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Clinical evaluation of 625 lacunar syndrome patients

Aim: Lacunar syndromes consist of a group of characteristic clinical presentations that are usually compatible with a small deep infarct. Validation of these syndromes could help neurologists predict the prognosis and type of cerebrovascular disease.

Materials and Methods: Consecutive stroke patients on 2 Iranian stroke registries compiled between 2001 and 2007 were enrolled in this prospective validation study. Lacunar syndromes were defined as pure motor, pure sensory, mixed sensory motor, ataxic hemiparesis, dysarthria clumsy hand, and atypical subtypes. All of the patients with ischemic stroke had at least one brain CT scan performed 48 h after stroke. Patients whose CT scan showed a corresponding lacuna and patients with no visible new lacuna or other new lesion were assumed as appropriate to the lacunar infarction.

Results: Lacunar syndrome was observed in 625 patients (286 female, 339 male; mean age: 68.05 ± 8.9 years), accounting for 21.3% of the patients on our stroke registry. Lacunar syndromes were detected with a sensitivity of 83.7%, specificity of 96.5%, PPV of 87.8%, and NPV of 95.4% (CI: 95%). Brain CTs of 546 patients (87.4%) were appropriate to lacunar infarct. All subtypes of lacunar syndrome had more than 97% specificity. Pure motor and mixed sensory motor syndromes were associated with a PPV of 82.9% and 81.5%, respectively. Pure sensory syndrome, ataxic hemiparesis, dysarthria clumsy hand, and atypical lacunar syndromes had a PPV of 96.6%, 97.5%, 100%, and 95.4%, respectively.

Conclusions: Lacunar syndromes have moderate to high sensitivity and high specificity for the detection of lacunar brain infarction. Brain CTs in 12.6% of patients with lacunar syndrome did not correspond with lacunar stroke.

Key words: Lacunar syndrome, sensitivity, specificity

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Introduction

A lacuna is an area of infarction within the territory of a single perforated artery. Lacuna patients may present with numerous clinical syndromes. Lacunae typically present with highly focal brain symptoms (1). The clinical expression of lacunar infarcts is related to their location. Lacunae are more frequent in the basal ganglia, internal capsule, pons, and corona radiate (1); therefore, cortical manifestations, including aphasia, apraxia, agnosia, and neglect, are not seen in these patients (2,3). Homonymous hemianopsia and seizure are very rare in patients with lacunar syndrome (2,3). These types of manifestations are exclusionary criteria for the diagnosis of lacunar stroke (2,3). A decreased level of consciousness and headache are rarely caused by lacunar infarction (2,3). Any clinical pattern that has been convincingly linked to a pathological lacuna or a corresponding small deep infarct based on neuroimaging should be referred to as a lacunar syndrome (4). The advantage of recognizing these syndromes in clinical practice is the high probability of underlying lacunar infarcts (4). Although magnetic resonance imaging (MRI) is superior to computerized tomography (CT) in detecting lacunar brain infarctions (5), validation of lacunar syndromes based on MRI in a large number of patients is too expensive. Most recent validation studies on lacunar syndromes were based on brain CT scanning. The present validation study investigated the diagnostic value of lacunar syndromes in patients on our stroke registries.

