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The Neuropathies of Waldenström's Macroglobulinemia (WM) and IgM-MGUS

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Abstract

Background—Neuropathy is common in Waldenström's macroglobulinemia (WM, an IgM-associated lymphoplasmacytic lymphoma) and in IgM-monoclonal gammopathy of undetermined significance (IgM-MGUS). Paraneoplastic or paraimmune mechanisms are thought to be involved in the pathogenesis of these neuropathies. Attempts at distinguishing WM and IgM-MGUS neuropathies are lacking especially among bone marrow (BM) confirmed patients.

Methods—Retrospective analyses were performed on BM confirmed WM (N=30) and IgM-MGUS (N=73) neuropathy patients with neurologic assessments and hematologic features.

Results—The presence of anemia and quantity of IgM monoclonal protein were significantly greater in WM. Based on multiple neurologic assessments differences were not found for: 1) length of time from neurologic symptom onset to evaluation; 2) chief complaint of painless loss of feeling in the feet, Romberg's sign and tremor; and 3) clinical motor, sensory and reflex abnormalities. Autonomic testing was normal in both diseases. Using nerve conduction (NCS) criteria for demyelination, 62% of IgM-MGUS and 27% of WM met this criteria ($p=0.013$). IgM MGUS patients had greater terminal conduction slowing by ulnar residual latency calculation (<0.01). The degree of axonal loss as measured by summated compound muscle action potentials and available nerve biopsy was not significantly different between diseases.

Conclusion—Although WM and IgM-MGUS must be distinguished for hematologic prognosis and treatment, clinical neuropathy presentations of WM and IgM-MGUS are similar and likely related to comparable axonal loss in both conditions. Despite these similarities, evidence of demyelination was found by electrophysiologic studies much more commonly in IgM-MGUS. This difference may reflect varied immune mechanism(s) in the two disorders.

In the evaluation of a patient with peripheral neuropathy the discovery of a serum monoclonal protein has implications for the neurologic and hematologic diagnosis, prognosis and treatment¹. Among such patients the type of neuropathy may suggest the specific underlying hematologic process. To illustrate, in a patient with a monoclonal protein having subacute painful multiple mononeuropathies the diagnosis of mixed cryoglobulinemia is likely and evaluation for viral hepatitis should be emphasized. In another patient, also with a monoclonal protein and with insidious onset of a symmetric painful autonomic, sensory motor polyneuropathy, primary amyloid light chain (AL) amyloidosis should be suspected. In a third example a monoclonal protein with insidious demyelinating polyradiculoneuropathy occurs in POEMS (Polyneuropathy, Organomegaly,

Endocrinopathy, M spike and Skin changes) and should lead to search of treatable osteosclerotic myeloma². Familiarity of these patterns, and others, leads to correct diagnosis and treatment.

Among persons having IgM-MGUS an insidious painless distal sensory ataxic neuropathy with demyelination has been felt to be so characteristic as to coin the acronym DADS (Distal, Acquired, Demyelinating, Sensory-neuropathy)³. By contrast descriptions of the neuropathy features occurring in another IgM condition, namely Waldenström's macroglobulinemia (WM) are limited^{4,5}. Waldenström's macroglobulinemia is defined by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) as having a bone marrow (BM) infiltrated lymphoplasmacytic lymphoma and IgM paraproteinemia⁶. In WM the hematologic features of anemia, hepatosplenomegaly, lymphadenopathy, and hyperviscosity have previously been reported but are variably present with current requirement of BM diagnosis⁷.

Some investigators have suggested there are more axonal features in the nerve conduction studies (NCS) in WM, but the diagnosis of WM did not appear to be based on current BM criteria^{4,5}. By contrast, distal, symmetric, chronic demyelinating neuropathy is more commonly described in IgM-MGUS neuropathy patients^{3,8} including the reports of reduced terminal latency index (TLI), indicating relative slowing in distal motor nerve segments⁹⁻¹¹. Tremor has also been described to be one of the possible clinical stigmata of the IgM-MGUS neuropathy¹². Some studies have suggested that the existence of myelin-associated glycoprotein antibodies (anti-MAG) may explain the clinical, electrophysiologic, and histologic features of the DADS-IgM-MGUS neuropathy¹³⁻¹⁵. However, other studies of IgM neuropathy have found little or no difference between the type and severity of neuropathies in IgM patients with or without anti-MAG antibodies^{16,17}. The MAG antibodies are commonly present in IgM amyloid neuropathy and IgM patients without neuropathy and therefore are not routinely used for diagnosis at many institutions including our own¹⁸.

