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Source / Izvornik: **Bone Marrow Transplantation, 2016, 51, 1513 - 1517**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1038/bmt.2016.158>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:127:843175>

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Download date / Datum preuzimanja: **2025-03-03**



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LETTER TO THE EDITOR

High prevalence of small- and large-fiber neuropathy in a prospective cohort of patients with moderate to severe chronic GvHD

Bone Marrow Transplantation (2016) 51, 1513–1517; doi:10.1038/bmt.2016.158; published online 6 June 2016

Increasing safety of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has also increased the number of patients at risk for developing chronic GvHD (cGvHD). Peripheral nerve neurological manifestations and symptoms are being increasingly recognized in cGvHD, however, prospectively planned clinical studies have rarely been reported. There is a substantial lack of understanding of the mechanisms that lead to peripheral neuropathy (PN) in cGvHD and therapeutic options are profoundly limited and mostly symptomatic. Currently, myasthenia gravis, muscle cramps and PN are considered as 'other' complications related to cGvHD, whereas myositis and polymyositis are considered as 'distinctive' neurological manifestations of cGvHD. Consequently, the diagnosis of neurological cGvHD can only be established when additional 'diagnostic' manifestations of cGvHD are present and the neurological manifestations are still not incorporated into the scoring system.^{1,2} This presents an important gap, because damage of the peripheral nervous system (PNS) in the context of cGvHD can produce severe disability, morbidity and mortality.²

In order to investigate the incidence and characteristics of PNS manifestations, with emphasis on small-fiber neuropathy (SFN), we have conducted a prospective cohort study on patients with cGvHD developed after allo-HSCT.

The study protocol consisted of hematologist work-up (evaluation and scoring performed according to 2005 NIH cGvHD Consensus recommendations), laboratory work-up for excluding common causes of PN (diabetes, folic acid, vitamin B12, zinc, selenium or copper deficiency), tissue biopsy and other subspecialist examination according to specific patient needs (neurology, dermatology, dental and so on).³ Neurologic evaluation was focused on determination of the type and pattern of nerve damage and consisted of nerve conduction studies (NCS) for sural and peroneal nerves, quantitative sensory testing (QST), The Pain Detect Questionnaire (PDQ) and Total Neuropathy Score.^{4,5} Peripheral nerves contain different types of nerve fibers. The largest nerve fibers (A-alpha and A-beta) are involved in voluntary movements and deep sensation and they were analyzed by NCS. The small fibers (A-delta and C) are involved in the temperature and pain sensation and they were analyzed by QST. IBM SPSS Statistics 20 program was used for statistical analyses. A Kendall's Tau b correlation was run to determine the relationship between cGvHD variables and fiber damage. Fisher's exact test and χ^2 -test were used for comparison of two or three and more independent groups. A value of $P < 0.05$ was deemed statistically significant.

A total of 27 patients enrolled in this study were referred to neurology for neuromuscular complications analysis. Prior laboratory work-up showed no significant micronutrient deficiencies that are associated with PN. None of the patients had pre-existing neuropathy or underlying disorder that could lead to PN. Patients' characteristics are shown in Table 1. Clinical and/or

electrophysiological signs of PN were observed in 25 (92.6%) patients with predominance of mixed small and large fiber neuropathy (LFN; $n = 18$, 66.7%). Twenty-two (81.5%) patients had signs of LFN on NCS, mostly axonal sensorimotor type ($n = 18$, 66.7%). Twenty-one (77.8%) patients had abnormal finding on QST, mostly with both A-delta and C-fibers damaged ($n = 10$, 37%). A-delta fibers were damaged in 17 (63%) and C-fibers in 14 (51.9%) patients. Neurological examination findings are shown in Table 2.