Materials and Methods

A prospective validation study was performed with patients on the Khorasan and Mashhad Stroke Registries compiled between 2001 and 2007. These stroke registries were established at Valie-Asr Hospital in Birjand and Ghaem Hospital in Mashhad. Consecutive patients with varying severity of stroke were hospitalized (6). Signed informed consent was obtained from each patient or his/her first-degree relatives. Those that died prior to admission or evaluation by a stroke neurologist and those that declined to provide informed consent were excluded (6). Stroke was defined as a sudden onset of focal neurological deficit that persisted for at least for 24 h (6). Complete pure motor stroke was diagnosed when weakness equally affected the face, arm, and leg on the same side sparing the sensation (7-9). Partial pure motor stroke was defined as brachiofacial or brachiocrural distribution of weakness or unequal involvement of the face, arm, and leg (7-9). Complete pure sensory stroke was defined as equal sensory disturbance on one side of the body, including the face, and proximal and distal parts of the upper and lower limbs, neck, and trunk (7,8,10). Partial pure sensory stroke was diagnosed based on partial or unequal involvement of one side of the body, including the face, arm, and leg (7,8,10). The affected parts in pure sensory stroke could feel stretched, hot, and pins sticking, with partial or complete sensation deficit. Mixed sensory motor stroke was restricted to both sensory and motor involvement of the face, arm, and leg (7,8). Complete and partial mixed sensory motor stroke were defined similarly as the above descriptions (7,8). Ataxic hemiparesis was diagnosed based on homolateral ataxia with crural paresis. This syndrome usually presented with mild to moderate weakness of the leg, especially the ankle, with little or no weakness of the upper limb and face, and was accompanied by ataxia of the arm and leg on the same side (7,8,11). However, weakness may involve the face and arm to the same degree as the leg in ataxic hemiparesis syndrome (7,8,11). The degree of ataxia should be more striking than the weakness and exceeds that attributed to the weakness alone (7,8,11). Dysarthria clumsy hand syndrome was defined as dysarthria and ataxia of one upper limb (7,8,12). This syndrome also included facial weakness, dysphagia, and mild weakness of the hand and leg. Reflexes on the side of the clumsy hand are often exaggerated, with extensor plantar response (7,8,12). Atypical lacunar syndromes were also included in our validation study, although these syndromes do not exist in the TOAST and PIC classification of lacunar syndromes (13,2). These miscellaneous and atypical syndromes consist of isolated hemichorea or hemiballismus, isolated internuclear ophthalmoplegia, one and a half syndrome, isolated vertical gaze palsy, and isolated horizontal gaze palsy (8). Sixth nerve palsy with contralateral hemiparesis, Millard-Gubler syndrome, Benedict syndrome, Claude syndrome, Weber syndrome, Foville syndrome, internuclear ophthalmoplegia with contralateral hemiparesis, dysarthria with facial palsy, and isolated dysarthria were also included in the atypical lacunar syndromes (14). As motor or sensory involvement may be followed by each other within hours of the onset of stroke, lacunar syndromes were detected at completion of the motor or sensory manifestations 24 h after the onset of stroke. The presence of cortical signs, hemianopsia, and seizure were considered exclusionary criteria for the diagnosis of lacunar syndromes (2,7). All the ischemic stroke patients had one or more brain CT scan 48 h after the event (15). A lacuna was considered responsible for lacunar syndrome when CT scanning showed that its location corresponded to the clinical manifestations (2,16). CT of these patients should demonstrate a new ischemic subcortical lesion < 2 cm, no new cortical lesion, and no new lesion ≥ 2 cm (2,6). In the brain stem, a new ischemic lesion < 1.5 cm was considered a lacuna (2,6). Brain CT scans with no visible new lacunar infarction and without other new abnormalities were also assumed to be appropriate for neuroimaging detection of lacunar infarct (2,6,16). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the lacunar syndromes were calculated in the study group. Statistical agreement for the detection of lacunar infarcts based on lacunar syndromes was assessed with the Spearman's rank correlation coefficient. The study protocol was approved by the ethics committees of Valie-Asr and Ghaem hospitals.

