

Neurological Soft Signs as the Stroke Risk in Sickle Cell Disease

ISMET MELEK, FERIT AKGUL,¹ TASKIN DUMAN, FATİH YALCIN¹ and EDİP GALI²

Department of Neurology, ¹Department of Cardiology, Faculty of Medicine, Mustafa Kemal University, Antakya, Turkey, and

²Department of Pediatrics, Antakya State Hospital, Antakya, Turkey

MELEK, I., AKGUL, F., DUMAN, T., YALCIN, F. and GALI, E. *Neurological Soft Signs as the Stroke Risk in Sickle Cell Disease.* Tohoku J. Exp. Med., 2006, **209** (2), 135-140 ——— Sickle cell disease (SCD) is a common form of hemoglobinopathy and is highly prevalent worldwide. Silent cerebral infarction, which represents infarction without clinical signs, is a risk factor for clinical stroke in patients with SCD. It is well known that silent infarction predisposes patients with SCD to overt stroke. The aim of the present study is to investigate the effect of silent infarction on neurological soft signs (NSS), which demonstrate subtle impairments in sensory integration, motor coordination and the sequencing of complex motor acts and to evaluate whether NSS can be used in clinical practice to evaluate the patients at risk of stroke in SCD patients with silent infarction. Fifty-nine SCD patients without any documented history of cerebrovascular accident and 28 healthy controls were included in this study. All the patients with SCD were evaluated with cerebral magnetic resonance imaging. We found that the NSS scores were significantly higher in patients with silent cerebral infarction than those in patients without silent infarction and control subjects ($p < 0.05$). Importantly, there was no significant difference in the NSS scores between the patients without silent infarction and control subjects. These results indicate that high NSS scores represent an important finding for diagnosis of silent infarction in SCD patients. As silent infarction increases the risk for stroke in patients with SCD, NSS can be used to provide additional information in diagnosis of the patients with possible stroke risk during the course of SCD. ——— sickle cell; cerebral infarction; soft signs

© 2006 Tohoku University Medical Press

Neurological soft signs (NSS) are impairments in sensory integration, motor coordination and the sequencing of complex motor acts (Buchanan and Heinrichs 1989; Negash et al. 2004; Sevincok et al. 2004). They are indicative of non-specific brain damage in a variety of medical and psychiatric conditions (King et al. 1991). Patients with schizophrenia, obsessive compulsive disorders have a higher prevalence of neurologi-

cal soft signs (Shibre et al. 2002). Increased NSS scores were associated with a smaller volume of the subcortical and cortical structures (Dazzan et al. 2004). Moreover, if there are increased NSS scores, more serious impaired performance is expected. Silent cerebral infarction, which is defined as an abnormal magnetic resonance imaging (MRI) of the brain without history or physical finding of a focal neurologic deficit lasting more

Received December 13, 2005; revision accepted for publication March 28, 2006.

Correspondence: Ismet Melek, M.D., Department of Neurology, Mustafa Kemal University School of Medicine, Nöroloji ABD. 31100, Antakya, Turkey.

e-mail: ismetmelek@yahoo.com

than 24 hrs, is the most common form of brain injuries in children with sickle cell disease (SCD) (Armstrong et al. 1996; Giele et al. 2004; Kuller et al. 2004). SCD is a common form of hemoglobinopathy and is highly prevalent worldwide (Sarnaik 2005). SCD patients with silent cerebral infarction are characterized by an increased risk for further neurologic progression, including overt strokes and new MRI lesions (Pavakis et al. 1988; Moser et al. 1996; Kinney et al. 1999).

The effect of the silent infarction on NSS scores in SCD patients is not known. Therefore, we planned to determine whether subjects with small cerebral lesions do have minor or soft neurological signs that could identify the SCD patients.

MATERIALS AND METHODS

This study included 59 consecutive patients (32 men and 27 women) between 16 and 35 years of age (mean age 22.1 ± 7.8 years) with SCD admitted to the Hemoglobinopathy Center of Antakya State Hospital for routine controls (Antakya, Turkey). Any subjects with focal neurological signs and severe head trauma were excluded. The control group comprised of 28 healthy subjects (15 men and 13 women; mean age 21.0 ± 7.4 years) matched for age, sex and educational level.

All examinations of the patients and healthy subjects were performed by the same neurologist (Melek, I.). Patients underwent a neurological examination focused on soft signs according to the basis of the Neurological Evaluation Scale and MRI scan (Buchanan and Heinrichs 1989).