Correlation was run to determine the relationship between different cGvHD variables and specific findings indicating peripheral nerve damage (Table 3). The intensity of immunosuppression showed moderately strong association with A-beta fiber damage ($\tau b = 0.576$, $P = 0.002$). cGvHD of lung had moderately strong negative correlation with A-delta and A-beta fiber damage ($\tau b = -0.655$, $P = 0.000$; $\tau b = -0.526$, $P = 0.005$ respectively). cGvHD of mouth had weak to moderately strong negative correlation with muscle cramps ($\tau b = -0.374$, $P = 0.044$). Weak to moderately strong positive correlation ($\tau b = 0.443$, $P = 0.015$) was established between cGvHD of skin and A-delta fiber damage. For five patients who received MAC the therapy data were missing or incomplete. Moderately strong, negative correlation was established between cyclophosphamide and A-beta fiber damage ($\tau b = -0.624$, $P = 0.004$). Weak to moderately strong, positive correlation considering A-delta and moderately strong correlation considering A-beta fiber damage was found for fludarabine ($\tau b = 0.498$, $P = 0.022$ and $\tau b = 0.516$, $P = 0.018$, respectively). Moderately strong correlation was found between TBI and neuropathic pain ($\tau b = 0.470$, $P = 0.016$).

Several significant differences were found comparing patients who received reduced intensity conditioning (RIC) and patients who received myeloablative conditioning (MAC), as well as between patients who received PBSC or bone marrow stem cells (BMSC). A-delta and A-beta fiber damage was significantly higher in patients who received RIC than MAC, and PBSC than BMSC ($P = 0.018$ and $P = 0.040$, $P = 0.006$ and 0.022 , respectively). Patients who received RIC and patients who received PBSC, had significantly higher incidence of SFN (mostly combined A-delta and C-fiber neuropathy) and mixed (small and large) fiber neuropathy comparing with patients who received MAC or BMSC ($P = 0.025$ and $P = 0.007$, respectively). Considering pure LFN the trend was the same, but did not reach the level of statistical significance.

This study shows a high prevalence (92.6%) of clinical and/or electrophysiological signs of PN, predominantly mixed SFN and LFN (66.7%). The results of studies in cGvHD patients also show that PNS damage is very common.^{6,7} Painful muscle cramps are present in a significant proportion of cGvHD patients (33.3% here and 50% in study of Kraus *et al.*).⁶ The neurologic assessment in our study was done at a 21-month median after allo-HSCT, when a significant number of patients were found to have very advanced neuropathy. Kraus *et al.*⁶ found that muscle cramps are more frequently present in patients with milder forms of neuropathy, whereas in advanced forms they diminish. According to our results, a large proportion of cGvHD patients (77.8%) have SFN

Table 1. Patient characteristics

Characteristics	Number of patients
Sex: male, female	14 (51.9%), 13 (48.1%)
Median age	41 (16–73) years
Hematologic disease	
Leukaemia or MDS	19 (70.4%)
Chronic myeloproliferative disease	2 (7.4%)
AA/PNH	3 (11.1%)
Lymphoma	2 (7.4%)
CLL	1 (3.7%)
Stem cell source	
Bone marrow	11 (40.7%)
Peripheral blood	16 (59.3%)
Donor type	
Matched related	19 (70.4%)
Matched unrelated	8 (29.6%)
Conditioning regimen^a	
MAC	13 (48.1%)
RIC	14 (51.9%)
GvHD prophylaxis	
CSA+MTX	14 (51.9%)
CSA+MMF	9 (33.3%)
CSA+ATG	4 (14.8%)
Previous acute GvHD sites involved	
Skin	17 (63%)
GI tract	17 (63%)
Liver	4 (14.8%)
	1 (3.7%)
cGvHD classification	
Classic chronic GvHD	24 (88.9%)
Overlap syndrome	3 (11.1%)
cGvHD onset	
Quiescent	9 (33.3%)
De novo	10 (37%)
Progressive	8 (29.6%)
Sites involved at cGvHD evaluation	
Skin	14 (51.9%)
Eyes	13 (48.1%)
Mouth	11 (40.7%)
Liver	9 (33.3%)
GI tract	4 (14.8%)
Lungs	13 (48.1%)
Joint and fascia	8 (29.6%)
Genital tract (women)	6 (46.15%)
No of sites involved at evaluation	
1 or 2	13
3	7
>3	7
Global NIH score	
Mild	1 (3.7%)
Moderate	14 (51.9%)
Severe	12 (44.4%)
Intensity of systemic immunosuppression^b	
None	16 (59.3%)
Moderate	9 (33.3%)
High	2 (7.4%)
Calculated time span in months for:	
Allo-HSCT to study enrolment	Median, range 19 (4–195)
Allo-HSCT to cGvHD diagnosis	9 (1–128)
cGvHD diagnosis to study enrolment	7 (0–176)
Allo-HSCT to neurologic assessment	21 (4–195)

