Peripheral neuropathy in thalassemia

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BACKGROUND: Patients with thalassemia may complain of numbness and weakness of the lower extremities. The aim of the study was to document whether these patients suffer from a polyneuropathy and to determine any contributing factors for the development of neuropathy.

PATIENTS AND METHODS: We examined 30 patients with thalassemia major and intermedia, clinically and electrophysiologically. We correlated these findings with demographics, blood status, and treatment and compared electrophysiologic data with 30 age- and sex-matched normal subjects or historical controls.

RESULTS: We found that 78% of thalassemic patients suffered from a mild sensory polyneuropathy. The neuropathy seemed to be worse in the intermedia type. Thalassemic patients who received blood transfusions and deferoxamine had better nerve function than those who did not, irrespective of the dose of deferoxamine. The neuropathy was worse for older patients, irrespective of sex. The hemoglobin level, and the fact that some patients underwent splenectomy, did not affect the status of the patients' nerves.

CONCLUSION: Patients with thalassemia may suffer from a sensory polyneuropathy especially as they grow older and if they are not optimally treated.

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β-thalassemia is an inherited disorder of haemoglobin characterized by an absence or reduced synthesis of the β-globin chain. The net result is an excess of α-chains, which precipitate and destroy the red cell precursors, leading to anaemia, skeletal changes, splenomegaly and numerous other complications. Treatment is by regular blood transfusion coupled with iron chelation therapy to prevent iron accumulation and organ damage.

There are two clinically important presentations of β-thalassemia. Homozygous β-thalassemia usually results in thalassemia major, a severe anaemia which requires regular blood transfusions and iron chelation therapy from early infancy for survival. A milder form of the disorder exists, called thalassemia intermedia, which encompasses a wide spectrum of clinical severity, ranging from transfusion-independency to the occasional need for transfusion. Thalassemia intermedia may result from a variety of molecular processes, but its milder clinical presentation is usually due to a less marked imbalance of the α:β globin chain ratio.

The dysfunction of several organ systems has been documented in patients with β-thalassemia.[1] However, few studies have evaluated the presence of any neuromuscular complications. Focal neurological episodes, nerve deafness, as well as the presence of a myopathic syndrome have been documented in a few cases.[2-4] More recently, Papanastasiou

et al[5] demonstrated an age-related peripheral neuropathy in patients with β-thalassemia, which might be due, at least partly, to chronic anaemia.

The neurotoxic effects of iron chelation therapy have also been documented in a few studies,[6-7] which showed that deferoxamine may cause ocular and acoustic nerve complications, in a dose-related fashion.

Only a few studies have appeared in the literature concerning the effects of thalassemia and its treatment on the peripheral nerves.[2,5] In this study, we have evaluated clinically and electrophysiologically 30 patients with thalassemia major or thalassemia intermedia, to identify any peripheral nerve damage and its possible etiology.

Patients and Methods

Thirty patients with thalassemia were included in the study. These patients were being treated and followed-up at the Chronic Care Center in Beirut, where ambulatory children with chronic diseases are managed. The patients were chosen as they consecutively presented to the center, without taking into consideration any symptoms or signs. The study was approved by the local ethical committee and informed consent was obtained from each subject or subject's guardian.

All the patients had been treated for thalassemia at the center for at least the last seven years. Eighteen patients (60%) were females and 12 (40%) were males. Ages ranged from 14 to 35 years, with a mean of 20.5 years. Seventeen patients (57%) had thalassemia major and 13 (43%) had thalassemia intermedia. Nine patients (30%) had undergone splenectomy. The patient weights ranged between 31.5 and 68.0 kilograms, with an average weight of 50.6 kilograms. The hemoglobin values in the patients, averaged over the last five years, ranged between 6.4 and 12.7 g/dL, with a mean of 9.0 g/dL.

Patients were transfused with packed red blood cells according to their hemoglobin level. Six patients (20%) had not been transfused in the past five years. Four patients (13%) had not been transfused in the past two years. The 20 patients (67%) that were transfused in the past two years received between 31.4 and 211.0 mL/kg/year. These patients also received deferoxamine subcutaneously at a dose ranging between 25 mg/kg/day to 40 mg/kg/day depending on the serum ferritin level. Fifteen patients (75%) received deferoxamine 30 to 40 mg/kg/day and five patients (25%) received 25 to 30 mg/kg/day (Table 1). The deferoxamine was given

five days per week, occasionally as intravenous infusions with blood transfusions. The serum ferritin level in the patients was less than 1500 ng/mL in 12 patients (40%), between 1500 and 3000 ng/mL in six patients (20%) and more than 3000 ng/mL in 12 patients (40%). All patients had a normal fasting blood sugar during the frequent routine testing over the past five years.

