



Incidence of Peripheral Neuropathy in Major Beta-Thalassemia Patients at Hasan Sadikin General Hospital, Bandung, Indonesia

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ABSTRACT

Background. Beta major thalassemia is the most common inherited blood disorder worldwide. It can lead to various neurological complications such as peripheral neuropathy. Toronto Clinical Neuropathy Score (TCNS) is helpful for peripheral neuropathy screening especially in diabetes mellitus. **Objective.** To investigate the prevalence of peripheral neuropathy in beta major thalassemia patient using Toronto Clinical Neuropathy Score (TCNS). **Method.** A descriptive study on beta major thalassemia patients aged more than 14 years who regularly underwent blood transfusions in Hasan Sadikin General Hospital Bandung, from July to August 2017. Normal TCNS value was < 4, mild neuropathy 5-7, moderate neuropathy 8-10 and severe neuropathy > 10. **Results.** Sixty subjects met the inclusion criteria, 48.3% were male with the mean (SD) age of 20.7 ± 7.6 years. Mean hemoglobin value was 6.7 ± 0.9 g/dL and median (IQR) blood ferritin serum was 2873 (1900-3859) $\mu\text{g/L}$. Thirty-two subjects had neuropathy; 19 (31.7%) with mild neuropathy and 13 (21.6%) with moderate neuropathy. **Conclusion.** The incidence of peripheral neuropathy in patients with thalassemia according to TCNS score is fairly high.

Keywords: Nerve conduction study (NCS), neuropathy, thalassemia, Toronto Clinical Neuropathy Score (TCNS).

ABSTRAK

Latar Belakang. Talasemia beta mayor adalah kelainan darah bawaan paling umum di dunia dan dapat menyebabkan berbagai komplikasi, salah satunya neuropati perifer. *Toronto Clinical Neuropathy Score* (TCNS) dapat digunakan untuk penilaian neuropati perifer terutama pada pasien diabetes melitus. **Objektif.** Menyelidiki prevalensi neuropati perifer pada pasien talasemia beta mayor menggunakan *Toronto Clinical Neuropathy Score* (TCNS). **Metode.** Penelitian ini studi deskriptif skrining menggunakan TCNS pada pasien talasemia beta mayor berusia lebih dari 14 tahun yang secara teratur menjalani transfusi darah di Rumah Sakit Umum Hasan Sadikin Bandung, dari Juli hingga Agustus 2017. Nilai TCNS normal adalah <4, neuropati ringan 5-7, neuropati sedang 8-10 dan neuropati berat >10. **Hasil.** Sebanyak 60 subjek memenuhi kriteria inklusi, 48,3% laki-laki dengan usia rata-rata (SD) $20,7 \pm 7,6$ tahun. Nilai hemoglobin rata-rata $6,7 \pm 0,9$ g/dL dan serum ferritin darah median (IQR) adalah 2873 (1900-3859) $\mu\text{g/L}$. Tiga puluh dua subjek mengalami neuropati; 19 (31,7%) pasien dengan neuropati ringan dan 13 (21,6%) pasien dengan neuropati sedang. **Simpulan.** Insidens neuropati perifer pada pasien dengan talasemia menurut skor TCNS cukup tinggi. **Fanny Adhy Putri, Uni Gamayani, Nushrotul Lailiyya, Ramdan Panigoro.** Kejadian Neuropati Perifer di Kalangan Pasien Beta-Thalassemia Major di RS Hasan Sadikin, Bandung, Indonesia

Kata kunci: Nerve conduction study (NCS), neuropati, talasemia, *Toronto Clinical Neuropathy Score* (TCNS).

BACKGROUND

Thalassemia is a hereditary-linked blood disease characterized by defect on hemoglobin synthesis and/or globin chain structure.¹ Indonesia is one of the countries known as thalassemia belt with high prevalence of beta-thalassemia carrier; up to 10% population.²⁻⁴

Beta major-thalassemia is the most severe type of thalassemia. Combination of routine blood transfusion and iron chelation therapy

contribute to an increase of patient's life expectancy. However, chronic progression of the disease leads to complications; among them is peripheral neuropathy.⁵⁻⁸

Peripheral neuropathy was first reported as a complication of beta-thalassemia by Papanastasiou in 1991.⁹ He showed that 22% of beta-thalassemia patients had peripheral neuropathy and its prevalence increased with age.⁹ Several studies showed that abnormal neural conduction was more

commonly seen in patients with low mean hemoglobin level, high serum ferritin level, older age, and insufficient blood transfusion and iron chelation therapy; this result supports the hypothesis of chronic anemia and iron deposition as the main risk factors for peripheral neuropathy in thalassemia.⁹⁻¹¹

Toronto Clinical Neuropathy Score (TCNS) consists of sensory symptom questionnaire, reflex and sensory test score. Sensory symptoms include foot pain, numbness,

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tingling, weakness and ataxia. The maximum TCNS score is 19 points; score 0-4 is considered normal, 5-7 is considered mild neuropathy, 8-10 is considered moderate neuropathy, >10 is considered severe neuropathy; the cut off point is 5.

