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Serum Nerve Growth Factor in the Occurrence of Peripheral Neuropathy in Rheumatoid Arthritis Patients

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ABSTRACT

Background Peripheral neuropathy (PN) is an extraarticular manifestation in rheumatoid arthritis (RA). In type-2 diabetes mellitus (DM) patients, Nerve Growth Factor (NGF) is associated with PN. The correlation between NGF level and PN among RA has not been concluded yet. This study aimed to determine the mean levels of NGF blood serum and its relationship to PN among RA patients. **Methods** A cross sectional study using consecutive sampling method including patient of rheumatology clinic Cipto Mangunkusumo Hospital was performed between July 2015 to March 2016. The NGF level measurement and Electromyography-Nerve Conduction Velocities (EMG-NCV) were examined to the subjects. Patients were classified into 2 groups; PN positive and PN negative. Bivariate analysis was done to investigate the relationship between NGF and PN among groups. Secondary data such as age, sex, Erythrocyte Sedimentation Rate (ESR), CRP, Disease Activity Score (DAS)28-ESR and CRP are obtained from medical record. **Results** Among 132 subjects, PN was found in 60 subjects. The median of NGF level in RA patients was 4.11 pg/mL (0.0-24.5). The median of NGF level of RA patients with PN was 4.11 pg/mL (1.1-20.83) and without PN was 3.89 pg/mL (0.0-24.5). Types of neuropathy among patients were polyneuropathy (21.97%), mononeuropathy multiplex (15.15%) and Carpal Tunnel Syndrome (11.36%). In this study we found no association between NGF serum level and PN among RA patients (p = 0.716). **Conclusion**s The median of serum NGF level among PN group was higher than without PN. There was no relationship between serum NGF level and PN among patients with RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease and affect intraarticular and also extraarticular organ. Peripheral neuropathy (PN) is one of extraarticular manifestation of RA and estimated to be found in 50-57.4% of patients.[1,2] PN is frequently undetected because its symptoms mimic and overlap to arthritis.[1,3] Type of PN among RA patients includes polyneuropathy, mononeuritis multiplex and carpal tunnel syndrome (CTS).[1] Mononeuritis multiplex is the most common type of peripheral neuropathy among RA patients. Motoric paralysis is the common complication among patient with mononeuritis multiplex, characterized with wrist and drop foot.[4,5]

Nerve growth factor (NGF), one of neurotropic factor, has been known to contibute to the pathogenesis of PN in diabetic neuropathy. On the other hand, the pathogenesis of PN among RA patients is still unclear. There is an evidence of increased level of NGF in RA patients compared to normal individual.[6] There are no data show the relationship between NGF level to the incidence of PN among RA patients. Thus, the purpose of this study is to determine the mean of serum NGF level and the relationship between serum NGF level and PN among patients with RA.

2.Methods

This study was an analytic study using cross sectional design, involving RA patients who were treated in outpatient rheumatology clinic Cipto Mangunkusumo Hospital. Subjects were recruited using consecutive sampling. The inclusion criteria of this study are patients aged over 18 year-old and we excluded the patients with another autoimmune diseases, history of trauma, deformity that cause limb amputation, diabetes mellitus, on biologic agent therapy, history of thyroid disease, drug consumption that induced neuropathy, HIV, tumor on chemotherapy, history of allergy and asthma, also patients who refuse participating the study.

All subjects who meet study criteria are examined for serum NGF level and nerve conducting velocity (NCV) to diagnose PN. Serum NGF level is measured by ELISA method using Abnova® reagent kit with sensitivity <1 pg/mL. NCV examination was done using XLTEK machine to evaluate the sensory and motoric component of peripheral nerve. Secondary data includes age, sex, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity score (DAS)-28 ESR and CRP obtained from patients' medical record as basic characteristic data. The protocol of this study was reviewed and approved by Ethical Committee of Faculty of Medicine, University of Indonesia.

3.Results

Total participants who fulfilled the inclusion criteria were 132 patients. Table 1 showed the characteristic of RA patients in rheumatology outpatient clinic Cipto Mangunkusumo Hospital. The subject of this study is dominated by woman (93.9%). Table 1 showed that the median of serum NGF level in RA patients with PN is slightly higher than patient without PN. Among RA patients with PN, peroneal nerves are the most affected nerve followed by median nerve. Ulnar and tibial nerve are the least nerve affected among RA patients with PN.