The patients were referred for neurophysiological testing irrespective of any neurological symp-

Table 1. Deferoxamine treatment in 30 patients with thalassemia.

Deferoxamine (mg/kg/day)	Number of patients
30-40	15
25-30	7
None	8
Total	30

tomatology. The neurophysiological tests included motor neurographies of the peroneal and posterior tibial nerves bilaterally, the right median nerve and a fractionated motor neurography of the right ulnar nerve across the elbow. Sensory neurographies were performed on the sural nerves in both legs as well as the right median and right ulnar nerves. The electrophysiological testing was performed by the same neurophysiologist in the classical method described in the literature.[8] The distal latencies were measured from the wrist or the ankle to the respective muscles of the hand or foot in the motor nerves and to the digits in the sensory nerves. The sural distal latency was determined by stimulation at the lateral edge of the foot and recording at the lateral malleolus. The motor conduction velocities were measured between the proximal stimulation at the elbow or knee and the distal stimulation. The motor and sensory distal latencies, proximal conduction velocities, and amplitudes were measured in each nerve separately, and averaged for the patient population. The distal latencies and proximal conduction velocities reflect the status of the myelin and axons of the nerve. A mild delay is suggestive of a mild axonopathy, while a severe delay may be compatible with demyelination or severe axonal damage. The amplitude and shape of the response reflect the number of intact axons, the presence of segmental demyelination, and may give evidence of nerve regeneration. Combining these

variables together one can deduce whether the nerve damage is primarily demyelinating or axonal, or a combination of both. The degree and extent of nerve damage can be estimated by the degree of abnormalities in these variables. Statistical analysis using the Student's t test and ANOVA were performed on each variable.

The data collected consisted of the averaged value for each variable (distal latency, conduction velocity and amplitude) for each examined nerve. The results were compared to data of normal controls, of the same age and sex as the patients, from our laboratory, and from those previously published in the literature for controls lacking from our laboratory.[8] Moreover, results for each nerve were correlated to the sex of the patient, the type of thalassemia, the level of serum ferritin, occurrence of transfusion, and the amount of deferoxamine received.

Results

On clinical examination twelve patients (40%) had complaints of paresthesiae and numbness, symmetrically, and distally in the lower extremities. These patients and the asymptomatic patients had a normal sensory examination for nociception and light touch in the four extremities. Except for one patient with right foot drop secondary to entrapment of the right peroneal nerve at the knee, the patients did not complain of weakness in the limbs and had normal motor power in the proximal and distal muscles of the limbs on neurological examination. Five patients (17%) had absent deep tendon reflexes in the knees and ankles, six patients (20%) had depressed reflexes and 17 patients (57%) had normal reflexes. Gait and tandem walking were normal in all the patients except the patient with the peroneal nerve lesion.

Comparing the results of the patients to the age-matched normal subjects, we found a statistically significant delay in the sensory distal latencies of the sural, median, and ulnar nerves in the patients. The distal motor latencies in the nerves of the arms and legs did not differ (Table 2).

The amplitudes of the sural responses were significantly lower in the patients. The sensory amplitudes of the median and ulnar nerves did not differ significantly between the patients and the normal subjects. The motor amplitudes of the posterior tibial, median and ulnar nerves were significantly higher in the patients than in the controls. The proximal motor conduction velocities in the ulnar nerve, but not the peroneal and posterior tibial nerves, were higher in the patients (Table 2).

In comparing the different electrophysiological variables to patient sex, we found that the distal motor and sensory latencies in all the examined nerves were longer in the male patients compared to the female patients. On the other hand, the sensory conduction velocities in the median and ulnar

Table 2. Electrophysiological data in thalassemics and controls.

