Symptom burden in patients with idiopathic multicentric Castleman disease and its impact on daily life: an international patient and caregiver survey

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Summary

Background Idiopathic Multicentric Castleman Disease (iMCD) is a rare inflammatory lymphoproliferative disorder with heterogenous clinical presentations. The symptomatology in iMCD patients remains poorly understood. The aim of this study was to identify the type, frequency and severity of iMCD-related symptoms and the impact of these on the daily lives of iMCD patients and informal-caregivers.

Methods We conducted two bespoke 45-question online surveys for iMCD patients and informal-caregivers of patients recruited from the US, UK, Australia and Canada between April 14 and November 8, 2021. Descriptive data was collected, and a Likert scale was used to quantify the impact of symptoms on various aspects of daily life. Ordinal logistic regression analysis was used to determine associations between age, gender, employment status and symptom burden with aspects of daily life.

Findings Eligible respondents included 51 iMCD patients and 11 informal-caregivers. Patients reported up to 27 unique symptoms, the mean number of symptoms experienced by a patient was 6.7 (range 0–22 symptoms). Most symptoms had a moderate to severe impact on patients' daily lives, with 'pain/discomfort', 'ability to travel', and 'sexual functioning' being the most impacted. iMCD patient characteristics such as being 40 years or older, female, and either disabled or unemployed was significantly associated with adverse impact on several aspects of daily life. Among caregivers, the aspects of daily life that were disproportionately affected was their own social life and freedom, emotional wellbeing, travel/relocation, and work.

Interpretation iMCD patients have widely varied and unappreciated symptomatology. High symptom burden adversely impacts several aspects of patient daily lives as well as their caregivers.

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Keywords: Idiopathic multicentric Castleman disease; Symptom burden; Patient and caregiver survey

Introduction

Multicentric Castleman Disease (MCD) is a heterogenous collection of lymphoproliferative disorders often associated with a hyperinflammatory state mediated by hypercytokinemia. Idiopathic MCD (iMCD) is diagnosed once other aetiologies of MCD are eliminated, in particular human herpesvirus-8 (HHV-8), HIV (human immunodeficiency virus), other infections, POEMS-associated MCD (polyneuropathy, organomegaly, endocrinopathy/oedema, monoclonal protein and skin changes), autoimmune conditions, and certain malignancies as per the international diagnostic criteria.[1] iMCD cases can be further classified into three distinct clinical entities–iMCD with thrombocytopenia, anasarca, fever, bone marrow reticulin fibrosis or renal dysfunction, and organomegaly (iMCD-TAFRO); iMCD with idiopathic plasmacytic lymphadenopathy (iMCD-IPL); and iMCD not otherwise specified (iMCD-NOS), a category that includes cases that do not meet the criteria for either iMCD-TAFRO or iMCD-IPL.[1,2] iMCD is a rare

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Research in context

Evidence before this study

To identify studies exploring symptom burden, severity and its impact on patients and their informal caregivers, we in late April of 2020 conducted an open literature search of Medline, Embase, Cochrane, health technology assessment databases supplemented with manual searching using the terms: 'Idiopathic Multicentric Castleman disease (iMCD)', 'Multicentric Castleman disease (MCD)', 'Castleman's disease', 'symptom burden', and 'disease burden'. Non-English citations were excluded. Citations reporting qualitative or quantitative measurement of symptoms in patients with MCD or iMCD were reviewed for inclusion. Six of the seven identified publications referred to the development and testing of the Multicentric Castleman Disease Symptom Scale (MCD-SS), the first MCD-specific patient reported outcome (PRO) scale. Most of our current knowledge on iMCD symptomatology is based on findings from the MCD-SS that was used in the phase 2 randomised trial in MCD patients for construct reliability and validity, responsiveness, and measurement of clinically meaningful symptomatic improvement with treatment. However, the MCD-SS was developed prior to the publication of the international evidence-based diagnostic criteria for iMCD, therefore it is not iMCD-specific as it included all MCD cases even those that were not iMCD. Even though the development of the scale explored the impact of symptom burden on daily life, this was not included in the final scale. The MCD-SS only included questions relating to symptoms and their severity rating on a 6-point scale.

Added value of this study

This is the first study to compile the most comprehensive listing of the symptomatology experienced by iMCD patients and their informal caregivers. It reports on the type, prevalence, and multiplicity of symptoms as well as the global impact of the symptom burden on everyday life, of both patients and their caregivers. The findings from this international survey reflect the daily experiences of iMCD patients receiving care outside the context of clinical trials and as such can be generalised to the management of these patients in routine clinical practice. Given the rarity of iMCD, this study included a sizable patient and caregiver sample.

Implications of all the available evidence

The mainstay of iMCD management is symptom control and prevention of severe complications. Therefore, a critical element when seeking to better manage these patients is a thorough understanding of the symptom burden experienced by these patients, and their informal caregivers who themselves might feel challenged dealing with the complexity of this rare condition. Symptom tracking provides a dynamic assessment of a patient's clinical condition at any point in their clinical course and is an important approach to capture the totality of disease impact beyond radiologic and laboratory assessment. Additionally, it enables the assessment of the impact of the current disease state and/or treatment effects on different domains of everyday life from a patient's perspective. The findings from this study forms the conceptual framework which is being used as part of our ongoing work towards the development of the first-ever iMCD symptom burden scale which will facilitate shared clinical decision making, better symptom response monitoring, pharmaceutical labelling claims, development of clinical trial endpoints, treatment guideline and health policy development.

condition with an estimated annual incidence of 3.1–3.4 cases and prevalence of 6.9–9.7 cases per million in the United States (US).[3] The clinical phenotype of iMCD can vary ranging from mild flu-like symptoms to generalised pain, chronic fatigue, and anasarca among others and in some cases, severe sepsis-like picture leading to multi-organ failure and death.[1] iMCD patients, particularly those not treated in a timely manner or with appropriate therapy, develop significant morbidities and have high rates of emergency room visits and hospitalisations.[3–5] iMCD-related symptoms have been shown to negatively impact patient quality of life.[6] As no curative therapies exist for iMCD, the primary focus of clinical management remains symptom control and prevention of serious complications.