Table 1. The characteristic and basic data of the subjects

Characteristic N = 132 (100%)	Frequency	Peripheral neuropathy N = 60 (45.5%)	Normal N = 72 (54.5%)
Sex			
Male	8 (6.1%)	5 (3.79%)	3 (2.3%)
Female	124 (93.9%)	55 (41.7%)	69 (52.3%)
Age*	50 (19-74)	57 (21-72)	44 (19-74)
< 55 years	84 (63.6%)	26 (19.7%)	58 (43.9%)
≥ 55 years	48 (36.4%)	34 (25.8%)	14 (10.6%)
Ethnic			
Javanese	37 (28.0%)		
Betawinese	37 (28.0%)		
Sundanese	23 (17.4%)		
Bataknese	11 (8.3%)		
Padangnese	10 (7.6%)		
Chinese	5 (3.8%)		
Others	9 (4.5%)		
NGF level (pg/mL)*	4 (0-24.5)	4.11 (1.1-20.8)	3.89 (0-24.5)
RF			
Positive	64 (48.5%)	28 (21.2%)	36 (27.3%)
Negative	68 (51.5%)	32 (24.3%)	36 (27.3%)
ESR (mm/jam)*	36.5 (5-105)	35 (8-100)	45 (5-105)
CRP (mg/L)	3.15 (0-122)	2.9 (0.2-30,4)	3.7 (0-122)
DAS28-ESR		3.25 (1.9-6.06)	3.71 (1.13-10)
Remission	34 (25.8%)		
Low disease	27 (20.5%)		
Moderate disease	52 (39.4%)		
High disease	19 (14.4%)		
DAS28-CRP		2.65 (0.9-6.46)	283 (0.96-5.39)
Remission	59 (44.7%)		
Low disease	26 (19.7%)		
Moderate disease	39 (29.5%)		
High disease	8 (6.1%)		
Disease therapy duration (years)*			
<2	53 (40.2 %)		
2-4	41 (31.1%)		
>4	38 (28.8 %)		
Type of neuropathy			
Polyneuropathy		29 (21.97%)	
CTS		15 (11.36%)	
Mononeuritis multiplex		20 (15.15%)	

Notes: NGF=Nerve Growth Factor, ESR=Erythrocyte Sedimentation Rate, CRP=C-Reactive Protein, DAS28=Disease Activity Score on 28 joints, CTS= Carpal Tunnel Syndrome. *Not normally distributed, data presented in median (range).

Table 2. The relationship between NGF level and PN

Peripheral Neuropathy	N	NGF Level*	p value
Positive	60	4.11 (1.1-20.83)	0.716
Negative	72	3.89 (0-24.5)	

Notes: NGF = nerve growth factor. *Not normally distributed, data presented in median (range).

Table 3. The relationship between NGF level and ESR, CRP in RA patients with and without PN

NGF Level	ESR	CRP
RA patients with PN	r = 0.053 p = 0.69	r = –0.152 p = 0.246`
RA patients without PN	r = –0.02 p = 0.98	r = –0.12 p = 0.317

Notes: NGF = nerve growth factor, ESR = erythrocytes sedimentation rate, CRP = C-reactive protein, RA = rheumatoid arthritis, PN = peripheral neuropathy

Table 4. The relationship between NGF level to DAS28-ESR and CRP in RA patients with and without PN

Group	Disease Activity		N	NGF Level (pg/mL)	p value
RA patients with PN	DAS28-ESR	Remission	14	4.2 (2.69-6.68)	0.408
		Mild	16	4.11 (1.46-11)	
		Moderate	24	3.67 (1.1-6.97)	
		High	6	4.16 (1.21-20.83)	
	DAS28-CRP	Remission	28	4.2 (1.46-20.83)	0.029*
		Mild	13	3.46 (1.1-18.32)	
		Moderate	15	4.11 (2.52-6.97)	
		High	28	2.80 (1.21-4.57)	
RA patients without PN	DAS28-ESR	Remission	20	4.33 (0-24.05)	0.92
		Mild	11	4.11 (1.46-13.79)	
		Moderate	28	4 (2.69-7.27)	
		High	13	3.89 (1.89-14.64)	
	DAS28-CRP	Remission	31	4.33 (0-24.05)	0.675
		Mild	13	3,89 (1.46-6.97)	
		Moderate	24	4 (1.89-14.64)	
		High	4	3.89 (3.26-4.11)	

Notes: NGF = nerve growth factor, ESR = erythrocytes sedimentation rate, CRP = C-reactive protein, DAS28 = disease activity on 28 joints, RA = rheumatoid arthritis, PN = peripheral neuropathy. *statistically significant.

