

Peripheral nervous system involvement in patients with sickle cell disease

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Keywords:

neuropathy, sickle cell disease

Received 25 September 2008

Accepted 11 February 2009

Background and purpose: Peripheral nervous system involvement is rare in sickle cell disease (SCD). The aim of this study is to determine the peripheral nerve involvement electrophysiologically in SCD patients without clinically evident neurological signs, symptoms and to determine the relationship between the frequency of sickle cell crisis and peripheral neuropathy.

Methods: Fifty-one patients with SCD and fifty-one healthy controls were enrolled to the study. Conventional electrophysiological studies of peripheral nerves were performed to all subjects. The data about the frequency of sickle cell crisis were obtained.

Results: Peripheral nervous system involvement was detected in ten (19.6%) patients. Five (9.8%) patients had sensorimotor axonal neuropathy, two (3.9%) sensory axonal neuropathy, one (2%) patient had ulnar sensory neuropathy and two (3.9%) had median sensory neuropathy. Sural nerve sensorial action potential was unobtainable in eight (15.7%) patients and prolonged F latencies were observed in three (5.9%). The frequency of neuropathy was higher in SCD patients when compared with the controls. The frequency of sickle cell crisis was not significantly correlated with peripheral neuropathy.

Conclusion: Subclinical peripheral nerve involvement may be seen in SCD patients. Electrophysiological examinations are recommended in routine examination to diagnose early neuropathy in SCD patients without neurologic symptoms.

Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by a single base substitution of the [beta]-globin subunit of hemoglobin. The most common and severe form is homozygous sickle cell anemia (HbSS) and less frequent forms of disorder include S-type with C-type hemoglobin, HbS-Beta thalassemia-plus and HbS-Beta thalassemia-zero; the remaining variants are rare. Certain complications may be more or less common, depending on the subtype [1].

Sickle cell disease is most common in equatorial Africa and less common in southern and northern Africa [2]. The gene is also found in Greece, Turkey, Sicily, Saudi Arabia, and India.

There has been increased knowledge and awareness of the range of the neurologic complications of SCD over the past two decades. Although central nervous system involvement is well described in SCD, peripheral nerve involvement is relatively uncommon [3,4].

Peripheral nervous system involvement is extremely rare, reported as case reports [5–13]. Silent neurologic involvement may occur in SCD and there is a possibility of subclinical involvement without neurologic signs and symptoms in some cases.

The aim of this study was to determine the peripheral nerve involvement electrophysiologically in SCD patients without clinically evident neurological signs and symptoms.

Materials and methods

Total number of patients with SCD seen in the geographic catchment area was 757 and 162 patients were seen in the clinic from this sample. Fifty-one of 162 patients who were admitted to hemoglobinopathy follow-up outpatient clinic of internal disease for routine controls and fifty-one healthy control subjects (age and sex matched volunteered hospital staff) were recruited in the study. All patients had HbSS. A complete neurological examination was performed for patients with SCD and control group; muscle weakness, paresthesias, hypoesthesia, abnormalities of deep tendon reflexes,

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and vibration threshold were evaluated for assessing peripheral nervous system involvement. Subjects diagnosed to have nervous system diseases and/or patients with neurological signs or symptoms and in active stage of disease were not included to the study. Data about demographic characteristics, drug intake, and the sickle cell crisis within the last year were obtained. The following investigations were carried out: full blood count, serum vitamin B12 level, folate level. Patients in whom neuropathy was detected were evaluated for other causes of polyneuropathy after electrophysiological examinations.

All patients underwent nerve conduction studies using standard neurographic procedures and the results were assessed according to the American Diabetes Association Diabetic Neuropathy Protocol [14]. A Medelec Synergy device was used for investigation. The temperature of room was maintained at 22–24°C and the temperature of the limbs was kept above 34°C. Median, ulnar, peroneal nerve motor nerve conduction studies, F waves, and median, ulnar, and sural nerve sensory nerve conduction studies were performed in all subjects using the techniques described by Oh [15]. In the upper limbs, the median and ulnar nerves were studied. Compound muscle action potentials (CMAPs) were recorded from the flexor pollicis and abductor digiti minimi, respectively. Motor conduction velocities were measured between the wrist and elbow. Compound nerve action potentials (CNAPs) were recorded at the wrist and the sensory nerve conduction velocity calculated using the orthodromic method. In the lower limbs, the tibial and peroneal motor nerves, and sural sensory nerves were studied. CMAPs were recorded from the flexor hallucis brevis and extensor digitorum brevis, respectively. Motor conduction velocities were measured between the ankle and knee. The antidromic method is used for sural nerve studies. The recording electrode was behind the lateral malleolus and the stimulation site was on the dorsal aspect of the calf, 14 cm proximal to the recording electrodes. F responses were determined using surface electrodes placed on the same extremities on which conventional ulnar and peroneal nerve conduction studies were conducted. A series of 20 maximal stimuli at 0.5 Hz frequency and 0.2 ms duration were delivered at the wrist and ankle. Only responses of $<20 \mu\text{V}$ were accepted as actual F responses [15]. Amplitudes of evoked motor and sensory responses were measured with surface electrodes.

