Pathogenetic and prognostic features of lacunar transient ischaemic attack syndromes

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Abstract
Lacunar ischaemic stroke syndromes are a well defined subgroup of ischaemic strokes. To determine whether a similar subgroup can be identified among patients with transient ischaemic attacks (TIAs) we studied prospectively 102 consecutive patients within 24 hours of their first TIA. Based on their history they were classified as lacunar TIA syndromes (LTIAS; n = 45) if isolated motor or sensory symptoms or their combination had involved at least two of three body parts (face, arm, leg), whereas all other subjects were grouped as non-lacunar TIA syndromes (NLTIAS; n = 57). All patients were investigated according to a standardised protocol and followed up for an average of 51.1 months. Cardiac and arterial sources of thromboembolism were more frequent among NLTIAS (p = 0.001). Survival curve analysis demonstrated that LTIAS had a significantly lower long term mortality and incidence of major vascular events. In a multivariate regression analysis, the type of TIA (that is, NLTIAS) was an independent predictor of stroke or death. LTIAS share the same distinct pathogenetic and prognostic features of lacunar ischaemic stroke syndromes. These findings have implications for management of TIAs and for studies of their natural history and treatment.

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The customary distinction between transient ischaemic attacks (TIAs) and ischaemic strokes, based conventionally on duration of symptoms up to or beyond 24 hours, conveys no information on the pathogenesis or prognosis of the attack. Subdivision of ischaemic strokes according to their clinical manifestations allows identification of lacunar stroke syndromes. These well defined constellations of neurological signs are generally caused by small deep cerebral infarcts, the lacunes, which in turn are attributed to a distinct vasculopathy leading to occlusion of small perforating arteries. The hypothesis that lacunar ischaemic strokes are caused by small vessel disease has been strengthened by several studies reporting a significantly lower prevalence of embolicigenic heart disease and of carotid artery stenosis among lacunar than among other ischaemic strokes. Diagnosis of lacunar ischaemic stroke syndrome has prognostic implications, too, as these patients have a more favourable long term outcome than those with other subtypes of cerebral infarction. Transposition of the lacunar hypothesis to TIAs is not straightforward, as their short duration usually precludes objective verification of symptoms; thus, diagnosis of a lacunar TIA syndrome would have to rest on the patient’s history and on the clinician’s possibility to fit it retrospectively into one of the lacunar syndromes. Despite this limitation, two papers have endeavoured to distinguish a subgroup with small vessel disease also among TIAs. One study considered patients with TIA who had an infarct at CT: the authors reported a significantly higher proportion of small deep (lacunar) infarcts on CT scan among patients with unilateral isolated motor and/or sensory symptoms consistent with a lacunar syndrome than among patients with symptoms suggestive of cortical dysfunction. In another study, limited to patients who had undergone angiography, subjects with a lacunar TIA syndrome had a significantly lower prevalence of symptomatic internal carotid artery stenosis than those with a cortical TIA. We have studied an unelected population with TIA to determine whether lacunar TIA syndromes share the same distinct pathogenetic and prognostic features of lacunar ischaemic stroke syndromes.

Patients and methods
This prospective study includes a consecutive series of patients visited from 1 September 1983 to 31 August 1990 by one of the study neurologists at the emergency room of the Policlinico Hospital in Milan within 24 hours of their first TIA. This is the only emergency room in the city’s inner district where all patients presenting with symptoms suggestive of cerebrovascular disease receive free neurological evaluation around the clock, and it is often resorted to for urgent specialist examination bypassing the lengthy waiting lists of the local health service. We defined TIA as an acute focal loss of cerebral or ocular function.
attributed to ischaemia with symptoms lasting less than 24 hours. Isolated vertigo, diplopia, dysphagia or dysarthria, drop attacks, transient global amnesia, as well as focal symptoms associated with migrainous headache or spreading with a pattern suggestive of epilepsy or migraine were not accepted as evidence of TIA. We excluded patients with previous stroke, even if it had occurred in the interval between TIA and emergency room evaluation. A detailed history of the attack was obtained, and the clinical features of all patients were reviewed and discussed with a second study neurologist to improve diagnostic interobserver reliability. Based on history, patients were subdivided in lacunar TIA syndromes (LTIA) and non-lacunar TIA syndromes (NLTIAS). LTIA were diagnosed if symptoms of isolated unilateral motor or sensory deficit or their combination had involved at least two of three body parts (face, arm, leg), partially or completely. Occurrence of dysarthria did not exclude a LTIA if the symptom was attributed to supranuclear weakness of the mouth or tongue. All other episodes consistent with diagnosis of TIA, as established by accepted criteria, were grouped as NLTIAS. One patient who had experienced both types of attack before evaluation was included in the NLTIAS group.