Results

During a 7-year period 2938 stroke patients (1629 female, 1309 male; mean age: 65.21 ± 7.1 years) were investigated. Lacunar syndromes were observed in 625 patients (286 female, 339 male; mean age 68.05 ± 8.9 years), accounting for 21.3% of patients on our stroke registry. Lacunar syndromes occurred with significantly more frequency in males; (df = 1, P < 0.001, OR = 1.64 (1.37-1.96). Table 1 shows the frequency, sensitivity, and PPV of various lacunar syndromes in our 625 patients. Brain CT scans of 330 patients (52.8%) with lacunar syndrome demonstrated lacunar infarct corresponding to the manifestations. In all, 216 patients (34.6%) did not have a new lesion based on brain CT scanning. Thus, neuroimaging of 546 cases (87.4%) was appropriate to lacunar infarct and they were classified as true positive. Brain CT scans in 79 cases (12.6%) did not correspond with lacunar infarction. This later group of stroke patients was classified as false positive for lacunar syndrome. Among these 79 false positive cases, cortical infarction, cortical and subcortical infarction, subcortical infarction ≥ 2 cm, and intracerebral hemorrhage accounted for 17.7%, 44.3 %, 26.6 %, and 11.4% of the brain CT findings, respectively. In total, all lacunar syndromes had a sensitivity of 83.7%, specificity of 96.5%, PPV of 87.8%, and NPV of 95.4% (CI: 95%). PPV of all lacunar syndromes was 91.6% in females and 83.7% in males. Pure motor syndrome was recognized with a specificity of 97.9% and PPV of 82.9% (CI: 95%), and partial pure motor syndrome constituted 65% of these cases. Pure sensory syndrome was detected with a specificity of 99.9% and PPV of 96.6% (CI: 95%), and 80% of these cases had partial pure sensory syndrome. Mixed sensory motor syndrome had a specificity of 98.8% and PPV of 81.5% (CI: 95%), and partial mixed sensory motor syndrome constituted 78% of these cases. Ataxic hemiparesis syndrome was detected with a specificity of 99.9% and PPV of 97.5% (CI: 95%). Dysarthria clumsy hand syndrome had a specificity of 100% and PPV of 100% (CI: 95%). Atypical lacunar syndromes were associated with a specificity of 99.8% and PPV of 95.4% (CI: 95%). Table 2 shows the frequency of atypical lacunar syndromes on our registry.

Discussion

The frequency rates of lacunar syndromes and their subtypes on our stroke registry were similar to those of other reported registries around the world (17-19). Lacunar syndromes occurred with significantly more frequency in our male stroke patients. Perhaps men are more serious regarding evaluation of their problems in Iran. Other studies on lacunar syndromes did not report a preference based on gender (17-19).

Lacunar syndromes were confirmed as true positive in 87.4% of our cases. Lacunar syndromes had a diagnostic accuracy of 73% and 61% in studies conducted in Scotland and Poland, respectively (20,21). Lacunar infarcts were observed in 85% of

Table 1. The frequency rate, sensitivity, and PPV of subtypes of lacunar syndromes in 625 stroke patients.

Type of lacunar syndrome	n (%)	Males (n)	Females (n)	Sensitivity	PPV
Pure motor stroke	275 (44%)	151	124	78.4%	82.9%
Pure sensory stroke	60 (9.6%)	33	27	94.7%	96.6%
Mixed sensory motor stroke	141 (22.5%)	78	63	73.2%	81.5%
Ataxic hemiparesis	40 (6.4%)	21	23	95.1%	97.5%
Dysarthria clumsy hand	44 (7.1%)	21	23	98.1%	100%
Atypical	65 (10.4%)	35	30	91.6%	95.4%
Total	625 (100%)	339	286	83.7%	87.8%

Table 2. The frequency rate of various atypical lacunar syndromes in 65 stroke patients.