Abbreviations: AA = aplastic anaemia; allo-HSCT = allogeneic hematopoietic stem cell transplantation; ATG = antithymocyte globulin; CSP = cyclosporine; cGvHD = chronic GvHD; MAC = myeloablative conditioning; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MTX = methotrexate; RIC = reduced intensity conditioning; PNH = paroxysmal nocturnal hemoglobinuria. ^aDrugs used in conditioning regimen included: busulfane (3.2 mg/kg), cyclophosphamide (60 or 70 g/m²), fludarabine (30 or 25 mg/m²); one patient received TBI (2 Gy); antithymocyte globulin was used in 14 patients (2.5 or 40 mg/kg); for 5 patients the data of used drugs were unknown. ^bModerate = prednisone \geq 0.5 mg/kg/day and/or any single agent/modality; high = 2 or more agents/modalities \pm prednisone \geq 0.5 mg/kg/day⁹.

Table 2. Clinical and electrophysiological findings

Neurological finding	Number of patients
Paraesthesia	7 (25.9%)
Muscle cramps	9 (33.3%)
Muscle atrophy of LE	14 (51.9%)
Superficial sensation	
Impaired sensation for cold stimuli	6 (22.2%)
Impaired sensation for hot and cold stimuli	4 (14.8%)
Vibration sense LE impaired \leq 4/8	7 (25.9%)
Neuropathy assessment	
Only SFN	3 (11.1%)
Only LFN	4 (14.8%)
SFN+LFN	18 (66.7%)
PN total	25 (92.6%)
NCS findings^a	
Sensory neuropathy	3 (11.1%)
Motor neuropathy	1 (3.7%)
Sensorimotor neuropathy	18 (66.7%)
LFN total	22 (81.5%)
QST findings^b	
SFN (A-delta fibers)	7 (25.9%)
SFN (C-fibers)	4 (14.8%)
SFN (A-delta and C-fibers)	10 (37%)
SFN total	21 (77.8%)
Small-fiber damage	
A-delta fibers damaged	17 (63%)
C-fibers damaged	14 (51.9%)
PDQ	
Nociceptive	21 (77.8%)
Unclear	5 (18.5%)
Neuropathic	1 (3.7%)
Neuropathic pain	4 (14.8%)
Mean TNS score	5.56 (s.d. 4.39, range 0–18)

Abbreviations: LE = lower extremities; LFN = large fiber neuropathy; NCS = nerve conduction studies; PDQ = pain detect questionnaire; SFN = small-fiber neuropathy; TNS = total neuropathy score; QST = quantitative sensory testing. ^aNCS were performed on Medelec Synergy Multimedia EMG/EP, Oxford Instruments; surface stimulation—bipolar electrodes, cathode/anode distance 2.5 cm (TECA/Medelec, reusable bipolar stimulating electrode); compound muscle action potential (CMAP)—TECA/Medelec bar recording electrode 20 mm; sensory nerve action potential (SNAP) – TECA/Medelec 'digital ring electrodes'. ^bQST was performed on CHEPS/PATHWAY with surface thermal stimuli according to protocols levels and limits based on standardized tests with random warm and cold stimuli.

(A-delta fibers are more frequently affected). However, whether this is a specific subtype of cGvHD neuropathy and associated with specific symptoms (muscle cramps or neuropathic pain) is currently unknown.