We conducted this retrospective review to characterize the neuropathies associated with WM and IgM-MGUS to answer whether there are clinical, electrophysiologic and nerve biopsy findings that distinguish the neuropathies associated with WM from IgM-MGUS. In an attempt to study distal predominant involvements we use the previously published formulas to calculate the residual latency (RL) and TLI from routine NCS. The RL¹⁹ is a subtraction of the calculated latency from the measured latency. It evaluates the distal segment of the motor nerves and has been reported to be associated with the neuropathy associated with IgM-MGUS²⁰. The TLI is the ratio between the calculated latency [distance/motor conduction velocity (MCV)] and the measured latency, i.e. distal motor latency (DML) and also assesses for selective distal conduction velocity slowing^{9-11,21}.

Methods

Subjects

With the approval of our institutional review board, an electronic record retrieval system was used to identify patients diagnosed with either WM or IgM-MGUS, who had peripheral neuropathy and had undergone NCS testing between January, 1973 and December, 2007. Hematology and neurology consultation with complete neurologic examination by specialists working in peripheral nerve disease was required for inclusion of cases. Possible hereditary motor and sensory neuropathy cases and cases with other acquired etiologies other than IgM-associated cause were excluded^{22,23}. This included clinical evaluation and laboratory testing for diabetes, thyroid disease, kidney disease, infectious hepatitis and alcoholic neuropathy. Detailed family histories had been obtained as part of our routine

practice to exclude inherited peripheral neuropathies. Also excluded were cases of amyloidosis and POEMS syndrome. No patients had amyloid on bone marrow biopsy and none had systemic sequelae of POEMS syndrome, all having undergone metastatic bone survey in exclusion of osteosclerotic myeloma. Only patients with NCS before neurotoxic or immunosuppressant therapies were studied in both WM and IgM-MGUS.

Bone marrow biopsy, hematologic parameters (levels of hemoglobin, IgM and other monoclonal proteins, platelets, creatinine, light chains), sural nerve biopsies, autonomic testing,^{24,25} neurologic examinations including neuropathy impairment score (NIS)²⁶ with individual motor, reflex, and sensory parameters were examined. Other features were also extracted from the records including presenting complaint, presence of tremor, age, sex, and length of symptoms to the time of NCS. The hematologic and clinical parameters were reviewed at the time of NCS.

Diagnosis of WM and IgM-MGUS

Bone marrow diagnosis of WM was based on the WHO classification by which lymphoplasmacytic cells must be seen diffusely without myeloma or other lymphomatous disorders present⁶. Diagnosis of WM or IgM-MGUS with bone marrow biopsy was made by hematologists and hematopathologists using the standard approach⁶. All patients had positive immunofixation for IgM-MGUS and simultaneously performed serum protein electrophoresis. We chose to include only BM confirmed IgM-MGUS to exclude inclusion of occult WM for this research study.

Nerve Conduction Study (NCS)

Nerve conduction study were performed by uniform technique by experienced and certified technicians, previously on Teca-TD20 and subsequently on Nicolet Viking with similar filter settings and electrode placement and stimulation technique²⁷. Skin temperature was measured at the dorsum of hand or foot, which was maintained above 32°C with electrode placement and stimulation similar between all patients. Using our standard peripheral neuropathy protocol, motor nerve conduction studies were reviewed in three motor (peroneal, tibial and ulnar) and two sensory (sural, median) nerves available in all patients. Median motor studies were also available among 8 WM and 32 IgM-MGUS patients, and done typically in evaluation of superimposed mononeuropathy. Normal values were defined based on standards set at the electromyogram (EMG) laboratory at Mayo Clinic, Rochester, MN, USA. Demyelination and axonal features were determined by standard criteria²⁸ widely used in research and clinical practice, i.e. demyelination if; 1) Reduction in conduction velocity in two or more nerves; <80% of lower limit of normal (LLN) if amplitude >80% of the LLN, <70% of LLN if amplitude <80% LLN; 2) Partial conduction block or abnormal temporal dispersion in one or more nerves; <15% change in duration between proximal and distal segments or >20% drop in negative peak area or peak-to-peak amplitude between proximal and distal sites; 3) And/or presence of one of these findings; a) Prolonged distal latencies in two or more nerves; >125% of upper limit of normal (ULN) if amplitude >80%, or >150% of ULN if amplitude <80% of LLN; b) Absent F waves or prolonged minimum F wave latency; >120% of ULN if amplitude is >80% of LLN or >150% of ULN if amplitude is <80% of LLN²⁸.