	Peroneal	Post-tibial	Sural	Median m	Median s	Ulnar m	Ulnar s
Distal latency (ms)							
Patients	3.6	3.7	3.7	3.2	2.5	2.5	2.5
Control	3.8	4	2.7	3.5	2.1	2.6	2
P value*	>0.5	>0.5	<0.5	>0.5	<0.5	>0.5	<0.5
Amplitude (mV or μV)							
Patients	5.1	10.7	12.2	12	40.6	10.6	37
Control	5.1	6	21	7	39	5.7	35
P value*	>0.5	<0.5	<0.5	<0.5	>0.5	<0.5	>0.5
Conduction velocity (m/s)							
Patients	52.9	49.7	52.5	60.9	60.8	64	46.4
Control	52.2	51.6	69.6	60.0	56.2	58.7	54.8
P value*	>0.5	>0.5	<0.5	>0.5	<0.5	<0.5	>0.5

*Patients vs. controls. Data are mean values.
m = motor ; s = sensory ; ms = millisecond ; m/s = meter per second ;
mV = millivolt; μV = microvolt.

nerves were faster in the female patients compared to the males. The motor conduction velocities, in the nerves of the arms and legs, did not differ between the sexes.

In comparing the different electrophysiological variables to the types of thalassemia we found that the distal motor latencies in the peroneal and posterior tibial nerves were significantly longer in the thalassemia intermedia group compared to the thalassemia major (4.0 milliseconds vs 3.5 milliseconds; $P<0.05$). The distal motor latencies in the nerves of the arms and the distal sural latencies did not differ between the different thalassemia types. On the other hand, the proximal conduction velocities of the posterior tibial nerves were slower in the thalassemia major patients compared to the thalassemia intermedia (48 milliseconds vs 51 milliseconds; $P<0.05$). The conduction velocities in the other nerves did not differ between the thalassemia types. The amplitudes of the sural nerves were greater in the thalassemia major compared to the intermedia (15 μV vs 9 μV; $P<0.05$). The amplitudes of all the motor nerves and of the sensory nerves in the arms did not differ between the thalassemia types.

The results further show that the patients who received blood transfusions had shorter distal latencies in the peroneal and sural responses (3.5 milliseconds vs 4.0 milliseconds; $P<0.05$), and higher sural amplitudes (14.0 μV vs 8.0 μV; $P<0.05$) compared to the patients who did not receive transfusions. The distal latencies in the nerves in the arms and the amplitudes, in general, except for the sural nerve did not differ with the occurrence of transfusions. Transfusion was not associated with any changes in the proximal motor conduction velocities. Patients who received deferoxamine more than 10 000 mg/year had significantly higher median sensory amplitudes compared to those who received less deferoxamine or no deferoxamine at all (45.0 mV vs 34.6 mV; $P<0.05$). The motor amplitudes in general and the rest of the sensory amplitudes did not differ with the amount of deferoxamine administered in the transfused patients.

The serum ferritin level is associated with higher amplitudes only in the sural nerves. The amplitudes increased from 9.18 μV in patients with serum ferritin to less than 1500 ng/mL to more than 15.37 μV in those with levels more than 3000 ng/mL. Motor amplitudes in general and sensory amplitudes in the arms did not differ significantly with the level of serum ferritin.

Discussion

Patients suffering from thalassemia frequently complain of paresthesias distally in the lower extremities. Few even lose the deep tendon reflexes in the legs. Thirty-nine percent of our patients had depressed or absent deep tendon reflexes in the legs. Objective evidence of mononeuropathies or polyneuropathies in thalassemic patients is sporadically reported in the literature.[5-9] Nerve deafness and neurotoxicity secondary to deferoxamine have been reported.[3,4,6,10] Papanastasiou et al reported mild sensory-motor polyneuropathy in 22% of their thalassemic patients.[5] Our results reveal a significant delay in the sensory distal latencies in the nerves in the upper and lower extremities, but no delay in the motor distal latencies. The proximal motor and sensory conduction velocities were not delayed. Moreover, the amplitudes in the sural nerves were lower than normal. Seventy-eight percent of the thalassemic patients had delayed sensory latencies and 54% had decreased sural amplitudes. Together with the clinical findings of depressed or absent deep tendon reflexes in the legs, these results suggest an early sensory peripheral polyneuropathy.

