervical (E) and thoracic spine, as well as axial image (G) of the cervical spine. Following treatment, above signal changes and enhancement significantly improved (data not shown).

cryoglobulinemic neuropathy that may increase suspicion are female predominance, asymmetric distribution, and painful sensory symptoms [6,16]. Laboratory findings that may suggest an association identified in our study were positive RF and low C4.

4.2. CNS complications of cryoglobulinemia

CNS manifestations of cryoglobulinemia have been scarcely described. In one report, CNS complications were 15 times less frequent than peripheral neuropathy [17]. In our series, CNS complications accounted for < 10% of patients with neurological complications. In a review of 279 patients with HCV and life-threatening cryoglobulinemia, 38 patients (13.6%) had cryoglobulinemic CNS involvement [18]. The diagnoses consisted of cerebral ischemia in 18 patients, CNS vasculitis in 15, transverse myelitis in 4, and cerebral hemorrhage in 2. Other reported CNS manifestations include seizures [17], transient hemiplegia or confusion [1,19,20], and PRES [21]. Recurrent myelitis is less frequently reported [22–24]. In one series, 2 of 7 patients with HCV and recurrent myelitis had MC [23]. Several cases of cryoglobulinemic CNS complications were successfully treated with plasmapheresis, presumably by the removal of the immunoglobulin complexes [25,26]. Our case of diffuse meningitis/myelitis was successfully treated with corticosteroid and IVIG, and significant improvement was obtained before antiviral therapy was initiated for HCV infection.

Similarly to PNS involvement, cryoglobulinemic CNS manifestations are likely under recognized. In a prospective study of 27 patients with HCV MC, 89% had cognitive impairment [27]. The frequency of cognitive impairment correlated with cryoglobulin levels. On MRI, total and periventricular white matter changes were 3 to 8 times higher compared to HCV patients and healthy controls. Authors concluded that these findings suggested inflammatory involvement of the CNS in HCV MC [27]. In our series, brain MRI was completed only in selected patients, likely underestimating the CNS complication rate. The presence of CNS complications has been reported as a baseline factor associated with poor prognosis [17].

4.3. Significance of cryoglobulin level

Higher cryoglobulin titers appeared more frequently in patients with neurologic symptoms. Only 22% of patients in the unlikely group possessed cryoglobulin levels exceeding 400 μg/mL, while 82% of patients in the associated group had levels above 1200 μg/mL (Table 2). Although levels between patients are not comparable, cryoglobulin levels in an individual patient may serve as a marker for disease activity (Tables 2 and 5) [2]. In our study, the median cryoglobulin level for patients with SFN was lower than patients with polyneuropathy or mononeuritis multiplex (202 μg/mL vs 635 μg/mL). The group of patients with CNS complications in our study had a higher median cryoglobulin level when compared to patients with PNS symptoms (1450 μg/mL vs 524 μg/mL), consistent with prior studies [6].

4.4. Immunotherapy

In patients with HCV MC, sustained virologic response with antiviral therapy can often be accomplished in patients with mild to moderate disease. It was previously demonstrated that the addition of corticosteroids to interferon alpha did not significantly increase the therapeutic response in HCV MC [28]. However, antiviral therapy does not allow for rapid improvement. It may be ineffective, contraindicated, or poorly tolerated in some patients. Those with severe vasculitis often require escalation of treatment with immunosuppression or plasmapheresis [17]. The illustrative case 2 in our series highlights the importance of immunotherapy in cryoglobulinemia associated with HCV.

We analyzed the association between occurrence of clinical improvement and usage of immunotherapy in the definite subgroup. No significant association was found between clinical improvement and use of immunotherapy for the entire subgroup. However, our analysis could be limited due to patient heterogeneity and small sample size. In addition to HCV, other associated conditions including connective tissue and lymphoproliferative disorders were encountered in the definite group. It remains likely that immunotherapy is effective for a subset of cryoglobulinemia in association with particular condition(s). Further large-scale study of cryoglobinemic patients with relatively uniformed associative conditions are still needed.

The immunosuppressive approaches used in cryoglobulinemic vasculitis including corticosteroids and cyclophosphamide were derived from treatment of other systemic vasculitides [3]. It was demonstrated previously that corticosteroids may prevent flares and alleviate arthralgia in many patients [29]. Our data suggest that corticosteroid treatment is clearly associated with clinical improvement, and should be considered for cryoglobulinemic patients with polyneuropathy. To minimize side effects associated with long-term corticosteroid usage, medications such as methotrexate, azathioprine or mycophenolate mofetil may be used for maintenance therapy [3]. In addition, our data suggested a possibly positive association between clinical improvement and cyclophosphamide treatment. This is consistent with a few previous reports indicating an efficacy of cyclophosphamide in treating cryoglobulinemia [30–32]. Although a large-scale study is needed, our data seem to imply that cyclophosphamide could be used as adjunctive therapy to corticosteroids, especially in selected cases of cryoglobulinemia with severe or rapidly progressive PNS or CNS complications.

