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NIHSS Scores in Ischemic Small Vessel Disease: A Study in CADASIL

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Key Words

National Institutes of Health Stroke Scale · Disability · Cognition · Gait · Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy · Cerebral small vessel disease

Abstract

Background: The National Institutes of Health Stroke Scale (NIHSS) is widely used to measure neurological deficits, evaluate the effectiveness of treatment and predict outcome in acute ischemic stroke. It has also been used to measure the residual neurological deficit at the chronic stage after ischemic events. However, the value of NIHSS in ischemic cerebral small vessel disease has not been specifically evaluated. The purpose of this study was to investigate the link between the NIHSS score and clinical severity in a large population of subjects with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a unique model to investigate the pathophysiology and natural history of ischemic small vessel disease. ***Methods:*** Demographic and clinical data of 220 patients with one or more lacunar infarcts confirmed by MRI examination and enrolled from a prospective cohort study were analyzed. Detailed neurological examinations, including evaluation of the NIHSS and modified Rankin Scale score (mRS) for evaluating the clinical severity, were performed in all subjects. The sensitivity, specificity, positive and negative predictive values of various NIHSS thresholds to capture the absence of significant disability (mRS <3) were calculated. General linear models, controlling for age, educational level and different clinical manifestations frequently observed in CADASIL, were used to evaluate the relationships between NIHSS and clinical severity. ***Results:*** In the whole cohort, 45 (20.5%) subjects presented with mRS ≥3, but only 16 (7.3%) had NIHSS >5. All but 1 subject with NIHSS >5 showed mRS ≥3. NIHSS ≤5 had an 85.3% positive predictive value for no or slight disability with only 33.3% specificity. The NIHSS, MMSE score and presence or absence of gait disturbances were found to be strongly and independently correlated with disability (all $p < 0.001$). Altogether, they accounted for 73% of the variance of mRS in contrast with the NIHSS alone accounting for only 50% of this variance. Among patients with NIHSS ≤5, subjects with mRS ≥3 showed a lower MMSE score than those with mRS <3 ($p < 0.001$). All patients with NIHSS ≤5 but with mRS ≥3 presented either with gait disturbances or MMSE score <25. ***Conclusions:*** The present results suggest that the NIHSS cannot reflect the extent of neurological deficit and clinical severity in subjects with lacunar infarctions in the context of a chronic and diffuse small vessel disease. A specific and global neurological scale, including the assessment of cognitive and gait performances, should be developed for ischemic cerebral microangiopathy.

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Introduction

The National Institutes of Health Stroke Scale (NIHSS) is widely used to assess the clinical severity in acute ischemic stroke [1]. It is considered as an equilibrated tool for evaluating multiple aspects of the neurological status after stroke including motor, sensory, visuospatial or language deficits as well as ataxia, hemianopia or decreased consciousness [1]. The NIHSS is also a practical and widely validated scale that can be used in daily practice to predict stroke outcome and for assessing the effectiveness of acute stroke treatment [2–8]. At 3 months, in addition to the modified Rankin Scale (mRS) mostly chosen for evaluating disability and dependence [9], the NIHSS has been used to capture the residual neurological deficit at a distance from the ischemic event [10, 11]. At the early or late stage of stroke events, it is strongly related to dependence [5, 12].

The value of the NIHSS in patients with chronic lacunar infarcts, particularly in the setting of diffuse cerebral small vessel disease (CSVD) has not been evaluated specifically. Herein, we sought to determine the extent to which the neurological evaluation as measured by the NIHSS can capture the severity of clinical deficits leading to disability and dependence in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a unique model of pure and diffuse ischemic CSVD.