Nerve conduction abnormalities include slow NCV, low CMAP or CNAP amplitude, conduction block, abnormal temporal dispersion and prolonged F wave latency [15]. The diagnosis of polyneuropathy was based solely on electrophysiologic criteria defined as

two or more electrophysiologic abnormalities at non-entrapment sites. Axonal pathology and demyelination of the nerves were described as diminished sensory or CNAP amplitude and slowing in the conduction velocity of sensory or motor nerves, respectively [15].

The Ethical committee of Mustafa Kemal University granted ethical approval for the study, and the participants gave written informed consent.

Statistical analysis

Demographic properties of the patients and electrophysiological findings were summarized by descriptive statistics. Chi-square test was used to determine the differences between the frequency of electrophysiological findings of the patient and control groups. Mann–Whitney *U*-test was conducted to identify the relationship between the frequency of pain crisis and the occurrence of peripheral neuropathy in patients with SCD. Statistical significance was determined at $P < 0.05$. All statistical analyses were performed by SPSS version 11.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Fifty-one (29 men and 22 women) SCD patients and 51 healthy control subjects with a mean age of 26.76 ± 8.8 (15–51) years were included to the study. None of the patients were in the active stage of the disease. All patients had normal serum vitamin B12 and folate level. At the time of the nerve conduction study, 35 patients were on hydroxyurea and 6 were on transfusion therapy. Ten patients were not being treated for SCD.

Nerve conduction studies were abnormal in ten (four female, six male) of 51 (19.6%) SCD patients. Two (3.9%) patients had prolonged distal latency of peroneal motor nerve. Four (7.8%) patients had decreased conduction velocity of median sensory nerve, two (3.9%) patients had decreased conduction velocity of ulnar sensory nerve and four (7.8%) patients had decreased conduction velocity of peroneal motor nerve. Two (3.9%) patients had decreased CNAP of median nerve and two (3.9%) patients had decreased CNAP of ulnar nerve. Five (9.8%) patients had decreased CMAP of peroneal nerve. Sural nerve sensorial action potential was unobtainable in eight (15.7%) patients and prolonged F latencies were observed in three (5.9%) patients. The distribution of electrophysiologic findings according to number of patients is shown in Table 1. The diagnosis of polyneuropathy was based on the occurrence of two or more electrophysiologic abnormalities at non-entrapment sites. So five (9.8%) patients had sensorimotor axonal neuropathy, two (3.9%)

Table 1 The distribution of electrophysiologic findings according to number of patients

	Prolonged distal latency (<i>n</i>)	Decreased conduction velocity	Decreased amplitude (CMAP or CNAP) (<i>n</i>)	Prolonged F latency (<i>n</i>)
Median motor nerve	–	–	–	–
Median sensory nerve	–	4	2	–
Ulnar motor nerve	–	–	–	–
Ulnar sensory nerve	–	2	2	–
Peroneal motor nerve	2	4	5	3
Sural sensory nerve	8 (unobtainable)	8 (unobtainable)	8 (unobtainable)	–

Table 2 The electrophysiological features of the patients with peripheral nervous system involvement