Recently, two clinical trials demonstrated rituximab as a favorable treatment option in patients with severe cryoglobulinemic vasculitis [33] and in patients with HCV MC who did not reach remission with antiviral therapy [34]. Treatment of the control group was at the discretion of the physician. Superiority of rituximab was demonstrated compared to 1) glucocorticoids, 2) azathioprine or cyclophosphamide, or 3) plasmapheresis, by the primary end point of survival at 12 months [33], or by 6 month remission compared to no therapy, glucocorticoids, or plasmapheresis [34]. Patients with neurologic complications have not been extensively studied, but results from one study suggested improvement in pain and paresthesia after rituximab [33]. Our study failed to demonstrate a positive association between rituximab usage and clinical improvement. However, a prospective study focusing on the use of rituximab in cryoglobulinemic patients with neurological manifestations is better suited to assess its efficacy.

There are several limitations to this study. The population came from a single center and may not be generalizable. Data was collected retrospectively, yielding variable clinical and follow up information. There was a lack of standardized diagnosis and management of the neurological complications. Immunological subtyping of cryoglobulin was performed in only a small portion of patients. In a portion of the cases (the possible group), there is a possibility that coexisting conditions may account for the occurrence of neurological disorders. Nevertheless, this study describes a large volume of patients with neurologic symptoms that may be attributed to cryoglobulinemia and provides a framework to approach this challenging diagnosis.