Integrating patient-reported symptom surveillance in addition to usual clinical care has been consistently shown to be associated with improved health-related quality of life,[7–12] improved survival,[10,12–15] and reduced use of healthcare resources.[10,13,16,17] This is attributed to tighter symptom monitoring and toxicity assessments, quick therapeutic interventions in cases of clinical deterioration, better compliance, and extended treatment durations. Recent epidemiologic data suggest that under recognised and undertreated iMCD-related symptoms might lead to treatment delays, increased risk of disease-related morbidity, and the need for healthcare resources.[3–5]

Insufficient comprehension of the symptomatology associated with iMCD may be a contributing factor for the lack of IL-6 directed therapy in the majority of diagnosed cases in the United States where treatment is recommended according to established treatment guidelines.[3,18] It is believed that poor understanding of iMCD symptomatology is among several reasons why significant number of cases in the US do not receive IL-6 directed therapy following diagnosis, which is contrary to treatment guidelines. In treated patients, the decision to treat was reserved to those who either had high symptom burden at presentation or were

hospitalised.[3] Despite iMCD being a highly symptomatic disease, there are no disease-specific assessments to measure symptom burden within this patient population. An in-depth understanding of the iMCD disease burden, based on the occurrence, pattern and multiplicity of symptoms and associated impact on daily living will enable us to monitor the clinical trajectory in real-time and better manage these patients with timely interventions.

To date, the only patient reported outcome (PRO) tool developed is the MCD-symptom scale (MCD-SS), which was used in one randomised phase II clinical trial and the patients sampled were broadly defined as having MCD as opposed to iMCD.[6,19–21] MCD-SS highlighted the negative impact of the symptoms experienced by MCD patients on their quality-of- life.[6] A major limitation of MCD-SS was that it was developed before the publication of international evidence-based diagnostic criteria for iMCD and it is therefore not specific to iMCD.[1] Additionally, not much is known about the impact on caregivers. Several published studies in rare diseases have shown that long-term care for an affected family member can negatively influence caregivers' physical, social, and emotional wellbeing, often resulting in reduced quality-of- life.[22,23] The MCD-SS did not explore the impact of symptoms on informal-caregivers. Incorporating patient and caregiver perspectives on the impact of the fluctuating nature of iMCD symptoms can facilitate timely initiation of treatment, better symptom monitoring, early detection of flare ups, and shared care leading to greater patient satisfaction and improved physician-patient communication. The primary objective of this study was to establish a comprehensive iMCD-centred symptom inventory from a patient perspective and quantifying the impact of symptom burden on various aspects of daily living. A secondary objective was to investigate caregivers' perspective on patients' iMCD-symptom burden and impact on the caregivers' daily life.

Methods

Study design and participants

The iMCD survey questionnaires were developed in a stepwise manner to ensure appropriate stakeholder (patient, clinician, caregiver and researcher) engagement and a systematic and evidence-based development of question content (Figure SI). Firstly, a literature review (Medline, Embase, Cochrane database of Systematic Reviews supplemented with a manual search) was conducted from the first date available till April 2020 to identify existing iMCD symptom disease scales and PRO tools, as well as the key themes for symptoms experienced by patients or reported by their caregivers (Figure SI). The literature search identified a PRO scale-specific to MCD, the MCD-SS.[6,19–21] Also identified was the CarerQol-7D for caregivers,[24] a questionnaire used in informal care research and economic evaluations of health care interventions. MCD-SS and CarerQol-7D were reviewed for context, terminology, and question phrasing. It was important that the survey questions reflected disease burden and impact on daily life, with the Short Form-36 domains providing a suitable reference point.[25] Following this, clinical validation of symptom themes and potential impact on daily lives was conducted.

The next step was the development and refinement of the survey questions. The initial draft survey questions were reviewed by all stakeholders, including the Castleman Disease Collaborative Network (CDCN) and clinicians. Following this review, the identification of sexual dysfunction as an additional symptom, commonly experienced by patients, resulted in elements of the Sexual Dysfunction Questionnaire to be incorporated in the iMCD surveys. The two surveys were subsequently piloted by an independent researcher who reviewed and refined the questions for appropriateness and functionality. Piloting of the surveys consisted of administering the survey to a sample of patients and caregivers respectively. Lastly, the CDCN and the authors reviewed both surveys for face and content validity. The surveys were made available on SurveyMonkey® for approximately 6 months, from April 14 to November 8, 2021, and are available in the (Appendix I and II). iMCD patients and caregivers (caregivers were not necessarily connected to the patients responding to the survey) registered with the CDCN were invited to complete the survey. The CDCN used several platforms for recruitment, including websites, social media, and newsletters to its members. Eligibility criteria for the patients included participants aged ≥18 years and reporting having a healthcare practitioner-confirmed diagnosis of iMCD. Exclusion criteria included patients who had enrolled in a clinical trial over the last 6 months. Caregiver eligibility criteria were those aged ≥18 years and their role had to be that of a primary informal caregiver (relative, spouse or friend) of a person who met the patient eligibility criteria.