In this current study, prior fludarabine was associated with PN, which is a new observation. Some therapeutic agents may activate the mitochondrial-based apoptotic pathway, which seems to have a role in toxic neuropathy development.⁸ Also, PN is a well-recognized manifestation of mitochondrial inherited diseases.⁹ Changes in mitochondrial dysfunction may contribute to the appearance of neuropathy in diabetes, especially in insulin neuritis, a rare iatrogenic form of SFN.^{10,11} The calcium-ion homeostasis dysregulation, together with possible altered function of blood–nerve barrier, may also be involved in this scenario.¹² It is challenging to point to a specific mechanism of toxic peripheral nerves damage in cGvHD, because of interplay of

Table 3. Relationship between different cGvHD variables and type of fiber damage

Kendall's τ_b	Muscle cramps	Paresthesia	A-delta fiber damage	A-beta fiber damage	C-fiber damage	Neuropathic pain
<i>cGvHD onset</i>						
Correlation Coefficient	-0.152	0.022	-0.035	0.223	-0.129	0.013
P-value	0.413	0.906	0.852	0.229	0.487	0.942
<i>Intensity of immunosuppression (Sandy's scale)</i>						
Correlation coefficient	0.068	0.358	0.193	0.576 ^a	-0.229	0.314
P-value	0.723	0.060	0.312	0.002	0.230	0.099
<i>Global NIH score</i>						
Correlation coefficient	0.175	0.006	0.033	0.006	0.011	0.254
P-value	0.365	0.975	0.864	0.975	0.956	0.187
<i>cGvHD of genital tract (women)</i>						
Correlation coefficient	0.201	-0.362	-0.201	-0.362	-0.065	-0.362
P-value	0.466	0.190	0.466	0.190	0.812	0.190
<i>cGvHD of foot and fascia</i>						
Correlation coefficient	-0.097	0.262	-0.095	-0.157	0.138	0.194
P-value	0.608	0.168	0.617	0.408	0.468	0.308
<i>cGvHD of lung</i>						
Correlation coefficient	0.279	-0.168	-0.655 ^a	-0.526 ^a	-0.122	0.171
P-value	0.137	0.373	0.000	0.005	0.518	0.363
<i>cGvHD of liver</i>						
Correlation coefficient	-0.046	-0.210	-0.067	0.314	-0.287	-0.053
P-value	0.806	0.261	0.719	0.092	0.124	0.775
<i>cGvHD of GI tract</i>						
Correlation coefficient	-0.289	-0.242	0.313	0.009	-0.015	-0.170
P-value	0.134	0.210	0.104	0.964	0.937	0.377
<i>cGvHD of eye</i>						
Correlation coefficient	-0.161	0.046	-0.073	-0.023	0.127	0.078
P-value	0.391	0.806	0.696	0.902	0.500	0.677
<i>cGvHD of mouth</i>						
Correlation coefficient	-0.374 ^a	-0.099	0.318	0.292	-0.020	-0.101
P-value	0.044	0.594	0.088	0.117	0.912	0.588
<i>cGvHD of skin</i>						
Correlation coefficient	-0.060	0.141	0.443 ^a	0.249	0.057	-0.127
P-value	0.740	0.440	0.015	0.172	0.755	0.486
<i>Busulfan</i>						
Correlation coefficient	-0.115	-0.200	-0.229	-0.115	0.015	-0.331
P-value	0.608	0.372	0.305	0.608	0.945	0.139
<i>Cyclophosphamide</i>						
Correlation coefficient	0.069	-0.277	-0.356	-0.624 ^a	-0.267	-0.097
P-value	0.752	0.204	0.102	0.004	0.222	0.658
<i>Fludarabine</i>						
Correlation coefficient	-0.018	0.184	0.498 ^a	0.516 ^a	0.259	0.025
P-value	0.935	0.398	0.022	0.018	0.236	0.909
<i>Antithymocyte globulin</i>						
Correlation coefficient	-0.204	0.032	0.408	0.408	0.138	-0.196
P-value	0.361	0.885	0.068	0.068	0.538	0.380
<i>TBI</i>						
Correlation coefficient	0.277	0.331	0.150	0.331	0.189	0.470 ^a
P-value	0.157	0.091	0.443	0.091	0.335	0.016

The magnitude of the correlation coefficient was used to gauge the strength of the correlation as follows: $|\tau_b| > 0.70$ strong, $0.50 < |\tau_b| < 0.70$ moderately strong, $0.30 < |\tau_b| < 0.50$ weak to moderately strong and $|\tau_b| < 0.30$ weak correlation. ^aStatistically significant.

many potential neurotoxic factors and drugs acting over a prolonged period of time.