Declarations of interest

Lauren Feldman and Megha Dhamne report no disclosures. Yuebing Li has served as a consultant at the Advisory Board for Alexion Pharmaceuticals.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] J.C. Brouet, J.P. Clauvel, F. Danon, et al., Biologic and clinical significance of cryoglobulins. A report of 86 cases, Am. J. Med. 57 (1974) 775–788.
[2] A. Dispenzieri, P.D. Gorevic, Cryoglobulinemia, Hematol. Oncol. Clin. North Am. 13 (1999) 1315–1349.
[3] M. Ramos-Casals, J.H. Stone, M.C. Cid, X. Bosch, The cryoglobulinaemias, Lancet 379 (2012) 348–360.
[4] C. Ferri, L. La Civita, C. Cirafisi, et al., Peripheral neuropathy in mixed cryoglobulinemia: clinical and electrophysiologic investigations, J. Rheumatol. 19 (1992) 889–895.
[5] A. Biasiotta, M. Casato, S. La Cesa, et al., Clinical, neurophysiological, and skin biopsy findings in peripheral neuropathy associated with hepatitis C virus-related cryoglobulinemia, J. Neurol. 261 (2014) 725–731.
[6] F. Gemignani, F. Brindani, S. Alfieri, et al., Clinical spectrum of cryoglobulinaemic neuropathy, J. Neurol. Neurosurg. Psychiatry 76 (2005) 1410–1414.
[7] E. Muchtar, H. Magen, M.A. Gertz, How I treat cryoglobulinemia, Blood 129 (2017) 289–298.
[8] F. Gemignani, G. Pavesi, A. Fiocchi, et al., Peripheral neuropathy in essential mixed cryoglobulinaemia, J. Neurol. Neurosurg. Psychiatry 55 (1992) 116–120.
[9] B. Bonetti, F. Invernizzi, N. Rizzuto, et al., T-cell-mediated epineurial vasculitis and humoral-mediated microangiopathy in cryoglobulinemic neuropathy, J. Neuroimmunol. 73 (1997) 145–154.
[10] J. Vallat, L. Magy, L. Richard, et al., Intranervous immunoglobulin deposits: an underestimated mechanism of neuropathy, Muscle Nerve 38 (2008) 904–911.
[11] S. Boukhris, L. Magy, U. Senga-mokono, et al., Polyneuropathy with demyelinating features in mixed cryoglobulinemia with hepatitis C virus infection, Eur. J. Neurol. 13 (2006) 937–941.
[12] K. Endo, A. Hoshi, M. Shimizu, et al., Marked thickening of the peripheral nerves in chronic inflammatory polyradiculoneuropathy associated with HCV infection, Rinsho Shinkeigaku 42 (2002) 27–31.
[13] P. Corcia, D. Barbereau, A.M. Guennoc, et al., Improvement of a CIDP associated with hepatitis C virus infection using antiviral therapy, Neurology 63 (2004) 179–180.
[14] F. Gemignani, G. Melli, C. Inglese, A. Marbini, Cryoglobulinemia is a frequent cause of peripheral neuropathy in undiagnosed referral patients, J. Peripher. Nerv. Syst. 7 (2002) 59–64.
[15] J.-L. Hsu, M.-F. Liao, H.-C. Hsu, et al., A prospective, observational study of patients with uncommon distal symmetric painful small-fiber neuropathy, PLoS One 12 (2017).
[16] F. Gemignani, A. Marbini, G. Di Giovanni, et al., Cryoglobulinaemic neuropathy manifesting with restless legs syndrome, J. Neurol. Sci. 152 (1997) 218–223.
[17] P. Cacoub, C. Comarmond, F. Domont, et al., Cryoglobulinemia Vasculitis, Am. J. Med. 128 (2015) 950–955.
[18] S. Retamozo, C. Díaz-Lagares, X. Bosch, et al., Life-threatening cryoglobulinemic patients with hepatitis C, Medicine (Baltimore) 92 (2013) 273–284.
[19] L. Origgi, M. Vanoli, A. Carbone, et al., Central nervous system involvement in patients with HCV-related cryoglobulinemia, Am J Med Sci 315 (1998) 208–210.
[20] G.W. Petty, J. Duffy, J. Houston, Cerebral ischemia in patients with hepatitis C virus infection and mixed cryoglobulinemia, Mayo Clin. Proc. 71 (1996) 671–678.
[21] D. Ahmad, H. Ilias Basha, B. Towfiq, G. Bachuwa, Resolution of neurological deficits secondary to spontaneous intracranial haemorrhage and posterior reversible encephalopathy syndrome (PRES) in a patient with hepatitis C-associated cryoglobulinaemia: a role for plasmapheresis, BMJ Case Rep. 2014 (2014).
[22] L. Mouelhi, H. Mekki, F. Houissa, et al., Transverse myelitis associated with chronic viral hepatitis C, Tunis Med. 88 (2010) 116–118.
[23] K.M. Aktipi, S. Ravaglia, M. Ceroni, et al., Severe recurrent myelitis in patients with hepatitis C virus infection, Neurology 68 (2007) 468–469.
[24] G. Zandman-Goddard, Y. Levy, P. Weiss, et al., Transverse myelitis associated with chronic hepatitis, C. Clin. Exp. Rheumatol. 21 (2003) 111–113.
[25] L. Reik, J.H. Korn, Cryoglobulinemia with encephalopathy: successful treatment by plasma exchange, Ann. Neurol. 10 (1981) 488–490.
[26] G. Pagano, K. Komici, G.D. Femminella, et al., Sudden onset of coma in a 70-year-old woman with cryoglobulinemia, Am J Case Rep. 15 (2014) 56–59.
[27] M. Casato, D. Saadoun, A. Marchetti, et al., Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests, J. Rheumatol. 32 (2005) 484–488.
[28] F. Dammacco, D. Sansonno, J.H. Han, et al., Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: a long-term, randomized, controlled study, Blood 84 (1994) 3336–3343.
[29] M. Pietrogrande, S. De Vita, A.L. Zignego, et al., Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients, Autoimmun. Rev. 10 (2011) 444–454.
[30] O. Cakir, O. Ayyildiz, A. Isikdogan, Type III mixed cryoglobulinemia associated with digital necrotic ulcer successfully treated with intermittent intravenous pulse cyclophosphamide, Angiology 56 (2005) 489–492.
[31] D. Saadoun, M. Pineton de Chambrun, O. Hermine, et al., Using rituximab plus fludarabine and cyclophosphamide as a treatment for refractory mixed cryoglobulinemia associated with lymphoma, Arthritis Care Res (Hoboken) 65 (2013) 643–647.
[32] M. Moraru, M. Yebra-Bango, E. Cisneros, et al., Cryofibrinogenemia triggered by a monoclonal paraprotein successfully treated with cyclophosphamide, J. Clin. Rheumatol. 20 (2014) 34–37.
[33] S. De Vita, L. Quartuccio, M. Isola, et al., A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis, Arthritis Rheum. 64 (2012) 843–853.
[34] M.C. Sneller, Z. Hu, C.A. Langford, A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis, Arthritis Rheum. 64 (2012) 835–842.