Data collection

The study consisted of two bespoke 45 question non-interventional surveys (patient and caregiver) administered online. Respondents answered a set of closed-ended pre-defined response questions (34/45) or open-ended questions (11/45) that allowed them to elaborate on their answers. The administration of the questionnaire was not timed to any particular aspect of treatment (agnostic of treatment timing or treatment type). The surveys took approximately 30 min to complete. To avoid respondent fatigue, the online survey included a facility for respondents to save their work at intervals and return to complete the survey later. In this qualitative survey, patients and caregivers were asked a series of questions relating to symptomatology experienced and its severity, and the impact of symptom

burden on their daily lives (five severity level options). Each of the five severity options related to impact on daily life was later assigned a numerical Likert scale value ranging from 0 to 4 (0, no impact; 4, severe impact). To minimise recall bias, patients and caregivers were asked about the symptoms experienced by the patient in the week preceding the survey. Some symptom-related questions in the survey were not time-dependant, in order to capture the full extent of the impact of symptoms on patients and caregivers. The questions in the two surveys were largely similar, however, there were some differences. For example, with regards to the number of symptoms, the patient survey included 27 symptoms versus 23 symptoms in the caregiver survey (the caregiver survey excluded swollen lymph nodes, cough, and dry mouth). To ensure researchers did not adversely affect the rights and welfare of participants, the online survey platform included links to information regarding data collection and privacy policy terms and conditions. The online survey platform was monitored by a single researcher who responded to follow-up emails, undertook potential pharmacovigilance reporting, considered ethical issues, and any emotional responses the questions may elicit. Storage of the data remained with Lumanity/BresMed; question responses were de-identified and saved on password-encrypted servers.

Ethics statement

Ethics review approvals or waivers were obtained for the online survey in Australia (Bellberry Human Research Ethics Committee), UK (ethics review waivers obtained for each country from the National Health Service Research Ethics Committee), Canada and the US (via Advarra Centre Institutional Review Board). Written consent was obtained before respondents were permitted to complete the survey.

Statistical analyses

Descriptive statistical analysis was performed on the close-ended questions. Central tendency (mean, median), standard deviations and ranges were calculated where appropriate. Additionally, thematic data analysis was applied to recognise patterns in the qualitative data obtained. Ordinal logistic regression analysis was used to assess the relationship between four explanatory variables (age, gender, employment status, and number of symptoms) and impact on different aspects of daily life. Age group was categorised as less than 40 years versus greater than or equal to 40 years. Employment status was categorised as 'working group' that included being full or part-time employed, full or part-time student or homemakers, and 'not working group' that included those that were retired, unable to work/on disability allowances or unemployed. The effect of each variable is reported as an odds ratio (OR) with 95% confidence intervals ($p < 0.05$). All statistical analyses were conducted in SPSS v23 and logistic regression utilised Minitab version 20.

Role of the funding source

Representatives of the funding body participated in the study and survey design, data analysis, interpretation, and reporting of the results. The study sponsor, and all investigators approved all aspects of the study. For advice on statistical analyses, expert input was sought. All authors had access to de-identified data, were involved in data analysis and interpretation and responsible for the decision to submit for publication. The corresponding author did not receive any financial compensation for this study.

Results

Of the 69 patients who took the survey, 12 were excluded for not meeting the inclusion criteria (Fig. 1). An additional six patients who reported having POEMS were excluded, as the consensus iMCD diagnostic criteria considers POEMS to have a different natural history and therapeutic approach from iMCD.[1] A total of 51 patients with confirmed iMCD diagnosis were analysed. Due to small number of iMCD-TAFRO patients (11/51), all the iMCD-NOS and iMCD-TAFRO were grouped together under the category iMCD for all analyses (results for TAFRO patients are reported in Suppl. Figures SII–SIV). Of the 25 caregivers that took the survey, 14 were excluded; 12 did not meet the eligibility criteria and two cared for patients who had POEMS (Fig. 1).

The demographics, disease characteristics and treatment information are presented in Table 1. Patient respondents were predominantly female (56.9%) with a mean age of 47.4 years (range, 22–78 years), while caregivers were predominantly female (81.8%) with a mean age of 54.9 years (range, 38–71 years). The caregivers had cared for their loved ones for an average of 4.9 years (range, 1.3–11 years). Less than half of patient respondents (41.2%) and majority of caregivers (63.6%) were employed full-time. Of the 51 patient respondents, 40 (78.4%) reported having iMCD-not otherwise specified (iMCD-NOS) subtype and 11 (21.6%) reported having the TAFRO variant. Caregivers reported that their loved ones primarily identified as iMCD-NOS (7/11, 63.6%) with the remaining having TAFRO syndrome (4/11, 36.4%). Thirty-six patients (70.6%) reported receiving iMCD-directed treatment—23/51 (45.1%) received an intravenous treatment and 13/51 (25.5%) received a combination of intravenous and oral treatment. Approximately, 25% of patients who received intravenous and oral treatment reported receiving an oral steroid. Of the 36 patients (70.6%) receiving iMCD treatment, 31 (86.1%) reported receiving an anti-interleukin-6 monoclonal antibody with the frequency of administration varying between once-a-week to once every six weeks.