METHOD

A descriptive study on major beta-thalassemia patients with routine blood transfusion therapy in Dr. Hasan Sadikin General Hospital. The subjects were all confirmed major beta-thalassemia patients with routine transfusion at the Hematology-Oncology Clinic, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia who met the inclusion and exclusion criteria:

Inclusion Criteria:

1. Age > 14 years old
2. Thalassemia diagnosis was confirmed

by Internist in Dr. Hasan Sadikin General Hospital, Bandung

3. Routine blood transfusion in Hematology-Oncology Clinic, Dr. Hasan Sadikin General Hospital, Bandung
4. Informed consent from the patients and their families

Exclusion Criteria:

1. Current or history of administration of agents with peripheral neuropathy as a potential side effect, such as chemotherapy agent (vincristine) or anti-tuberculosis agent (isoniazid).
2. Patient with diabetes mellitus
3. Patient with liver disease
4. Patient with renal impairment

All subjects were screened for peripheral neuropathy using Toronto Clinical Neuropathy

Score (TCNS) with following interpretation: 0-4: Absence of neuropathy; 5-7: Mild neuropathy; 8-10: Moderate neuropathy; >10: Severe neuropathy

The study consisted of interview, questionnaire filling, general and neurological physical examination, and screening using Toronto Clinical Neuropathy Score (TCNS), conducted at the Hematology-Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung during July to August 2017.

RESULTS

Sixty patients with major beta-thalassemia were included in the study; 29 (48.3%) were male and 31 (51.7%) were female with a mean age (SD) of 20.7±7.6 years old. Fifty-six (93.3%) subjects received iron chelation therapy; 21 subjects were given deferiasirox, 30 subjects received deferiprone, 5 subjects used desferal. Mean hemoglobin level (SD) was 6.7±0.9 g/dL and the median level of ferritin (IQR) 2873 (1900-3859) µg/L. Thirty-two patients were confirmed to have neuropathy; 19 (31.7%) with mild neuropathy, 13 (21.6%) with moderate neuropathy, and 0 (0%) with severe neuropathy.

DISCUSSION

In this study, the TCNS result was normal in 46.7% of the patients, 31.7% had mild neuropathy and 21.6% had moderate neuropathy. It confirms that the incidence of peripheral neuropathy among thalassemia are relatively high. Most subjects were not aware of peripheral neuropathy symptoms, as the median (IQR) score of the symptoms in TCNS was 3 (1-4). and despite 46.7% subject had normal result, the subject had the symptoms of peripheral neuropathy with the minimum symptoms score in TCNS. Subjects with normal TCNS score needed further nerve conduction studies to confirm subclinical peripheral neuropathy.

Chronic anemia and high level ferritin are considered as the main factors in peripheral neuropathy among thalassemia patients. Stamboulis¹⁰ mentioned that peripheral neuropathy in thalassemia were found in patient with haemoglobin level below 10 g/dL and related with chronic anemia. In this study, the mean haemoglobin level was 6.7 ± 0.9 g/dL. Chronic anemia leads into low haemoglobin level and chronic hypoxic state.

Table 1. Demographic characteristics

Variable	n=60
Age (year)	
Mean ± SD	20.7 ± 7.6
Min – Max	14.6 – 60.0
Gender, n (%)	
Male	29 (48.3)
Female	31 (51.7)
Iron Chelation Agent [n (%)]	
Deferiasirox	21 (35.0)
Deferiprone	30 (50.0)
Desferal	5 (8.3)
No Iron Chelation (n (%))	4 (6.7)
Hemoglobin (g/dL)	
Mean ± SD	6.7 ± 0.9
Min – Max	4.5 – 8.9
Hematocrit (%)	
Mean ± SD	20.1 ± 3.3
Min – Max	13.5 – 30.3
Ferritin Level (ng/mL)	
Median (IQR)	2873 (1900 – 3859)
Min – Max	600 – 8915

Table 2. Neurological signs

Variable	Number of Patients (n=60)
Symptoms (Toronto)	
Median (IQR)	3 (1 – 4)
Min – Max	0 – 6
Reflex (Toronto)	
Median (IQR)	0 (0 – 2)
Min – Max	0 – 4
Sensoric (Toronto)	
Median (IQR)	0 (0 – 1)
Min – Max	0 – 2
Toronto Score	
Median (IQR)	5 (1 – 7)
Min – Max	0 – 10
Interpretation (n (%))	
Normal	28 (46.7)
Mild Neuropathy	19 (31.7)
Moderate Neuropathy	13 (21.6)



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As the result, it can damage vasa nervosum, disrupting the blood supply and Na-K ATPase pump at the axon of peripheral nerves.^{1,2,9,10}

The mean ferritin level in this study were $5,032.50 \pm 3,423.07 \mu\text{g/L}$. Borgna-Pignatti¹² and *Thalassemia International Federation* (TIF) in 2014 stated that ferritin level above $1000 \mu\text{g/L}$ showed excessive accumulation of iron in human body, acting as a *reactive oxygen species* (ROS) and damaging the myelin sheath, resulting in peripheral neuropathy. In

this study, the mean ferritin level is far above $1000 \mu\text{g/L}$, and considered as one factor in beta major thalassemia that causes the complication of peripheral neuropathy.

CONCLUSION

Thalassemia patients with peripheral neuropathy need optimal management to prevent further complication. However, peripheral neuropathy can be subclinical symptom and is confirmed only after a complete neurologic and neurophysiology

examination. TCNS score is an easy and applicable tool for peripheral neuropathy screening. The nerve conduction study (NCS) is needed to confirm peripheral neuropathy diagnosis.

Limitation of The Study

Subjects are limited to Hasan Sadikin General Hospital patients and peripheral neuropathy is assessed using scoring system instead of standard electrophysiological test.

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