Terminal latency index was calculated on motor studies. The TLI is the ratio between the calculated latency [distance/motor conduction velocity] and the measured latency, i.e. distal motor latency²¹ and was determined by the previously published formula:

$$TLI = (1/DML \text{ (milliseconds)}) \times (\text{distal conduction distance (millimeters)} / \text{distal MCV (meters/second)})$$

. Motor studies with no response were not included in the calculation of TLI and RL calculations. Terminal latency index was used to compare the wrist-to-thenar muscle (distal

segment) with the elbow-to-wrist conduction velocity in median nerve, the wrist-to-hypothenar muscle (distal segment) with the elbow-to-wrist conduction velocity in ulnar nerve, the ankle-to-extensor digitorum brevis muscle (distal segment) with the knee-to-ankle conduction velocity in common peroneal nerve, and the ankle-to-abductor hallucis muscle (distal segment) with the knee-to-ankle conduction velocity in posterior tibial nerve.

Residual latency considers differently the distal motor axonal slowing and was determined on available NCS attributes. Residual latency is a subtraction of the calculated latency (distance/MCV) from the measured latency (DML) and was determined by the previously published formula¹⁹:

$RL = DML(\text{ms}) - [\text{distal conduction distance (mm)} / \text{distal MCV (m/s)}]$. This calculation was derived from the same NCS studied for TLI.

Ascertainment of Axonal Loss

To assess the degree of nerve fiber loss in motor and sensory nerves, percentiles were used to compare summated compound motor unit potentials (peroneal, tibial, ulnar) and summated sensory nerve action potential (sural and median) between WM and IgM-MGUS²⁹⁻³¹. This approach was chosen in order to allow for comparison of axonal loss between individuals of different ages, heights, weights and gender correcting to a comparison of normal. Axonal involvement was also examined by needle examination standard techniques in muscles comparably examined in all patients (tibialis anterior, medial gastrocnemius, vastus medialis) using summated abnormalities of fibrillations or motor unit potential amplitudes, motor unit duration and recruitment with which a composite abnormality was created. The Mayo needle EMG classification scheme of semi-quantification using a 0-4 plus scale of each of these parameters was utilized³². Zero is normal and 4 are the most affected for fibrillations and motor unit parameters of amplitude, duration and recruitment.

In further review of neuropathic features available, sural nerve biopsies, including paraffin and epoxy embedded sections and by teased fiber preparations, were reviewed. Characterization of axonal and demyelinating features of whole sural nerve biopsy was determined using standard techniques³³.

Autonomic testing

Available autonomic reflex testing including study of cardiovagal, adrenergic, and sudomotor functions were reviewed by standard techniques^{24,25}.

Statistical analysis

Descriptive statistics were used to assess for clinical, electrophysiologic, and other features of the neuropathies of WM and IgM-MGUS. Two tailed test and $p < 0.05$ were used to determine significant differences. Associations between the presence of WM and putative risk covariates were evaluated by Student's t-test or Wilcoxon Rank-Sum test for continuous variables and with Chi-square test or Fisher's exact test for nominal variables. Multiple logistic regression analysis was performed for evaluating the importance of neuropathy type in establishing the probability of developing WM with IgM. Multivariate two-step logistic regression models for the presence of WM were also performed to create cut-off values for predictive purposes of individual nerve conduction and hematologic parameters found significant in the total cohort.

Results

The disease characteristics of the 30 WM and 73 IgM-MGUS neuropathy patients are given in Tables 1–3. Among both groups, “numb toes and feet” was the most common chief complaint with “tremor” the second most common occurring in 10% or less of both groups. Romberg’s sign and presence of tremor were not significantly different between WM and IgM-MGUS. Between the two diseases, there was no significant difference in gender, age, duration of symptoms and severity of peripheral neuropathy as determined by NIS. A significant difference was not found between diseases for motor, sensory and reflex abnormalities. Autonomic reflex screens were performed on 11 WM and 26 IgM-MGUS patients and all showed normal adrenergic, cardiovagal function and only slight sudomotor abnormalities not significantly different between the two groups²⁵.