Methods

Two hundred and twenty subjects having at least 1 identified lacunar infarction were drawn from a large prospective cohort of genetically confirmed CADASIL patients. The complete study design has been detailed elsewhere [13]. Briefly, in all cases, clinical, demographic and MRI data were collected. Detailed neurological examinations, including evaluation of the NIHSS and mRS, were performed in all subjects at baseline. Clinical severity was measured by mRS and categorized as favorable when the patient remained independent (score 0–2) or poor when he became dependent (score 3–5). The sensitivity, specificity, positive and negative predictive values for various NIHSS cut points to detect the independence measured by mRS were calculated. In the whole sample, association between NIHSS and mRS was examined using general linear model controlling for age. To further explore the potential factors influencing dependence, clinical manifestations frequently observed in CADASIL (psychiatric symptoms, i.e. mainly mood disturbances, gait disturbances, disequilibrium, urinary disturbances and cognitive function measured as MMSE score) and educational level were also added to the model. Since all patients but 1 with NIHSS >5 presented with mRS >3, further stratified comparisons between subjects with lower mRS (<3) and higher mRS (≥3) were performed in subjects with NIHSS ≤5.

Table 1. Main characteristics of patients with CADASIL (n = 220)

Demographic data	
Age, years	53.35 ± 10.18
Range	28–77
Male gender	110/220 (50)
History of stroke	166/220 (75.5)
Psychiatric symptoms	112/220 (50.9)
Gait disturbance	86/220 (39.1)
Disequilibrium	78/220 (35.5)
Dementia	34/220 (15.5)
Neurological scores	
NIHSS	1.71 ± 3.28
Range	0–25
mRS	1.28 ± 1.51
Range	0–5
MMSE	25.94 ± 5.03
Range	6–30

Values are means ± SD or numbers with percentages in parentheses.

Comparison of the mean MMSE score between these two subgroups was performed by using the independent-sample t test. Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc.) All p values were two-tailed, and the criterion for significance was $p < 0.05$.

Results

The main characteristics of the individuals included in the study are summarized in table 1. The mean NIHSS and mRS values were 1.71 and 1.28, respectively, in the whole population. Forty-five (20.5%) CADASIL patients had mRS scores ≥3, only 16 (7.3%) presented with NIHSS scores >5. Subjects with NIHSS ≤1 were unlikely to present with mRS ≥3, while all but 1 of those with NIHSS >5 presented with mRS ≥3 (table 2).

Table 3 shows the sensitivity, specificity, positive and negative predictive values for various NIHSS thresholds to detect undisabled or minor disabled subjects measured by mRS. A higher threshold led to a higher sensitivity, though a lower cutoff point resulted in a higher specificity. The positive predictive value of NIHSS ≤5 for capturing independence was 85.3%, its negative predictive value was 93.8%. The sensitivity of NIHSS ≤5 for this purpose was found excellent (99.4%), while its specificity was only 33.3%. Even with NIHSS ≤2, the specificity was lower than 80%.

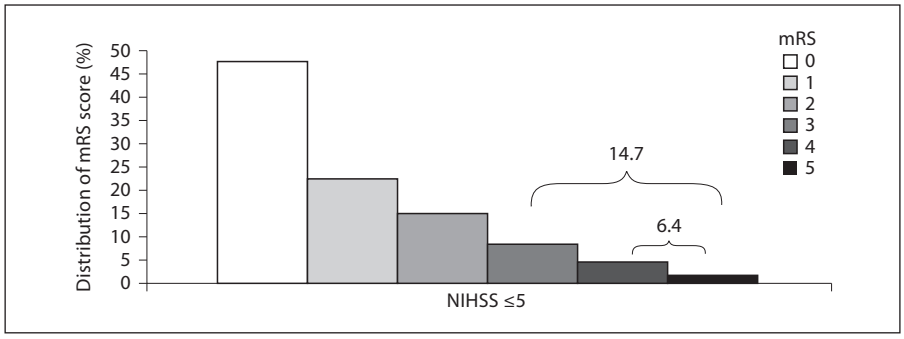


Fig. 1. Distribution of mRS score among subjects with NIHSS ≤5.