Patients	CNAPs	SNCV	CMAPs	MNCV	Motor Distal	F responses Upper/Lower
1	Unobtainable sural responses	N	0.5 mV In C(R)	N	N	N/64.10 ms
2	Unobtainable sural responses	N	1.3 mV In C(R)	37.2 m/s In C (R)	N	N/N
3	Unobtainable sural responses	N	1.20 mV In C(R)	35 m/s In C (R)	4.50 ms C(R)	N/65.20 ms
4	Unobtainable sural responses	34.3 m/s M(L) 31.3 m/s U(L)	1.4 mV In C(R)	N	N	N/N
5	8.50 μ V M (R)	33.7 m/s M(R)	N	N	N	N/N
6	Unobtainable sural responses 8.20 μ V U (R)	N	N	N	N	N/N
7	5.50 μ V M (L)	28.60 m/s M(L)	N	N	N	N /N
8	Unobtainable sural responses 9.70 μ V M (L)	39.50 m/s M(L)	0.5 mV In C(L)	38.6 m/s In C (L)	5.0 ms C (L)	N/55.15 ms
9	7.70 μ V U (L)	36.30 m/s U (L)	N	N	N	N/N
10	5.2 μ V S (L)	38.20 m/s S (L)	N	N	N	N/N

CMAP indicates compound muscle action potential; (L), left; M, median; MNCV, motor nerve conduction velocity; N, Normal; (R), right; S, sural; CNAP, compound nerve action potential; SNCV, sensory nerve conduction velocity; C, common peroneal; U, ulnar.

patients had sensory axonal neuropathy, one (2%) patient had ulnar sensory neuropathy and two (3.9%) patients had median sensory neuropathy. In the control group, there were no abnormalities. In patients with polyneuropathy, lower extremity nerves were more affected than upper-extremity nerves. The frequency of neuropathy was higher in the patients with SCD when compared with the control subjects and the difference was statistically significant ($P < 0.05$). The electrophysiological features of SCD patients with peripheral nervous system involvement are given in Table 2. The electrophysiologic studies indicated demyelination and axonal degeneration in the examined nerves. Sensory nerves were affected more prominently than motor nerves.

Forty-one SCD patients without peripheral neuropathy had 3 ± 3.85 times sickle cell crisis within 1 year, whilst 10 SCD patients with neuropathy had 5 ± 5.83 times. The average number of sickle cell crisis is nearly two times greater in those patients who have had peripheral neuropathy. But the difference was not statistically different ($P = 0.306$; Mann–Whitney U -test).

Discussion

Peripheral neuropathy describes damage to the peripheral nervous system, which transmits information from the brain and spinal cord to every other part of the body. The incidence of peripheral neuropathy is not known, but it is a common feature of many systemic diseases. Peripheral neuropathy has numerous causes, including hereditary, toxic, metabolic, infectious, inflammatory, ischaemic and paraneoplastic disorders [16]. Although, peripheral neuropathy has multiple etiologies, the nerve has a limited number of ways to respond to injury [17]. The damage can occur at the level of axon (axonopathy). A disruption of the axons results in degeneration of the axon and the myelin sheath distal to the site of the injury (Wallerian degeneration). In toxic and metabolic injuries, the most distal portion of the axons degenerates, with concomitant breakdown of the myelin sheath (dying-back neuropathy). Neuronopathies occur at the motor neuron or dorsal root ganglion, with degeneration of their peripheral and central processes. Myelinopathies occur

at the level of the myelin sheath and can be inflammatory or hereditary [18].

Central nervous system (CNS) involvement of SCD is well known, but peripheral nerve involvement is a rare complication of SCD. Clinically evident peripheral nerve involvement is unusual, isolated cases of peripheral neuropathy have rarely reported [5–13].

Lawrence CT *et al.* reported a case of lower extremity peripheral neuropathy induced by a sickle cell vasoocclusive crisis after spinal anesthesia for cesarean delivery [6]. They conclude that there is no single mechanism responsible for vasoocclusion, the leading catalyst is to be the cellular efflux of potassium induced by deoxygenation, which causes an increase in the density and tendency of sickle cells to interact with each other, endothelial cells, and plasma constituents [19].

Shields *et al.* described a patient with an acute proximal median mononeuropathy in a young woman with sickle cell anemia in pain crisis. The clinical and electrophysiological features of this patient are suggestive of an ischaemic mechanism from the intravascular sickling process as the most likely mechanism of nerve injury. According to them, ischaemia can produce a wide range of electrophysiological and pathological reactions in peripheral nerve. Depending on the severity of ischaemic insult, changes from transient metabolic conduction block to segmental demyelination or wallerian degeneration may occur [5].