Using the standard electrophysiological criteria described in the method section, demyelination was found more frequently in IgM-MGUS (62%) than in WM (27%) ($p=0.001$). The specialized NCS calculations (motor TLI and RL) also showed that ulnar-RL was significantly greater in IgM-MGUS ($p=0.009$) which is consistent with distal slowing, although ulnar-TLI, median, peroneal and tibial RL as well as TLI did not reach significant difference between these two groups. Hemoglobin, IgG and IgA levels were all significantly reduced while IgM levels were significantly elevated in WM group compared to IgM-MGUS group. The multiple logistic regression analysis showed demyelinating findings in IgM-MGUS were significant (odds ratio = 11.1, $p = 0.005$). In contrast, ulnar-RL did not reach significance with multivariate regression analysis, suggesting ulnar-RL may be correlated with the other factors.

The degree of axonal loss was not significantly different between IgM-MGUS and WM determined by composite score of motor and sensory CMAPs (Table 3); summated needle EMG abnormalities (Table 4); and by available nerve biopsies (Table 5) and the Figure. Summated deficits of tibialis anterior, medial gastrocnemius, vastus medialis or vastus lateralis muscles were not significantly different between IgM-MGUS and WM.

Further analysis of hematologic parameters by calculating the area under the ROC curve (AUC) suggested two predictive values for WM including a hemoglobin level less than 12.6 g/dl (anemia) [71% sensitivity; 88% specificity, $p<0.001$] and IgM level greater than 1830 mg/dl [85% sensitivity; 93% specificity, $p<0.001$]. The predictability of the hematologic cut-off values were independent of nerve conduction status, these values achieved the same specificity and sensitivity in axonal IgM-MGUS and demyelinating WM. Individual nerve conduction parameters (RL, TLI) were also analyzed using AUC calculation. The only statistically significant predictive value for WM was an ulnar –RL less than 0.43 [89% sensitive; 44% specific, $p=0.0311$].

Discussion

The distinction of IgM-MGUS from WM is important but complex. Previous studies have shown that the prevalence of IgM-MGUS is higher in familial occurrence of WM, but there is no evidence that IgM-MGUS progresses to WM with each appearing to be a different disease from their onset³⁴.

In this retrospective study, we found that 73% of bone marrow biopsy confirmed WM patients had only primary axonal features on nerve conduction whereas 62% of IgM-MGUS patients had demyelinating features. Despite apparent demyelinating nerve conduction differences the clinical presentations were similar. The main presenting complaint of distal sensory loss and gait ataxia and similar and not infrequent occurrence of tremor was indistinguishable. Those similar impairments and severity of impairments likely

relate to the comparable amounts of axonal loss seen in both groups, i.e. a mixed demyelinating-axonal pathogenesis. The apparent axonal predominant changes in WM patients do not appear related to symptom duration. Specifically, axonal features in WM related neuropathy are unlikely a simple evolution of demyelinating to axonal features as the length of time from symptom onset did not correlate with the type of nerve conduction abnormality. The more common occurrence of demyelination in our IgM-MGUS group over WM group is consistent with earlier observations without report of bone marrow biopsy^{4,5}.

Our findings emphasize the complexity of electrophysiologic presentations in these two primary IgM hematologic disorders. The divergent electrophysiologic findings lead to speculation that a spectrum of immunity is responsible with overlap between some. The careful exam of the other aspects of clinical presentation such as the levels of hemoglobin and IgM can also provide assistance in distinguishing WM from IgM-MGUS and deciding whether to perform bone marrow biopsy. Specifically our study showed that using the cut-off level of IgM greater than 1830 mg/dl and hemoglobin level less than 12.6 g/dl (anemia) can achieve 71% of sensitivity and 88% specificity for predicting WM cases independent of nerve conduction status. The fact that markedly elevated IgM level and anemia are more frequent in WM than in IgM-MUGS is also supported by previous study³⁵.