Table 2. Distribution of clinical severity (defined by mRS) by NIHSS score

NIHSS score	n	mRS score	
		<3	≥3
0	111	110 (99.1)	1 (0.9)
1	40	35 (87.5)	5 (12.5)
2	19	15 (78.9)	4 (21.1)
3	18	8 (44.4)	10 (55.6)
4	11	4 (36.4)	7 (63.6)
5	5	2 (40.0)	3 (60.0)
7	7	0	7 (100)
8	2	0	2 (100)
9	2	0	2 (100)
12	1	0	1 (100)
17	1	0	1 (100)
19	2	1 (50.0)	1 (50.0)
25	1	0	1 (100)

Results are numbers with percentages in parentheses.

Table 3. Sensitivity, specificity, positive predictive and negative predictive values (%) of NIHSS assessment of clinical severity as measured by mRS

NIHSS	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≤1	82.9	86.7	96.0	56.5
≤2	91.4	77.8	94.1	70.0
≤3	96.0	55.6	89.4	78.1
≤4	98.3	40.0	86.4	85.7
≤5	99.4	33.3	85.3	93.8

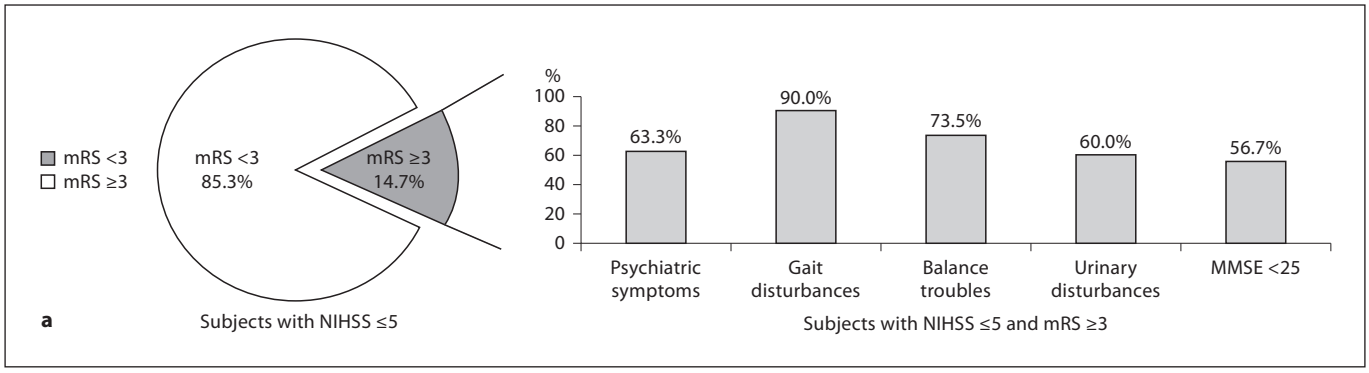
In the overall population, the NIHSS increased with the severity of mRS after adjustment for age ($p < 0.001$) and explained 50% of the variance in mRS. However, 14.7 and 6.4% of patients with NIHSS ≤5 were found to have an mRS ≥3 and ≥4, respectively (fig. 1).

To further explore the impact of different clinical symptoms frequently observed in CADASIL on disability, a general linear model controlling for age, educational level and for different clinical parameters, including the NIHSS, was produced. Both the NIHSS, the MMSE score and the presence or absence of gait disturbances were found strongly and independently associated with the severity of disability as assessed by the mRS (all $p < 0.001$). All together, these three clinical parameters accounted for 73% of the variance of mRS.

Among patients with NIHSS ≤5, subjects with mRS ≥3 had a much lower MMSE score than those with mRS <3 (20.38 ± 7.43 vs. 27.35 ± 2.73, $p < 0.001$). After further adjusting for age and educational level, this difference still remained significant ($p < 0.001$). Among subjects scoring ≤5 on the NIHSS but whose mRS was >3, 63.3% presented with psychiatric symptoms, 90.0% with gait disturbances, 73.3% with balance troubles, 60.0% with urinary disturbances, and 56.7% scored less than 25 on the MMSE (fig. 2); finally, 100% of these individuals presented either with gait disturbances or an MMSE score <25.