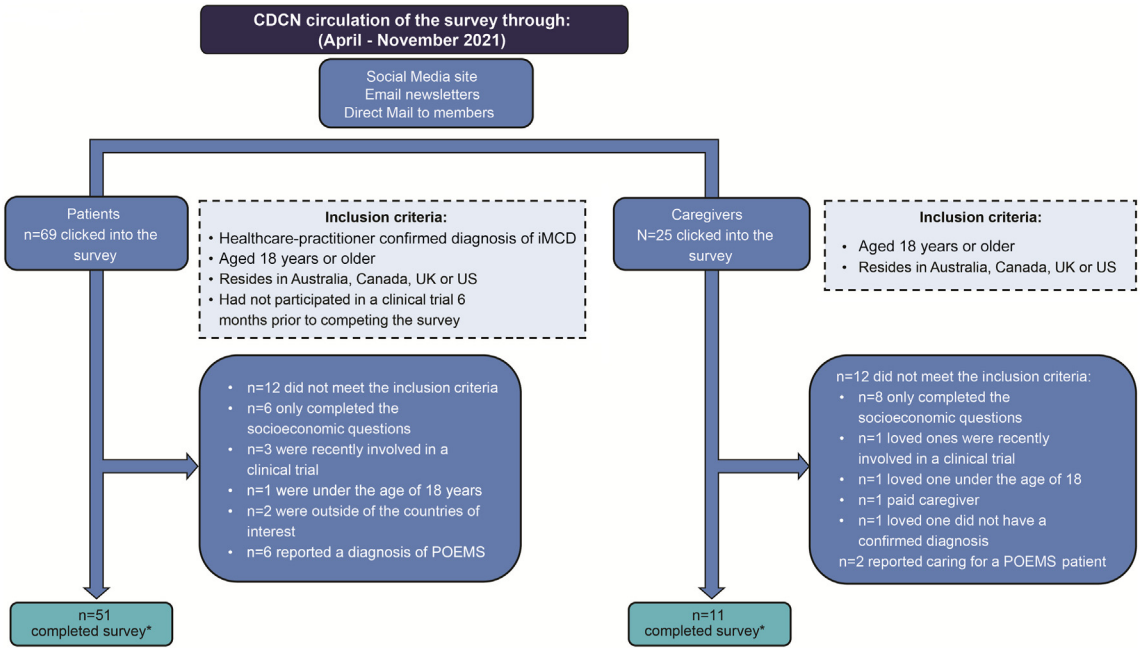

***Fig. 1:* Selection of Study Cohort for iMCD Survey**. CDCN: Castleman disease collaborative network; iMCD: idiopathic multicentric Castleman's disease; US: United States; UK: United Kingdom.

A total of 27 unique symptoms were experienced by the 51 patients in the week prior to completing the survey (Fig. 2A). Five patients experienced no symptoms. In patients reporting symptoms, tiredness was the most prevalent symptom (78.4%), followed by weakness (41.2%), night sweats (39.2%) and numbness/tingling (37.3%). Even though not all patients experienced every symptom, patients in general reported experiencing multiple distinct types of symptoms.

As shown in Fig. 2B, most patients (88.3%) reported experiencing at least one symptom from the questionnaire symptom inventory. The mean number of symptoms experienced by a patient was 6.7 (range, 0–22 symptoms) with 70.6% reporting having experienced four or more symptoms. The 27 unique symptoms were classified into seven clinically relevant categories as shown in Fig. 2C, with most patients (84.3%) reporting constitutional symptoms. Neurologic symptoms were reported by 58.8%, neuropsychiatric symptoms by 45.1% of patients, and 41.2% reported gastrointestinal symptoms. Almost a third of the iMCD cohort reported experiencing palpable lymphadenopathy, dermatologic and respiratory symptoms.

When analysed by specific symptom type, most patients reported that the symptom/s they experienced had a slight to moderate effect on their daily life (Fig. 3). The patient-reported symptoms that had the most severe impact on daily life included lethargy (50.0%), nausea/vomiting (60.0%), weakness (52.4%) and sluggishness (53.3%). To obtain a more granular understanding of how the symptom burden impacted various aspects of daily life, we looked at the impact on 11 specific domains of daily life that encompassed physical, mental, social, financial, sexual function, and work as shown in Fig. 4. Of the 46 respondents who had symptoms, approximately half or more of patients reported moderate to very severe impact on their pain/discomfort (65.2), ability to travel (60.8%), sexual function (56.5%), emotional/psychological wellbeing (52.2%), financial wellbeing (52.1%), general routine (52.1%), social life (50.0%) and mobility (47.8%). Patient quotes regarding the impact of symptoms on their daily life are reported in the Table SII.

We then performed ordinal logistic regression analysis to determine any association between age, gender, employment status and multiplicity of symptoms with different aspects of daily life. The ability to travel was significantly impacted in patients 40 years of age or older compared to those less than 40 years (OR = 0.24; 95% CI 0.06–0.98) (Figure SV). Apart from travel, age did not have an adverse effect on other aspects of daily life. When analysed by gender, the only observed difference between the sexes was the ability to perform general routine that included household activities and personal care. Females were more significantly affected than males (OR = 9.44; 95% CI 2.31–38.61) (Figure SVI). When analysed by employment status, certain aspects of daily life particularly pain/discomfort (OR = 3.73; 95% CI 1.07–13.04), ability to travel (OR = 4.12; 95% CI 1.14–14.94), mobility (OR = 5.14;