The significant association of distal slowing came from only the results of the ulnar-RL in distinction of IgM-MGUS from WM. That association did not bear out with multiple regression analysis and in other nerves suggesting possible outlier statistical phenomena. Similarly we did not find reduced median-TLI significantly associated with IgM-MGUS as had been suggested in the earlier reports^{8,9}. This difference may be due to the fact that earlier described samples used for the TLI association analysis were tested positive with anti-myelin associated glycoprotein assay, of which the occurrence may select for a specific distal phenomenon. We used retrospective study design, with this antibody not routinely tested at our institution, and therefore do not have the status of IgM antibodies against MAG,⁹⁻¹¹ suggesting reduced TLI is not associated with patients without anti-MAG.

Conclusions

What are the practical implications of our findings? In cases where IgM monoclonal proteins are found in neuropathy patients, an axonopathy on NCS favors the diagnosis of WM over IgM-MGUS, especially if the neuropathy associates with anemia and elevated IgM concentration. Therefore, bone marrow biopsy would be more likely to yield positive WM diagnosis in the presence of axonal features. However, if the electrophysiology reveals evidence of demyelination, the decision to advance to bone marrow confirmatory diagnosis of WM should not be excluded, especially if anemia or other worrisome features are present. The decision to advance to BM should remain for those where the extent of neurologic or hematologic involvements would warrant therapeutic approaches. Based on this study, individual NCS parameters such as TLI and RL may not be as helpful, with comprehensive NCS being more helpful.

A spectrum of divergent and shared immune mechanism is implicated by both the similar and different clinical and electrophysiological features identified in WM and IgM-MGUS. Future prospective studies looking to identify the implicated varied immune paraneoplastic or paraimmune neuropathy mechanisms will be important.

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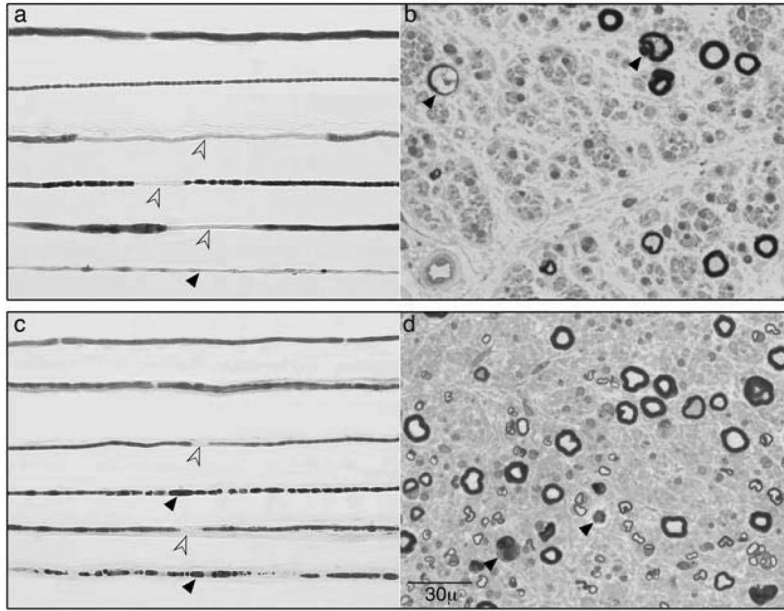


Figure. Teased and epoxy embedded sections from representative sural nerve biopsies of a patient with IgM-MGUS (a, b) and Waldenström's macroglobulinemia (WM) (c, d) neuropathy. Both biopsies show combination axonal fiber loss and degeneration (black arrows) with de and remyelination (open arrows). By the electrophysiologic criteria²⁸ the shown IgM-MGUS patient had demyelinating features with axonal loss whereas the WM patient had axonal nerve conduction despite occasional demyelinating teased fibers. Both these patients presented with insidious onset sensory gait ataxia without pain or significant weakness.