Type of the syndrome	n (%)
Isolated internuclear ophthalmoplegia	20 (30.8%)
Internuclear ophthalmoplegia and hemiparesis	4 (6.2%)
Isolated one and a half syndrome	3 (4.6%)
Isolated vertical gaze palsy	1 (1.5%)
Isolated horizontal gaze palsy	1 (1.5%)
6th nerve palsy and contralateral hemiparesis	1 (1.5%)
Millard Gubler syndrome	4 (6.2%)
Weber syndrome	10 (15.4%)
Benedict syndrome	2 (3.1%)
Claude syndrome	1 (1.5%)
Foville syndrome	1 (1.5%)
Dysarthria and facial weakness	10 (15.4%)
Isolated dysarthria	5 (7.7%)
Hemiballismus	1 (1.5%)
Hemichorea	1 (1.5%)
Total	65 (100%)

stroke patients with lacunar syndrome evaluated in Barcelona (9). A corresponding small deep infarct was demonstrated with brain CT scans in 52.8% of our patients with lacunar syndrome. In another study, 22% of Swedish patients with lacunar syndrome had a corresponding lacunar infarct according to brain CT scans (22). The main reason for the lower detection rate of lacunar infarction could be performance of brain CT within the first 48 h after stroke. In the American Stroke Data Bank, a lacunar lesion was observed in 39% of cases with lacunar syndrome with the first CT scan and repeated CT scanning increased the rate to 55% (23). Among the patients on our stroke registry, 79 with lacunar syndrome (12.6%) had CT findings inconsistent with lacunar infarction, which is in agreement with the results of other studies (24-26). Cortical involvement of the infarction was observed with brain CT scans in 8% of Swedish and 7.8% of our Iranian patients with lacunar syndrome (22). Intracerebral hemorrhage was detected with brain CT scans in 1.4% of our lacunar syndromes cases and 3.8% of lacunar syndromes cases reported by Arboix et al. (27).

The sensitivity and specificity of all the lacunar syndromes on our stroke registry were similar to those of a North American stroke registry (28). Lacunar syndromes were detected with a sensitivity of 64%, specificity of 96%, PPV of 76%, and NPV of 93% based on brain CT scans performed within the first 6 h of stroke on this North American stroke registry (28). All subtypes of lacunar syndrome on our stroke registry were associated with a high specificity, which reached 100% in dysarthria clumsy hand syndrome.

PPV, as the most accurate diagnostic marker of lacunar syndrome, was moderate in pure motor and mixed sensory motor syndromes, and high in the other subtypes of lacunar syndromes on our stroke registries. Other large studies that evaluated complete and partial sensory motor syndrome have been associated with prediction rates ranging from 79% to 90% for a corresponding lacunar infarction (24-26). The presence of a deficit involving the face, arm, and leg in previous studies was highly predictive of a lacunar infarction, but a faciobrachial deficit was less predictive than a brachiocrural deficit (24-26). Close anatomic and vascular relationships between the motor and sensory rolandic cortices makes the possibility of a mixed sensory motor syndrome more likely than a pure motor syndrome from a cortical infarction (29); however, this hypothesis was not confirmed by our stroke registry because a large subcortical infarct could make a mixed sensory motor syndrome (30). The diagnostic validity of mixed sensory motor syndrome was also low in a Japanese study (31). Brain CT scans did not correspond with lacunar infarction in up to 9% of cases and a brachiocrural deficit had higher predictive value than a faciobrachial deficit in studies evaluating both complete and partial pure motor syndromes (26,27). The Northern Manhattan Stroke Registry reported a PPV of 79% for pure motor syndrome (25). Overall, about 10% of stroke patients with a lacunar syndrome have a lesion other than a lacunar infarction according to brain CT scans, which explains the neurological symptoms (32). The proportion of such atypical patients seems to be higher for mixed sensory motor syndrome than other lacunar syndromes (32). Miscellaneous or atypical subtypes constituted 10.4% of our 625 patients with lacunar syndromes and 6.8%

of lacunar syndromes detected by Arboix et al. (14). The higher frequency rate of atypical subtypes on our stroke registry could be due to our definition criteria for atypical subtypes of lacunar syndrome. In community-based studies the overall sensitivity, specificity, PPV, and NPV of lacunar syndromes were reported to be greater than 90% based on brain CT scans (26); however, these studies included brain CT scans without new visible lesions appropriate for lacunar infarction.

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