Respondents characteristics	Patient respondents	Caregiver respondents
Number of respondents, N	51	11
Gender, n (%)		
Female	29 (56.9%)	9 (81.8%)
Male	22 (43.1%)	1 (9.1%)
Prefer not to answer		1 (9.1%)
Age mean (SD, Range), years	47.4 (1.9, 22–78)	54.9 (8.7, 38–71)
Years under caregiver care, mean (SD, range)		4.9 (3.4, 1.3–11)
Country, n (%)		
Australia	4 (7.8%)	
Canada	4 (7.8%)	1 (9.1%)
UK	3 (5.9%)	
US	40 (78.4%)	10 (90.9%)
Employment status, n (%)		
Disabled (unable to work/on disability allowances)	13 (25.5%)	1 (9.1%)
Employed full time	21 (41.2%)	7 (63.6%)
Employed part time	4 (7.8%)	1 (9.1%)
Homemaker	3 (5.9%)	1 (9.1%)
Prefer not to say	1 (2.0%)	
Retired	3 (5.9%)	1 (9.1%)
Unemployed/seeking opportunities	6 (11.8%)	
Ethnic Group, n (%)		
Asian	7 (13.7%)	
Black or African American	1 (2.0%)	
Native Hawaiian or Other Pacific Islander	2 (3.9%)	
Prefer not to answer	3 (5.9%)	
White	38 (74.5%)	10 (90.9%)
Hispanic		1 (9.1%)
Disease characteristics of patients	**Patient survey**	**Caregiver survey**
Sub type, n (%)		
iMCD NOS	40 (78.4%)	7 (63.6%)
TAFRO	11 (21.6%)	4 (36.4%)
Treatment for iMCD patients, n (%)	**Patient survey**	**Caregiver survey**
Not receiving treatment	8 (15.7%)	1 (9.1%)
Treatment for iMCD symptoms	3 (5.9%)	
Receiving treatment for iMCD	36 (70.6%)	9 (81.8%)
IV treatment only	23 (45.1%)	7 (63.6%)
Both IV and oral treatment	13 (25.5%)	2 (18.2%)
Missing	4 (7.8%)	1 (9.1%)

iMCD: idiopathic multicentric Castleman's disease; iMCD NOS: idiopathic multicentric Castleman's disease not otherwise specified; SD: standard deviation; TAFRO: thrombocytopenia, anasarca, fever, bone marrow reticulin fibrosis or renal dysfunction and organomegaly.

Table 1: **Characteristics of patients and caregivers participating in the iMCD survey.**

95% CI 1.39–19.01), general routine (OR = 5.36; 95% CI 1.34–21.49), work/education (OR = 5.67: 95% CI 1.58–20.39) and financial wellbeing (OR = 6.41; 95% CI 1.70–14.94) were significantly more impacted in those who were not working compared to those who were still employed ($p < 0.05$); Fig. 5A). When analysed by multiplicity of symptoms, the higher the number of symptoms' the more likely it negatively impacted the daily life activities, and this was true for all aspects of daily life (OR<1; Fig. 5B).

Forty-three percent (22/51) of patients reported that they received caregiver assistance, and that care was provided from multiple sources though predominantly they were either a spouse (22/22) or a child (5/22). Of the 11 caregivers that participated in the survey, the majority were women (81.8%), consistent with caregiver distribution in the literature.[26] The relationship of caregivers and their loved ones was mainly that of parent to their adult offspring (63.6%) with the remainder being partners (36.4%) to patients. The mean duration of time spent caring for their loved one was 4.9 years (range, 1.3–11.0 years). The caregivers reported that the week before completing the survey, their loved one experienced a mean of 4 symptoms (range, 0–8.0) compared to an average of 6.7 symptoms reported by patients. The most frequently observed category of symptoms reported by caregivers were constitutional symptoms (90.9%), gastrointestinal (54.5%) and neuropsychiatric (54.5%). These mirrored the key symptom categories reported by patients. Caregivers reported that the most impacted aspect of daily life were their emotional and psychological wellbeing (90%), ability to travel (80%) and social life (80%) (Figure SVII). Half of all caregivers noted a moderate to severe impact on their sexual functioning. Caregiver quotes reflect the emotional burden they experience (Table SII).

Discussion

This international iMCD survey is the first large survey to systematically evaluate the spectrum of symptoms experienced by patients and extensively evaluate the impact of the symptom burden on everyday life, from both the patient and caregiver perspectives. The disease symptomatology captured indicates extensive symptom burden in iMCD patients that remain widely under recognised and unappreciated. The current body of work significantly expands the symptomatology explored earlier in the MCD-SS used in the phase II trial.[6,21] Similar to the phase II trial, where symptoms grouped into the 'fatigue cluster' were the most reported symptom, patients in this survey also frequently reported symptoms of tiredness, weakness (physical), lethargy and sluggishness. In a previously published systematic review of 128 case reports of MCD, patients frequently reported oedema, swollen lymph nodes, fever, night sweats and weight loss[26]–all symptoms also captured in this survey. In this survey, patients reported a total of 27 unique symptoms with most (~70%) reporting four or more symptoms and a third reporting a clustering of more than ten symptoms. To our knowledge, this is the most comprehensive characterization of symptom profile in iMCD patients reported to date. An important consideration when drawing comparisons across studies is that the two earlier studies[6,26] predated the development of international diagnostic criteria for iMCD and therefore, likely