NSS consists of 26 items which are scored on a 3-point scale as follows: 0 = no abnormality, 1 = mild but definite abnormality, and 2 = marked impairment. NSS is a structured scale that presents scores in four subscales (sensory integration, motor coordination, sequencing of complex motor acts and others. The subscale "Sensory Integration" consists of audiovisual integration, Extinction, Right-left confusion, stereognosis (R-L) and graphesthesia (R-L); the latter two are scored on the right and left side separately (R-L). The subscale "Motor Coordination" consists of the following items: tandem walk, rapid alternating movements (R-L), Finger-thumb opposition (R-L), and Finger -nose test (R-L). In the subscale "Sequencing of Complex Motor Acts," the following items are compiled: fist ring (R-L), fist edge palm

(R-L), ozeretski and rhythm tapping test B. The fourth subscale "Others" include adventitious overflow, the romberg test, tremor, short term memory, mirror movements rhythm tapping test A, synkinesis, convergence, gaze impersistence, glabellar reflex, snout reflex, grasp reflex and suck reflex.

NSS testing took approximately 15 min and was performed in the same order throughout the study. The total NSS scores were calculated separately for the right and the left sides of the patients.

The Ethical Committee of Mustafa Kemal University granted ethical approval for the study, and the participants gave written informed consent. MRI was done with a 1.5-Tesla GE unit with super conducting magnet. T1- and T2-weighted sagittal and axial sections and proton density axial images were obtained in 5-mm sections. MRI studies of the brain without contrast were performed in accordance with standard practices.

RESULTS

Twenty-one (35.6%) patients showed MRI evidence of infarctions on T1-and T2-weighted images. The infarction size ranged from 6 mm to 42 mm. They were located in the following areas frontal 12, parietal 5, basal ganglia 2, and occipital 1 and multi-infarction 1 (Fig. 1). The mean age of patients with infarctions (25.3 ± 7.3 years) was significantly ($p < 0.02$) higher than those of the unaffected group (20.3 ± 7.2 years).

The distribution of total NSS sub-categories scores among patients and controls are summarized in Table 1. Total NSS, total sensory integration and total sequencing motor acts scores were significantly higher in SCD patients with infarction than the SCD patients without infarction and control group ($p < 0.05$). However, there were no significant differences in the total motor coordination scores between SCD patient and control groups.

When the groups were compared for the frequency of abnormal NSS items, it was seen that stereognosis, graphesthesia and fist palm-edge test were significantly higher in SCD patients with infarction than the SCD patients without infarction and control group ($p < 0.05$) (Table 2). For other items, there were no significant differences between control group, SCD patients with and without infarction.

Among the SCD patients with silent infarction 95.2% had at least one soft sign. The frequencies of individual signs ranged between 0% and 47.6% in those patients with silent infarction. The most common signs were fist palm edge test (47.6%), graphesthesia (38.0%), stereognosis (33.3%), in SCD patients with silent infarction.

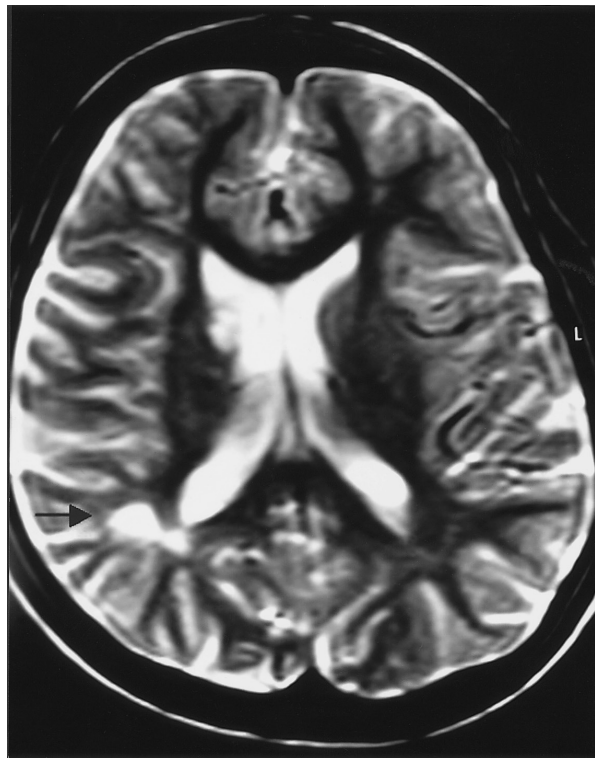


Fig. 1. T2 weighted MRI revealing a cerebral infarction 29 × 16 mm in size (arrow) on the right parietal lobe.