In toxic neuropathies one usually finds axonal damage due to cytoskeleton damage or altered apoptotic mechanisms, whereas in autoimmune neuropathies the typical finding is demyelination of large fibers. This paradigm, however, has some exceptions. In some autoimmune neuropathies like acute or chronic inflammatory demyelinating neuropathy (AIDP and CIDP), it is also possible to find damage of unmyelinated or poorly myelinated fibers, primarily resulting in neuropathic pain and autonomic dysfunction. cGvHD entity most closely resembles an autoimmune-mediated inflammatory disease and these typical autoimmune neuropathies could represent models of nerve damage in cGvHD as well. However, CIDP and AIDP have previously been reported to be present in only 2–3% of cGvHD patients.¹³ Clinical symptoms found in cGvHD patients (pain with some characteristics of neuropathic pain, painful muscle cramps, paraesthesia, sensory and/or motor loss, and attenuated myotatic reflexes) could reflect the unique and complex pathophysiology of this distinct disease entity and the importance of SFN in the background of the PNS manifestations in cGvHD.

Significant, positive correlation was established between cGvHD of skin and A-delta fiber damage. It is difficult to say whether A-delta neuropathy is caused only by cGvHD, or A-delta fibers are damaged directly by skin changes in cGvHD. PN occurs at a higher frequency in scleroderma, but these findings cannot be ascribed to compression neuropathies, but rather involvement of large and small fibers in a non-length-dependent manner.^{14,15} Dominant A-delta neuropathy found in our study may indicate cGvHD-mediated damage, because C-fibers (tiny unmyelinated) are more vulnerable to mechanical compression, whereas A-delta fibers (small myelinated) are more vulnerable to demyelination and autoimmune diseases.

Association of RIC (in contrast to MAC) and transplantation of PBSC (in contrast to BMSC) with specific peripheral nerve damage and SFN strongly suggests the implication of immune-mediated mechanisms in cGvHD related neuropathy, rather than transplant-conditioning-induced damage.

In spite of several limitations of this study (relatively small sample, different duration of cGvHD among patients at the beginning of the study, a lack of follow-up, which would enable insight into the dynamics of the changes), it still provides compelling evidence of the magnitude of the problem. The presented data show high prevalence of SFN or LFN in cGvHD patients. Future studies, with larger sample, monitored for a longer time period with collection of the control data in transplanted patients without cGvHD, may address some of the unsolved questions. Factors contributing to the development of neuropathy should be vigorously studied, as therapeutic options are mostly symptomatic. It is clear, however, that peripheral nerve damage has a central place in cGvHD and development of better monitoring and treatment strategies should be a focus of future clinical investigations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Statistical analyses were performed by Assist Professor Milan Milosevic MD PhD, University of Zagreb School of Medicine. We show our gratitude to Dina Ljubas, Ljubica Rajic, Nadira Durakovic, Zinaida Peric, Davorka Dusek, Ines Bojanic, Magdalena Grce, Drago Batinic, Renata Zadro, Igor Petricek, Tamara Vukic, Ema Prenc and Iva Ozana Prah for their valuable work and collaboration in this multidisciplinary team. The opinions expressed here are those of the authors and do not represent the official position of the NIH or the US Government. All patients or their parents (for paediatric patients) signed informed consent approved by ethical committees of the University Hospital Centre and Medical School University of

Zagreb, Zagreb, Croatia. This work is funded by the Unity Through Knowledge Fund project entitled 'Clinical and biological factors determining severity and activity of chronic GvHD after allogeneic hematopoietic stem cell transplantation'. In part support is also provided by the Center for Cancer Reserach, the intramural program of the National Cancer Institute, National Institutes of Health, USA.

AUTHOR CONTRIBUTIONS

Ervina B, SZP, RV, LD and DN contributed to the conception and design of the work. Ervina B, VD, LD, DP, MMS, RC, TKP, Ernest B, MB, RSS, IA, OM and RV contributed to acquisition and analysis of the data. Ervina B, VD, LD, DP, Ernest B, MB, LMC, MMS, RC, TKP, IA, RV, DN and SZP contributed to interpretation of the data. The manuscript was drafted by Ervina B, VD, Ernest B, DP and LMC. All authors revised the work critically for important intellectual content, approved final version of the manuscript and agreed to be accountable for all aspects of the work.

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