Discussion

To our knowledge, this is the first study of NIHSS in patients with chronic lacunar infarctions detected using MRI examination in the setting of CSVD. The results obtained in CADASIL showed that the neurological evaluation by NIHSS is not specifically related to the severity of disability. Values of NIHSS ≤5 would result in a false prediction of independence in more than two thirds of



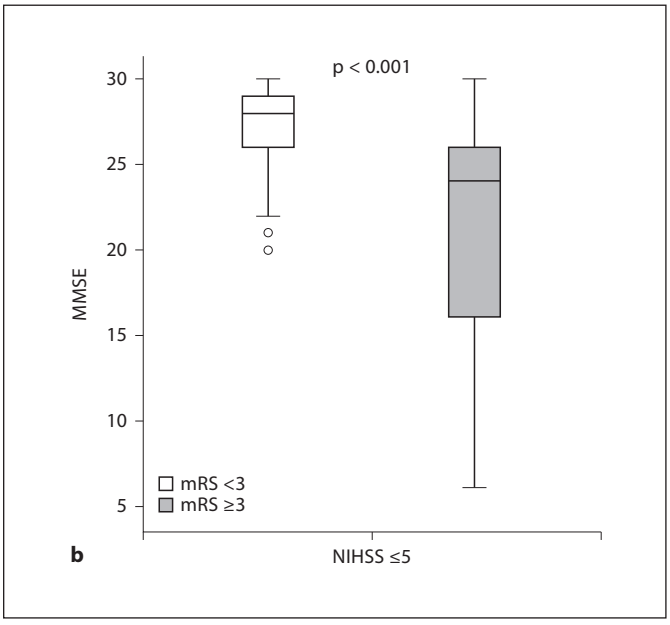


Fig. 2. a Percentage of poor outcome within subjects with NIHSS ≤5 and the distribution of clinical presentations among them. **b** Comparison of MMSE scores between subjects with mRS <3 and mRS ≥3 among subjects with NIHSS ≤5.

cases. Even using NIHSS ≤2 would result in a similar false prediction in a quarter of cases.

The present results are in contrast with data obtained from acute stroke patients whose NIHSS >5 at 3 months was found to have a sensitivity of 72% and a specificity of 92% for capturing dependency [12]. This discrepancy may have several origins. First, the NIHSS was measured at a distance from stroke events in CADASIL patients while it was recorded early after occurrence of the deficit in most previous samples [3–8]. Second, only few subjects with lacunar infarcts were included in these studies in contrast to our population all individuals of which were confirmed to have such cerebral lesions by MRI investigations [3–6, 12]. Finally, the results may also stem from the nature of the NIHSS itself which does not directly assess neurological functions with respect to disability or handicap as much as focal neurological deficits observed at the basic clinical examination. Moreover, the NIHSS is strongly weighted by deficits of cortical origin while major components of disability in CSVD such as cognitive decline or gait disturbances are not currently assessed. In the present study, more than half of CADASIL patients with NIHSS <5 but mRS >3 had actually altered cognitive performances in line with previous data showing that stroke patients with predominantly cognitive dysfunction can present with low NIHSS values despite a large disabling stroke [14]. All of these CADASIL patients presented with either gait disturbances or cognitive decline. In line, we observed in CADASIL that the variance of mRS was better explained with combining the NIHSS to other clinical parameters such as the presence of gait disturbances and MMSE score than with its use in isolation.

Altogether, the results of this study suggest that the evaluation of focal neurological deficits as performed us-

ing the NIHSS cannot substitute for a comprehensive neurological examination including the assessment of cognitive and gait performances in the evaluation of clinical severity in CSVD. The present data illustrate that a specific and global neurological scale for evaluating the clinical severity of patients with lacunar infarctions particularly in the setting of CSVD might be developed in future.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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