Table 1

Clinical characteristics of WM compared to IgM-MGUS

		WM (N=30)	IgM-MGUS (N=73)	p-value
Age (yrs.)		median 65.5, range 46–82	median 64.0, range 31–82	0.821
Gender	Male	22 (73%)	53 (73%)	0.939
	Female	8 (27%)	20 (27%)	
NIS at time of NCS (points)		median =17.5, range 0–75	median =24, range 0–92	0.055
Chief first complaint number abnormal (percent)	“Numb toes & feet”	28 (93%)	66 (90%)	0.633
	“Tremor”	2 (7%)	7 (10%)	0.633
Romberg’s sign number abnormal (percent)		9 (30%)	29 (41%)	0.352
Tremor by examination number abnormal (percent)		6 (20%)	20 (27%)	0.432
NIS reflex abnormality		median = 6, range 0–20	median = 8, range 0–20	0.543
NIS sensory abnormality		median = 7, range 2–26	median = 10, range 2–32	0.352
NIS motor abnormality		median = 7, range 0–46	median = 8, range 0–64	0.442
Duration (yrs.) of symptoms prior to NCS		median = 2.0, range 0.1–20.0	median = 3.0, range 0.2–29	0.329

NIS=Neuropathy Impairment Score; NCS= Nerve Conduction Studies

Table 2

Significant nerve conduction and hematologic differences of WM vs IgM-MGUS

		WM	IgM-MGUS	p-value
Demyelinating nerve conduction ⁽²⁸⁾		8/30(27%)	45/73 (62%)	0.001
Nerve conduction study	Ulnar RL ⁽¹⁹⁾	N=27 median 1.72, range 1.22–6.46	N=70 median 2.43, range 1.70–7.43	0.009*
Hematologic findings	Hemoglobin (gm/dl)	N=30 median 11.8, range 7.3–14.5	N=73 median 14.4, range 7.4–18.0	<0.001
	IgM (mg/dl)	N=30 median 3100, range 658–6360	N=73 median 650, range 169–2960	<0.001

Shown are statistically significant differences: NIS =neuropathy impairment score; RL= residual latency; No response conduction responses are not included in the calculations.

* Multiple regression analysis was not significant for ulnar RL.

Table 3

Assessment of axonal loss by summated motor and sensory nerve conduction amplitudes in WM, IGM-MGUS, and healthy subjects

	WM (N=30)	IgM-MGUS (N=73)	Healthy subjects	WM vs healthy subjects	IgM-MGUS vs healthy subjects	IgM-MGUS vs WM
CMAPs * Percentiles of mean (range)	8.08 (0.06 – 40.79)	6.34 (0.03 – 85.15)	50.92 (3.22 – 96.86)	P<0.001	P<0.001	p=0.419
SNAPs * Percentiles of mean (range)	0.09 (0.03 – 17.23)	0.20 (0.03 – 53.59)	49.48 (0.70 – 98.66)	P<0.001	P<0.001	p=0.376

* The mean of mean values of summed ulnar, peroneal, and tibial compound motor action potential (CMAPs) (mV) or median and sural sensory nerve action potential (SNAPs) corrected for age, gender, height and weight as compared to reference values of healthy subjects (29–31).

Table 4

Assessment of axonal loss by summated needle EMG abnormalities WM vs IgM-MGUS

	WM (N=30)		IgM-MGUS (N=73)		WM vs IgM-MGUS
	Median	Range	Median	Range	p-value
Motor unit potentials*	8	0-18	6	0-24	0.327
Fibrillations*	2	0-10	2.5	0-8	0.525

* Summated tibialis anterior, medial gastrocnemius, vastus medialis muscle EMG abnormalities (studied in all patients) for motor unit amplitude, duration, recruitment or fibrillation abnormalities using semi quantification plus scale (0-4, 0=normal, 4=most severely affected) summed in routine needle EMG³².

Table 5

Teased fiber nerve preparations for WM and IgM-MGUS

	WM (N=4)		IgM-MGUS (N=12)		WM vs IgM-MGUS	Healthy controls (N=14)	
	Median	Range	Median	Range	p-value	Median	Range
Normal A, B (%)	73	65-82	50	25-82	0.016	85.1	72-95
Demyelination C, D (%)	10	5-20	11	1-37	0.800	0.0	0-2
Axonal Degeneration E, H (%)	4	3-5	4	2-29	0.700	0.0	0-3
Remyelination F, G (%)	10	10-10	16	3-25	0.480	13.7	5-28
Axon loss by empty strands (number)	30	15-40	35	3-45	0.470	6.0	0-19

Teased fiber types: A = normal, B = myelin wrinkling, C = demyelination, D = demyelination and remyelination, E = axonal degeneration, F = remyelination, G = myelin reduplication, H = regeneration after axonal degeneration, empty = strands with loss of fibers.