DISCUSSION

SCD is highly prevalent worldwide (Sarnaik 2005), and children with SCD carry a 300-fold increased risk of stroke, making SCD the most common cause of childhood stroke (Ohene-Frempong et al. 1998). By 20 years of age, 11% of patients with SCD will have suffered a clinical stroke, and a further 17-22% will have subclinical evidence of cerebral infarction defined as silent infarction on cerebral MRI. These patients with silent lesions predispose to the development of new or progressive neurological silent lesions (Wang et al. 1998). Furthermore, among the various clinical and laboratory parameters, the presence of silent infarctions on MRI was the strongest independent risk factor for stroke and was associated with a 14 fold increased risk factor of developing overt stroke (Kugler et al. 1993; Pegelow et al. 2002; Hoppe 2005).

Kral et al. (2003) have reported that the frontal lobes of the brain were most vulnerable to cerebro-vascular injury in SCD patients. Another study conducted in SCD patients using PET studies have shown that the presence of metabolic abnormalities particularly in the frontal lobes and areas of low perfusion are undetectable by conventional MRI (Powars et al. 1999). Previous MRI-based studies have shown that the affected areas in case of silent infarction are the same as the overt stroke in patients with SCD (Hoppe 2005). The most affected lobe was frontal lobe (81%), followed by the parietal lobe (45%), the basal ganglia or thalamus (16%), and the temporal

TABLE 1. Comparison of mean of NSS scores in healthy controls, SCD patients with and without infarction.

NSS	Healthy controls (n = 28)	Patients without infarction (n = 38)	Patients with infarction (n = 21)
Total NSS	0.82	1.57**	4.04**
Total sensory integration	0.14	0.29**	1.09**
Total motor co-ordination	0.29	0.39	0.71
Total sequencing motor acts	0.07	0.29*	0.76**
Total others	0.32	0.60	1.47**

P value: patients without infarction vs patients with infarction, patients with infarction vs healthy controls, * $p < 0.01$, ** $p < 0.001$.

TABLE 2. Comparison of frequency of NSS between SCD patients without and with infarction.

NSS subgroup	Patients without infarction (n = 38)	Patients with infarction (n = 21)	p
<i>Sensory integration</i>			
Audio-visual integration	3	5	NS
Sterognosis	3	7	0.02
Graphesthesia	3	8	0.01
Extinction	1	0	NS
R/L conf	1	3	NS
<i>Motor coordination</i>			
Tandem walk	6	6	NS
Rapid alternating movements	1	2	NS
Finger thumb opp	5	4	NS
Finger nose test	3	3	NS
<i>Sequencing motor acts</i>			
Fist ring test	1	1	NS
Fist edge palm test	4	10	0.003
Ozeretski	3	2	NS
Rhythmic tap B	3	4	NS
<i>Others</i>			
Adventitious overflow	3	3	NS
Romberg	3	6	0.06
Tremor	3	4	NS
Memory	8	9	NS
Rhythmic tap A	1	1	NS
Mirror	1	3	NS
Synkinesis	2	0	NS
Convergence	0	1	NS
Gaze impersistence	1	0	NS
Glabellar	0	1	NS
Snout	0	1	NS
Grasp	0	0	-
Suck	0	0	-

NS, non significant.

lobe (9%) of SCD patients with a history of overt stroke (Ohene-Frempong et al. 1998; Pegelow et al. 2001, 2002). In our study, we found that 35.6% of adult sickle cell patients had silent cerebral infarction. Most of the lesions are located unilateral involvement of frontal and parietal lobes.

In the current study, we investigated the relation between silent infarction and NSS scores in patients with SCD. NSS is an important test, which is used in patients without focal neurologic findings to express the various functional impairments of the brain systems.

NSS have been extensively studied in differ-

ent diseases like schizophrenia and obsessive compulsive disorders. A high incidence of increased soft neurological signs including motor coordination, sequencing of motor acts and sensory integration deficit have been reported in schizophrenia and obsessive compulsive disorder (Buchanan and Heinrichs 1989; Schroder et al. 1991; Gupta et al. 1995; Arango et al. 1999).

A functional MRI study of repetitive motor movement that is similar to "motor coordination" signs has identified specific activation of the supplementary motor area and sensory motor cortex in schizophrenia patients. Smaller volume of the subcortical and cortical structures in frontal and parietal lobes that are involved in sensory and motor integration are shown in schizophrenia patients (Schroder et al. 1995, 1999). In another study, Bolton et al. (1998) have reported that obsessive compulsive disorder patients had increased NSS scores and increased obsessive compulsive symptoms correlate with increased NSS scores.