Mental neuropathy is the most seen peripheral nervous system complication of SCD [7,8,20]. Although the mechanism of mental neuropathy is still unknown, it may result from compression of the mental nerve in the mental canal of mandibula, as a result of bone infarct [17]. Cranial mononeuropathies, including anterior and posterior optic neuropathies have also been reported in SCD [9–12].

Ogundipe and *et al.* reported three cases of peripheral sensorimotor neuropathy in patients with SCD who all received nitrous oxide analgesia [13]. There are also reports of children with pica and SCD who developed a lead-induced polyneuropathy [21,22]. Sodium cyanate induced generalized axonal degenerative polyneuropathy has been observed by Peterson and *et al.* in patients with SCD [23].

Kehinde and *et al.* determined the neurological complications of sickle cell anemia in Nigerian Africans as a case control study and evaluated the relative frequencies. They found neurologic abnormalities significantly higher in patients (76%) compared with controls (32.1%). The abnormalities included paraplegia, epileptic seizures, and localized sensory neuropathy [24].

Current literature has less detailed information about subclinical peripheral nerve involvement in SCD disease. The lesser information about peripheral nerve

involvement in SCD may be explained as follows: first, the involvement may be subclinical and electrophysiologic examinations are not routinely used in patients without clinical symptoms; second, in patients with CNS involvement symptoms related to peripheral neuropathy cannot be noticed, because these symptoms are thought to be related to CNS involvement.

In our study, we have performed electrophysiologic studies including conventional sensory and motor peripheral nerve conduction, evaluation of peripheral late responses like F response to 51 SCD patients and the frequency of subclinical neuropathy was found in 19.6% of patients. Sensory nerves were affected more prominently than motor nerves and lower extremity nerves were also more affected than upper extremity nerves. The mild to moderate slowing of nerve conduction velocities affecting our patients' sensory nerves might represent the first sign of polyneuropathy [15]. Latencies and conduction velocities of motor nerves were slightly affected and the type of involvement was axonal degeneration. F response was recently proposed as a useful technique for detection of mild peripheral neuropathy [15]. F response studies show the function of entire course of motor axon, because of this mild abnormalities in any segment can be detected [19]. In our study, we also included F responses. In three patients (5.9%), we detected prolonged F response as a finding of mild neuropathy.

As a part of study, we obtained the data about the frequency of sickle cell crisis to determine the relationship between the crisis and peripheral neuropathy in patients with SCD. Although, the average number of sickle cell crisis is nearly two times greater in those patients who have had peripheral neuropathy, but there is no statistical difference between the frequency of pain crisis in SCD patients with peripheral neuropathy and without peripheral neuropathy. The peripheral nerves' microvasculature has a feature contributing to the avoidance of vaso-occlusion and ischaemia. It is proposed that the pathophysiological and anatomical basis for the rarity of ischaemic neuropathy in SCD is dependent upon the extensive vascular supply of the peripheral nerves and the large size of the capillaries in this vascular network. Thus, peripheral nerves seem to be protected from the effects of sickle vaso-occlusion [5]. So it might be suggested that much more than the frequency of sickle cell crisis, the severity of crisis and the combination of many factors such as hypoxemia, acidosis, erythrocyte dehydration, aggregation, adhesiveness may play role to produce the rare occurrence of ischaemic injury to peripheral nerve [5].

Neurologic complication secondary sickling and anemia, such as the presence of silent infarcts, is considered to be predictive factors for clinical stroke

[25,26]. Both small and large vessels are involved in the pathogenesis of stroke in SCD. The combined effects of vasoocclusion and severe anemia may lead to ischaemic damage to brain tissues, silent infarcts. In Kinney's study, 18% of SCD patients had silent infarcts, whilst Miller *et al.* found this incidence 23% [27,28]. The rate of peripheral neuropathy reported in our study is very similar to the reported rates of silent cerebral infarction in SCD. Because of the similar underlying mechanism, further research is required to investigate the relationship between the peripheral neuropathy and silent cerebral infarction in SCD patients.

There are limitations of our study. Needle EMG and nerve biopsies were not performed in SCD patients with neuropathy. As the cases were subclinically involved, invasive diagnostic techniques were not preferred. Because of this, asymptomatic axonal motor neuropathy may be underestimated and the pathophysiology of neuropathy was certainly not explained.

In conclusion, subclinical peripheral neuropathy is another site of involvement in patients with SCD. Detailed studies of this complication must be required further insight into its significance.

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