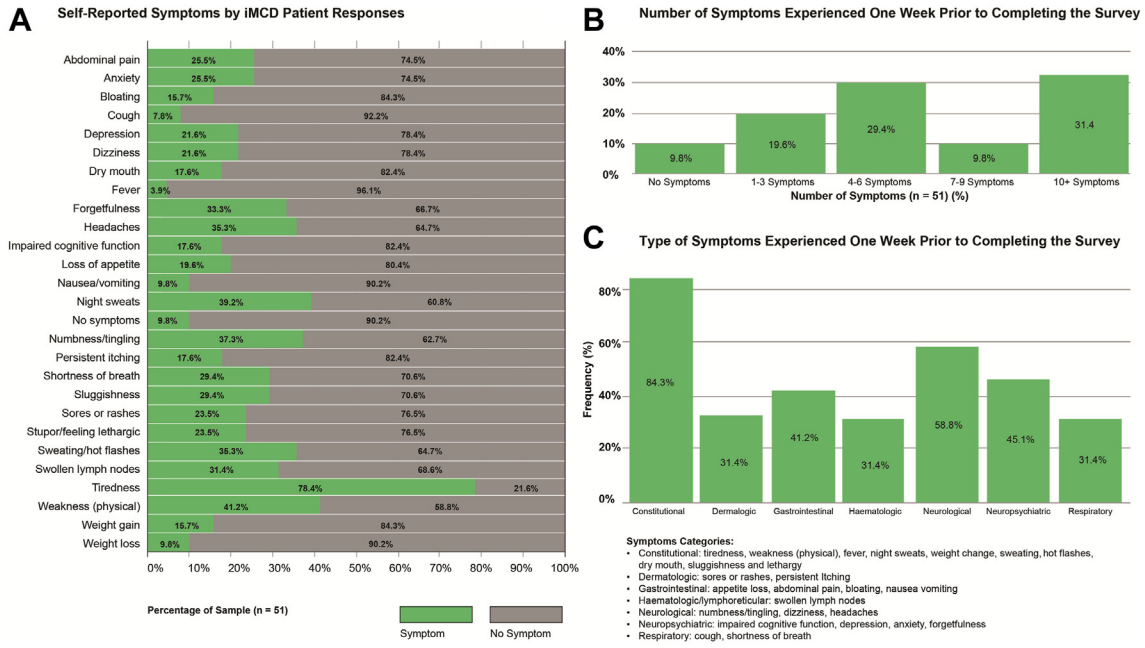

Fig. 2: **Multiplicity and types of symptoms reported by iMCD patient respondents: A: Self-reported symptoms by iMCD patient responses; B: Number of symptoms experienced once week prior to completing the survey; C: Type of symptoms experienced one week prior to completing the survey**. iMCD: idiopathic multicentric Castleman's disease.

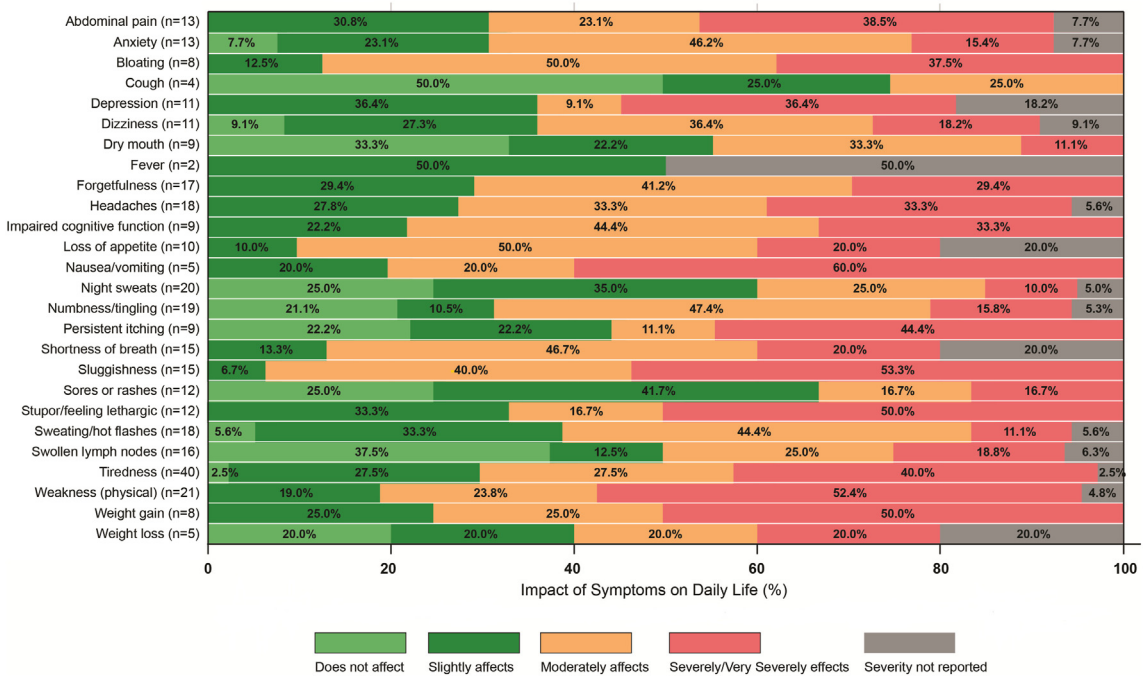

Fig. 3: **The impact severity on daily life for iMCD patients experiencing a symptom**. Note: Sample size of symptoms corresponds to the number of patients who reported experiencing the relevant symptoms one week prior to completing the survey.