There is only one NSS study in the literature conducted in SCD patients. Mercuri et al. (1995) have reported that there is a relationship between NSS and silent infarction in SCD patients. Zürich test was used for NSS test in that study. However, we used Buchanan Henrich test at the first time in SCD patients. In this study we found that NSS total scores and sub-scores were normal in SCD patients without silent infarction. However, graphesthesia, stereognosia, fist-palm-edge test and total NSS scores were significantly increased in our patients with silent infarction. It can be speculated that increased NSS indicate a nonspecific predictive factor for silent infarction and may represent a possible stroke risk in SCD patients.

CONCLUSION

Although SCD patients with silent infarction have normal neurological findings, these patients have increased NSS scores. As asymptomatic silent infarction on MRI is considered as a risk factor for the development of further lesions and cannot be detected on a standard neurological examination, NSS are important clinical signs that facilitate early identification of patients at maxi-

mum risk of developing stroke. This population could then be closely monitored for early intervention.

References

- Arango, C., Bartko, J.J., Gold, J.M. & Buchanan, R.W. (1999) Prediction of neuropsychological performance by neurological signs in schizophrenia. *Am. J. Psychiatry*, **156**, 1349-1357.
- Armstrong, F.D., Thompson, R.J., Wang, W., Zimmerman, R., Pegelow, C.H., Miller, S., Moser, F., Bello, J., Hurting, A. & Vaas, K. (1996) Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. *Pediatrics*, **97**, 864-870.
- Bolton, D., Gibb, W., Lees, A., Raven, P., Gray, A., Chen, E. & Shafran, R. (1998) Neurological soft signs in obsessive compulsive disorder: standardised assessment and comparison with schizophrenia. *Behav. Neurol.*, **11**, 197-204.
- Buchanan, R.W. & Heinrichs, D.W. (1989) The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res.*, **27**, 335-350.
- Dazzan, P., Morgan, K.D., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., Salvo, J., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J. & Murray, R.M. (2004) The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain*, **127**, 143-153.
- Giele, J.L., Witkamp, T.D., Mali, W.P. & van der Graaf, Y. (2004) SMART Study Group Silent brain infarcts in patients with manifest vascular disease. *Stroke*, **35**, 742-746.
- Gupta, S., Andreasen, N.C., Arndt, S., Flaum, M., Schultz, S.K., Hubbard, W.C. & Smith, M. (1995) Neurological soft signs in neuroleptic-naïve and neuroleptic treated schizophrenic patients and in normal comparison subjects. *Am. J. Psychiatry*, **152**, 191-196.
- Hoppe, C. (2005) Defining stroke risk in children with sickle cell anaemia. *Br. J. Haematol.*, **128**, 751-766.
- King, D.J., Wilson, A., Cooper, S.J. & Waddington, J.L. (1991) The clinical correlates of neurological soft signs in chronic schizophrenia. *Br. J. Psychiatr.*, **158**, 770-775.
- Kinney, T.R., Sleeper, L.A., Wang, W.C., Zimmerman, R.A., Pegelow, C.H., Ohene-Frempong, K., Wethers, D.L., Bello, J.A., Vichinsky, E.P., Moser, F.G., Gallagher, D.M., DeBaun, M.R., Platt, O.S. & Miller S.T. (1999) Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. *Pediatrics*, **103**, 640-645.
- Kral, M.C., Brown, R.T., Nietert, P.J., Abboud, M.R., Jackson, S.M. & Hynd, G.W. (2003) Transcranial Doppler ultrasonography and neurocognitive functioning in children with sickle cell disease. *Pediatrics*, **112**, 324-331.
- Kugler, S., Anderson, B., Cross, D., Sharif, Z., Sano, M., Haggerty, R., Prohovnik, I., Hurler-Jensen, A., Hilal, S. & Mohr, J.P. (1993) Abnormal cranial magnetic resonance imaging scans in sickle-cell disease. Neurological correlates and clinical implications. *Arch. Neurol.*, **50**, 629-635.
- Kuller, L.H., Longstreth, W.T., Jr., Arnold, A.M., Bernick, C., Bryan, R.N. & Beauchamp, N.J. (2004) Cardiovascular Health Study Collaborative Research Group White matter

- hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*, **35**, 1821-1825.
- Mercuri, E., Fandez, J.C., Roberts, I., Flora, S., Bouza, H., Cowan, F., Pennock, J., Bydder, G. & Dubowitz, L. (1995) Neurological 'soft' signs may identify children with sickle cell disease who are at risk for stroke. *Eur. J. Ped.*, **154**, 150-156.
- Moser, F.G., Miller, S.T., Bello, J.A., Pegelow, C.H., Zimmerman, R.A., Wang, W.C., Ohene-Frempong, K., Schwartz, A., Vichinsky, E.P., Gallagher, D. & Kinney, T.R. (1996) The spectrum of brain MR abnormalities in sickle-cell disease: a report from the Cooperative Study of Sickle Cell Disease. *Am. J. Neuroradiol.*, **17**, 965-972.
- Negash, A., Kebede, D., Alem, A., Melaku, Z., Deyessa, N., Shibrie, T., Fekadu, A., Jacobsson, L. & Kullgren, G. (2004) Neurological soft signs in bipolar I disorder patients. *J. Affect. Disord.*, **80**, 221-230.
- Ohene-Frempong, K., Weiner, S.J., Sleeper, L.A., Miller, S.T., Embury, S., Moohr, J.W., Wethers, D.L., Pegelow, C.H. & Gill, F.M. (1998) Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*, **91**, 288-294.
- Pavakis, S.G., Bello, J., Prohovnik, I., Sutton, M., Ince, C., Mohr J.P., Piomelli, S., Hilal, S. & De Vivo, D.C. (1988) Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. *Ann. Neurol.*, **23**, 125-130.
- Pegelow, C.H., Wang, W., Granger, S., Hsu, L.L., Vichinsky, E., Moser, F.G., Bello, J., Zimmerman, R.A., Adams, R.J. & Brambilla, D. (2001) STOP Trial Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. *Arch. Neurol.*, **58**, 2017-2021.
- Pegelow, C.H., Macklin, E.A., Moser, F.G., Wang, W.C., Bello J.A., Miller S.T., Vichinsky, E.P., DeBaun, M.R., Guarini, L., Zimmerman, R.A., Younkin, D.P., Gallagher, D.M. & Kinney, T.R. (2002) Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood*, **15**, 3014-3018.
- Powars, D.R., Conti, P.S., Wong, W.Y., Groncy, P., Hyman, C., Smith, E., Ewing, N., Keenan, R.N., Zee, C.S., Harold, Y., Hiti, A.L., Teng, E.L. & Chan, L.S. (1999) Cerebral vasculopathy in sickle cell anemia: diagnostic contribution of positron emission tomography. *Blood*, **93**, 71-79.
- Sarnaik, S.A. (2005) Sickle cell diseases: current therapeutic options and potential pitfalls in preventive therapy for transcranial Doppler abnormalities. *Pediatr. Radiol.*, **35**, 223-228.
- Schroder, J., Niethammer, R., Geider, F., Reitz, C., Binkert, M., Jauss, M. & Sauer, H. (1991) Neurological soft signs in schizophrenia. *Schizophr. Res.*, **6**, 25-30.
- Schroder, J., Wenz, F., Schad, L.R., Baudendistel, K. & Knopp, M.V. (1995) Sensorimotor cortex and supplementary motor area changes in schizophrenia; A study with functional magnetic resonance imaging. *Br. J. Psychiatr.*, **167**, 197-201.
- Schroder, J., Essig, M., Baudendistel, K., Jahn, T., Gerdson, I., Stockert, A., Schad, L.R. & Knopp, M.V. (1999) Motor dysfunction and sensorimotor cortex activation changes in schizophrenia: A study with functional magnetic resonance imaging. *Neuroimage*, **9**, 81-87.
- Sevincok, L., Akoglu, A., Topaloglu, B. & Aslantas, H. (2004) Neurological soft signs in schizophrenic patients with obsessive-compulsive disorder. *Psychiatry Clin. Neurosci.*, **58**, 274-279.
- Shibre, T., Kebede, D., Alem, A., Kebreab, S., Melaku, Z., Deyessa, N., Negash, A., Fekadu, A., Fekadu, D., Medhin, G., Negeri, C., Jacobsson, L. & Kullgren, G. (2002) Neurological soft signs (NSS) in 200 treatment-naïve cases with schizophrenia: a community-based study in a rural setting. *Nord. J. Psychiatry*, **56**, 425-431.
- Wang, W.C., Langston, J.W., Steen, R.G., Wynn, L.W., Mulhern, R.K., Wilimas, J.A., Kim, F.M. & Figueroa, R.E. (1998) Abnormalities of central nervous system in very young children with sickle cell anemia. *J. Pediatrics*, **132**, 994-998.