Contrary to Papanastasiou et al[5] we found significant differences in the neurophysiological findings between the different thalassemia types. The distal motor latencies in the legs were longer in the thalassemia intermedia compared to the thalassemia major, and the sensory amplitudes in the legs had lower amplitudes. This suggests that the neuropathy may be slightly worse in patients with thalassemia intermedia compared to thalassemia major. An intervening variable in this finding is that patients with thalassemia major, but not intermedia, received blood transfusions and deferoxamine. The treatment in itself may have affected the results or nerve function. Whether the difference in the neurophysiological variables between the groups is inherent in the type of thalassemia or the treatment is not known, but the fact remains that patients with thalassemia major on treatment fair better than patients with thalassemia intermedia who do not receive therapy.

We found a difference in the distal motor and sensory latencies between the sexes with longer latencies in the male thalassemics. This difference is not more than can be seen in the normal population. An interesting finding is the significant correlation of some of the neurophysiological variables with age. This finding supports data previously reported in the literature.[5] The posterior tibial amplitudes and con-

duction velocities, as well as the sural amplitudes and the ulnar motor amplitudes had an indirect correlation with age. As age increased, the posterior tibial, sural and ulnar amplitudes decreased and the posterior tibial conduction velocities even decreased. These findings were further emphasized when comparing the group of patients older than 20 years (53%) to those younger (47%).

Sixty-seven percent of our thalassemic patients received a blood transfusion. The distal motor and sensory latencies in the legs were significantly delayed in patients who did not receive transfusions compared to those who did. Moreover, the sensory amplitudes in the legs were significantly higher in patients who had received blood transfusion. This finding suggests that blood transfusion may delay or protect against the development of a polyneuropathy in thalassemics.

Deferoxamine, when given in doses equal to or above 10 000 mg/year, is associated with significantly higher sensory amplitudes in the median nerves. There was no correlation between the motor or sensory conduction velocities and the dose of deferoxamine or the level of serum ferritin in the blood. This finding suggests that the use of deferoxamine may improve the sensory function of some nerves, which is in agreement with the results of Papanastasiou et al.[5]

The hemoglobin level in our patients ranged from 6.4 to 12.7 mg/dL. Nineteen (63%) had a level less than 10 mg/dL and 11 (37%) had a level above that value. There was no correlation between the level of hemoglobin and any of the neurophysiological variables. Furthermore, there was no significant difference in the electrophysiology of the nerves of patients who had undergone splenectomy compared to those who had not.

The fact that the electrophysiological results improved significantly in association with blood transfusion and deferoxamine therapy, but not with the rise in the hemoglobin level, suggests that the neuropathy may be associated with overload of iron, or other heavy metals, or the loss of essential nutrients or minerals, rather than anemia. Iron chelation and replacement of blood constituents is associated with better neurographic results irrespective of the hemoglobin level. Zinc, which may predispose patients to

a neuropathy, was not measured.

The observation that motor amplitudes in thalassemic patients were significantly higher than controls is difficult to explain. We think that the neuropathy in these patients affects primarily the distal nerve endings. In the sensory fibers this presents as delayed distal latencies. In the motor fibers the neuropathy may cause degeneration followed by reinnervation via collateral sprouting. The latter phenomenon classically causes some increase in CMAP amplitude and area. The only way to confirm this hypothesis is by performing needle EMG examination of the distal muscles, which we found to be unethical in this group of patients. If the involvement of the motor fibers can be confirmed by later studies then the neuropathy may really be a sensory-motor polyneuropathy rather than only a sensory one.

The proximal nerve segments are preserved as evidenced by normal conduction velocities in the long nerves. This is further emphasised by the fact that blood transfusion improves distal latencies without affecting proximal conduction velocities. There is no electrophysiological evidence for myelin damage.

In conclusion, we find that patients with thalassemia may have an associated sensory axonal polyneuropathy affecting the distal segments of the nerves. The neuropathy seems to be more prominent in the thalassemia intermedia type rather than the thalassemia major. This may be due to the fact that the latter group receives therapy. There may not be any sex predisposition for the neuropathy, but it seems that as patients become older the neuropathy becomes more pronounced. Frequent blood transfusions and adequate chelation are associated with better nerve function or possibly delayed nerve damage. The mean hemoglobin level and splenectomy are not associated with any nerve dysfunction in thalassemic patients. In view of our interesting results, we recommend that a larger study be performed to allow more reliable statistical analysis.

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