4.Discussion

The subject in this study is dominated by woman with median age of 50-year-old. It is in accordance to study conducted by Ramadhani, et al. that the prevalence of RA is higher in woman and increase by age.[7] In our study, we found balanced data between seropositive-RF and seronegative-RF. It is in contrast to Ingegnoli, et al. which stated that the prevalence of RA patients with seropositive-RF is 70-90% so that RF could be one of diagnosis criteria of RA with sensitivity 60-90% and specificity 85%.[8] The disease activity is evaluated using DAS28-ESR and CRP. DAS28-ESR showed that most of the patients in this study are in moderate disease activity, while DAS28-CRP showed that most of the subjects are in remission state. These are also reported by Wells, et al. that DAS28-CRP resulted in better EULAR response compared to DAS28-ESR.[9] There are 45.5% RA patients in this study is diagnosed peripheral neuropathy. The type of neuropathy is polyneuropathy, mononeuritis multiplex and CTS. It is similar to Abdullah, et al. study which stated that the type of PN in RA patients is CTS, polyneuropathy and mononeuritis simplex.[10]

In this study, the median of serum NGF level is 4,11 pg/ml with minimum level is undetected (very low) and the maximum level is 24,05 pg/mL. The study conducted by Del Porto, et al. showed that the mean of serum NGF level in 20 RA patients is 190,58±243,55 pg/mL.[11] Other study conducted by E Dicou, et al. stated that among 24 RA patients, the serum and synovial fluid NGF level are 74,8±39,6 pg/mL and 4-100 pg/mL.[12] The lower NGF level in this study might be caused by steroid and DMARD therapy in certain period of time. The NGF level data is supported by disease activity (DAS28-CRP) which showed that most of the patients are in remission state. The steroid and DMARD medication could suppress the inflammation process which is represented by the decrease of NGF level as inflammatory cytokines.[13]

The mean of NGF level in RA patients with PN is higher than patients without PN. Nevertheless, there is no statistically significant difference due to several factors affecting NGF level and/or unevaluated neuropathy during

the study (p=0.716). Daily routine medication of steroid and immunosuppressant could suppress proinflammatory cytokines level so that the NGF level also decreased.[14] Genotype polymorphism on NGF and its receptors are also suspected to results various NGF level as the phenotype. Study by Chang, et al. found genotype polymorphism in NGF receptor Ser205/Se205 (Ser205Leu) which play a role in the regulation of vagal autonomic nervous system.[15] This study is the first study which evaluates the relationship between serum NGF level and the incidence of PN. Thus, there is no other study to compared related our findings.

This study revealed significant association between serum NGF level and disease activity based on DAS28-CRP among RA patients with PN. It clarifies that there is an interaction between NGF level and diseases activity among RA patients with PN compared to those without PN. In type-2 DM patients with PN, hyperglycemia state causes damage or degeneration in peripheral nerve fibers and results in deficiency of NGF and its receptor.[16,17] There is significant difference in NGF level of patients with mild disease activity compared to high disease activity. Patients with mild disease activity have higher median of NGF level. It showed that NGF might have neuroprotective characteristic rather than proinflammation. Moreover, high level of NGF in patient with PN is followed by the lower level of ESR, CRP, and disease activity (DAS28-ESR and CRP) compared to patient without PN. It emphasizes that NGF in RA patients has protective function, especially in neuron tissues, although there is no statistically significant association. Study by Prencipe, et al. showed that NGF could stimulate anti-inflammatory cytokines and suppress the production of proinflammatory cytokines.[18] However, this study did not evaluate the level of pro- and anti-inflammatory cytokines.

This study is the first study which analyze the relationship between serum NGF level and the incidence of PN in patients with RA. A study conducted by Apfel, et al. showed that recombinant NGF therapy could improve the PN in phase I and II clinical trials. However, their phase III clinical trial did not show significant results.[19] A literature review by Seidel, et al. explained that NGF is overexpressed on patient with inflammatory rheumatic diseases and degenerative disease in different concentrations. Seidel stated that NGF level corelates with the degree of inflammation or disease activity. On the other hand, NGF also acts as inflammation mediator and modulator. In the end of the review, Seidel concluded that NGF could become detrimental agent or regenerative agent.[20]

Conclusion

The median of serum NGF level of patients with RA was 4 pg/mL, and the median level of serum NGF in RA patient with PN is slightly higher than patients without PN. There was no significant difference on serum NGF level of RA patient with PN and without PN.

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