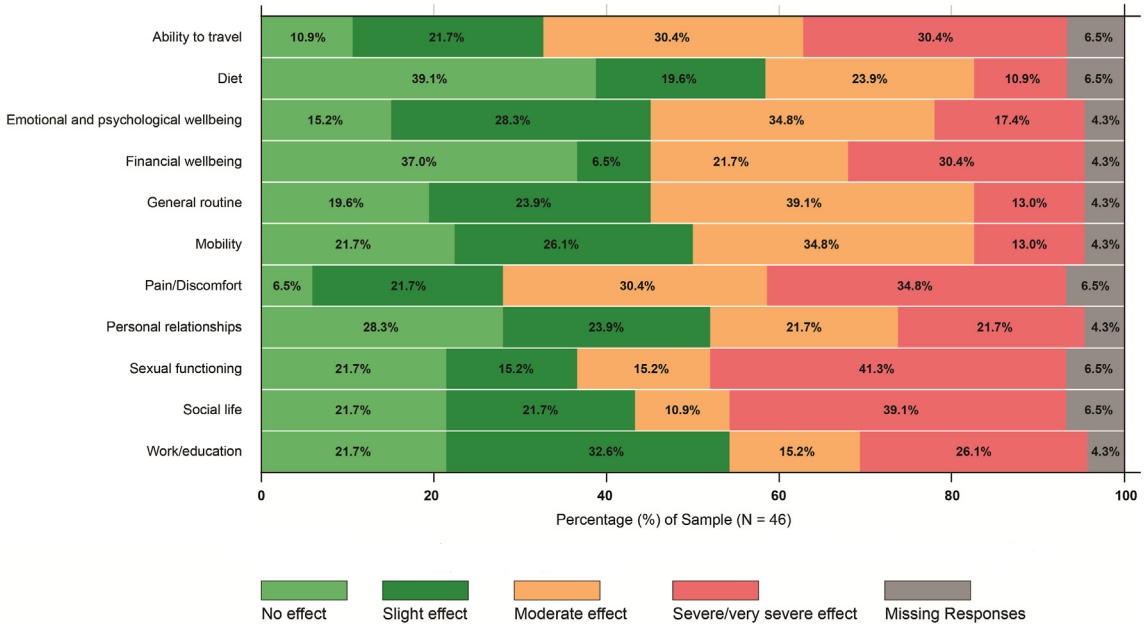

Fig. 4: **Severity Impact of symptoms on aspects of daily life**. Note: Sample size of N–46 accounts for only those patients which reported experiencing symptoms, with five patients having reported not experiencing any iMCD symptoms.

included non-iMCD cases. Secondly, the proportions of patients treated with recommended IL-6 directed therapy across these studies differ, making it difficult to make comparisons of symptomatology. These symptoms are diverse, comprising systemic as well as different organ-specific symptoms. Constitutional symptoms, a recognised symptomatology in iMCD,[6] were identified as the most common symptom category by both patients and caregivers occurring in over 80% of patients. Among organ-specific symptoms, we report a high burden of neurological, neuropsychiatric, and gastrointestinal symptoms. Neuropsychiatric symptoms, the second most frequently experienced category of symptoms in the current survey, were not previously identified in the MCD-SS.

These symptoms were reported by a largely treated iMCD population (~80% of patients in this survey), suggesting that symptom control in these patients remains challenging and inadequately controlled despite patients being on therapies. Some of these symptoms (lethargy, weakness, sluggishness) had the most severe impact on daily life and yet, they are not routinely measured or evaluated as part of treatment response monitoring which relies heavily on radiologic and

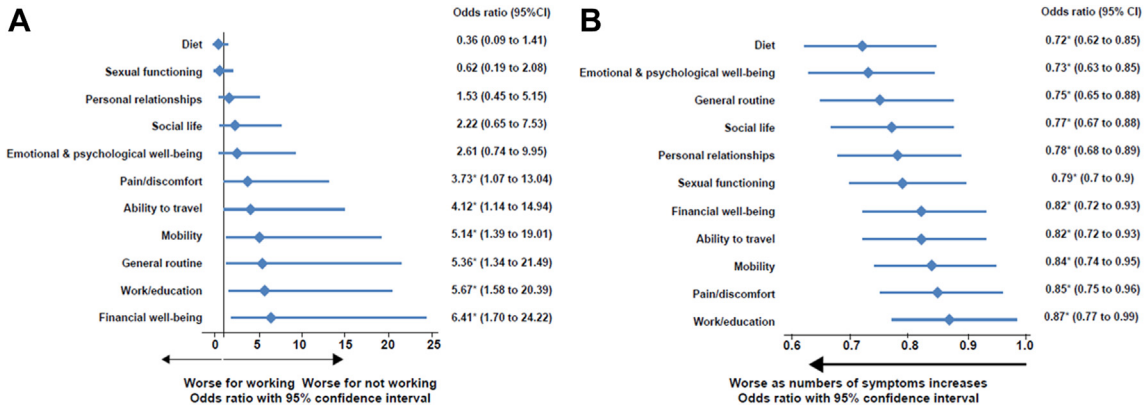

Fig. 5: **Forest plot of the odds ratios of impact on daily life by (A) Employment status (working vs not working) and (B) Multiplicity of symptoms**. The multivariate regression model was adjusted by age, gender, and number of symptoms. *Level of significance was set at $p < 0.05$.

laboratory assessments. Given that symptom management is a key element of iMCD treatment strategy, these findings identify a key gap in the current clinical management of these patients.

This survey also provides new and important data regarding the negative effects of iMCD on activities of daily living of both patients and caregivers. More than half of patients who experienced any symptom reported moderate to very severe impact on their ability to travel, emotional/psychological wellbeing, financial wellbeing, household activities, mobility, pain, sexual function, and social life. This was the first survey that explored the impact of symptoms on sexual function in iMCD patients. Sexual functioning (including sexual interest, desire and arousal, orgasm, satisfaction, activity, relationship, masturbation) was the third most impacted aspect of daily life with 59.1% of patients affected.

In contrast to age and gender which had a limited impact on daily life, the multiplicity of symptoms had a significant detrimental impact on all aspects of daily living in adjusted analyses. In a high percentage of patients (43%) who reported not working because of disability, retirement or being unemployed, our findings identified disease-related pain/discomfort, inability to travel, impaired mobility, limitations in performing household activities, interruptions in work/education and financial difficulties as possible reasons. Not surprisingly, most caregivers (>80%) reported that their ability to travel, social life, emotional and psychological wellbeing and sexual functioning were severely impacted by symptoms experienced by their loved ones. These findings indicate that the adverse impact of iMCD extend beyond the patients and profoundly affects the lives of their families and caregivers. Given the key role of caregiver support in the management of these patients on lifelong treatments, consideration should be given to identifying caregiver burden and providing necessary support services as a part of integrated care of iMCD patients.

Our findings merit discussion on integrating periodic assessment of patient-reported symptom burden as an outcome measure in the clinical management of patients. Considering the negative impact of the multiplicity of symptoms (symptom burden) on daily life, adopting a symptom-centric approach would be meaningful and relatable to patients and providers alike. Identification of substantial symptom burden in patients on iMCD-therapies as shown in this survey suggests that reliance of tumour-centric endpoints (regression of lymphadenopathy or normalization of laboratory abnormalities or progression-free survival) may not convey the true extent or the degree of treatment response. Even more challenging, is that for several of the frequently reported symptoms such as impaired cognition, depression, forgetfulness, lethargy, and constitutional symptoms, there are no reliable laboratory or imaging tests. Therefore, for a chronic hyperinflammatory symptomatic disease with no curative options such as iMCD, having symptom-based endpoints to monitor treatment response is an imperative goal for symptom alleviation and improvement of quality of life. While pre-specified radiologic and laboratory response criteria are helpful, longitudinal tracking of symptom burden can significantly enhance discrimination of disease symptoms (worsening or improvement of existing symptoms or new symptoms) versus treatment toxicities at the individual level, allowing for personalized and informed intervention.

This study has inherent limitations primarily related to its descriptive design, self-reported nature of the survey and challenges related to the rarity of iMCD. Identification of patients for this survey relied on respondents self-reporting their healthcare practitioner-confirmed diagnosis of iMCD as opposed to direct physician reporting or clinical documentation of histopathologic, laboratory and radiologic data. This symptomatology-focused survey did not have the scope to ascertain diagnostic certainty of these cases, but we feel reasonably confident about the accuracy of respondents' iMCD diagnosis based on our recruitment approach. Patients were recruited via the CDCN which has a reliable process for reporting iMCD and additionally, the caregivers of such patients were appointed from the same source. As for this survey, all individual specific iMCD clinical entities were grouped under the broad category of iMCD for analysis due to small numbers, the symptomatology captured by this survey cannot discriminate the differences in number and severity of symptoms between these entities. This is important to consider while interpreting the data as iMCD-NOS and iMCD-IPL typically tend to have milder course than iMCD-TAFRO. While the survey had questions on current treatment, the data lacked sufficient detail with regards to type of therapy, dosages, treatment line, and treatment duration. A limitation of this kind of cross-sectional assessment is that it limits the ability to distinguish disease-related symptoms from treatment side effects. Recruitment might have been affected by the cognitive complexity of the survey. Additionally, considering COVID-19 restrictions were in place during the survey period, it is likely that restricted movement might have affected respondents' answers to questions concerning the impact of symptoms on social activities and ability to travel.[27,28]

In summary, we describe a multistep methodological process of developing a patient-centred comprehensive symptom inventory for iMCD showing high symptomatology. Using a hybrid qualitative and quantitative analyses we demonstrate the broad impact of high symptom burden on several aspects of daily life. These findings can inform diagnostic criteria, clinical assessment, and patient care, and form the foundational work of our ongoing investigation of its psychometric

properties with the goal of eventual development of the first ever iMCD-specific symptom scale.

Contributors

Contributors FS, GWW, NZ, EJ and NM contributed to the conception and design of the study.

EJ and NM contributed to the oversight and management of data collection.

SM, FS, GWW, EJ, NM, MF, JB contributed to data analysis and accessed and verified the data, SM, FS, GWW, EJ, NM, MF, JB contributed to the interpretation of results.

SM, FS, GWW, EJ, NM, MF, JB drafted the manuscript and provided critical review of the manuscript.

All authors read and approved the final version of the manuscript. All authors were responsible for the decision to submit the manuscript.

Data sharing statement

Additional data shared has been provided in the supplement. For any additional data please contact the authors.

Declaration of interests

SM has reports research funding for investigator-initiated trials from Bristol Myers Squib (Grant Number—CELG1611SM), Jazz Pharmaceuticals (three trials) and Novartis (one trial), all research support was provided to the institution (no personal salary). He has received consulting fees or honoraria for lectures, presentations or educational events from BioPharm, Celgene, Novartis, Blueprint Medicines, EUSA Pharma, Aplastic Anemia and MDS International Foundation, Celgene (now Bristol Myers Squib), Bristol Myers Squib, McGraw Hill Hematology Oncology Board Review and Partnership for Health Analytic Research, LLC (PHAR, LLC). He is a member of the Scientific Advisory Board of the CDCN and American Society of Hematology, Committee on Promoting Diversity (with no payments received for these memberships). FS is an employee of EUSA Pharma. GWW is an employee of EUSA Pharma. NZ is a former employee of EUSA Pharma.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102192.

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