All patients were screened for the presence of vascular risk factors: hypertension (blood pressure repeatedly higher than 160/90 mmHg or regular use of antihypertensive drugs); diabetes (fasting blood sugar higher than 140 mg/100 ml or regular use of antidiabetic drugs); smoking (at least 10 cigarettes daily during the previous 6 months), hyperlipidaemia (fasting plasma cholesterol and/or triglycerides higher than 240 mg/100 ml and 170 mg/100 ml, respectively, or regular use of lipid-lowering drugs). A continuous wave Doppler study of the extracranial vessels was performed as described by Buedingen et al. ECG, chest radiograph, and cardiological examination were carried out in all cases, depending on specific diagnostic needs. M-mode and B-mode echocardiograms were obtained in 28 cases (18 with LTIA and 10 with NLTIAS), and 24 hour ECG monitoring in eight cases (two with LTIA and six with NLTIAS). Potential cardioembolic sources were diagnosed in patients with atrial fibrillation, endocarditis, mitral valve disease (including mitral valve prolapse in patients under 45 years of age), left ventricular aneurysm, or thrombus. Ischaemic heart disease was diagnosed in patients with a typical history of angina or acute myocardial infarction, or with clear cut ECG evidence of previous myocardial infarction. A CT scan was performed as part of the emergency room evaluation, and was repeated after 5 to 8 days; all scans were reviewed by a neuroradiologist (EB) who was blind with respect to clinical diagnosis of LTIA or NLTIAS. Cerebral infarcts were defined as circumscribed hypodense lesions and were considered as congruous if appropriate to the side of symptoms. They were further subdivided into superficial and deep; the latter were diagnosed as lacunar infarcts if their maximum diameter did not exceed 15 mm on no more than two adjacent 10 mm tissue sections. Cerebral angiography was carried out in 24 patients (except one patient due to carotid endarterectomy (14 with LTIA and 10 with NLTIAS)). Four of them were randomised in the European carotid surgery trial and two of them underwent carotid endarterectomy (one with LTIA and one with NLTIAS); no other patient had carotid endarterectomy. There were no angiographic or surgical complications.

Emergency room examination was taken as zero time from which event-free survival was measured. All patients were followed up for at least 12 months or until death (average, 51±1 months), and all survivors were re-examined by one of us in September 1991. Antiplatelet treatment with aspirin (300 to 500 mg/day) or with ticlopidine (500 mg/day) was generally prescribed with the exception of five patients with NLTIAS who received oral anticoagulants. We considered patients as treated with antithrombotic drugs if they had taken this therapy for at least half of their total follow up time. Control of vascular risk factors was pursued in all cases. Occurrence of new cerebrovascular events (which were classified as TIAs or strokes according to duration of symptoms up to or beyond 24 hours) was ascertained for carotid endarterectomy performed whenever possible in case of stroke. Stroke disability was evaluated at approximately 3 months by the modified Rankin scale; and strokes were classified as follows: not disabling (Rankin grades 0–1); partially disabling (grades 2–3); severely disabling (grades 4–5); or fatal. Occurrence of myocardial infarction was also recorded. Diagnosis was accepted if at least two of the following criteria were fulfilled: typical chest pain, concordant ECG changes, and enzymatic alterations. Causes of death were ascertained by reviewing clinical records and necropsy reports; if the cause remained uncertain, relatives and attending physicians were also consulted. Vascular deaths included those due to stroke, myocardial infarction, cardiac failure, peripheral arterial disease, and ruptured aortic aneurysm, as well as sudden presumed cardiac deaths.

STATISTICAL METHODS
Statistical analyses were performed using Epilog Plus software package. The strength of association between the considered variables and the type of TIA (LTIA or NLTIAS) was calculated by means of odds ratio (OR), taking LTIA as reference category, and their statistical significance was evaluated by the $\chi^2$ test. Confidence intervals (CI) of OR were calculated as suggested by Cornfield. The significance of the difference between means was tested with two tailed t tests for unequal data. Analyses of the cumulative time dependent probability of event free survival were carried out by Kaplan-
Meier method, and the strength of association of these probabilities with possible prognostic variables was evaluated by hazard ratio (HR). Cox’s model was employed to carry out multivariate regression analysis.

Results
A total of 102 patients with first TIA within the previous 24 hours were seen during the study period, 45 (44%) with LTIAS and 57 (56%) with NLTIAS. All had experienced TLIAs of the brain, and none reported isolated amaurosis fugax. Twenty four (53%) of the 45 LTIAS had presented isolated motor symptoms, three (7%) isolated sensory symptoms, and 18 (40%) a combination of sensorimotor symptoms. The average age of patients was 64-7 years (range 24-83) for those with LTIAS and 68-7 (range 43-89) for those with NLTIAS (t = 1-76, p = 0-08). The prevalence of vascular risk factors is reported in table 1. No significant difference was observed between the two groups. Results of cardiological and instrumental evaluations are also reported in table 1. Although the proportion of infarcts on CT scan was rather similar in the two groups, six of the eight congruous infarcts among LTIAS were of the lacunar type, as opposed to four out of 10 among NLTIAS (OR = 0-22, 95% CI 0-01–2-42, p = 0-31). Overall, 11 patients had a CT incongruous infarct, six with LTIAS (five lacunar and one non-lacunar infarct) and five with NLTIAS (four lacunar and one non-lacunar infarct). The prevalence of ischaemic heart disease was similar in the two groups. In patients with embolicgenic heart disease, embolicogenic heart disease was significantly more frequent among NLTIAS (p = 0-004). Occlusion or more than 50% stenosis of the symptomatic arterial district was demonstrated by angiography in four of 10 patients with NLTIAS and in one of 14 with LTIAS. However, since angiography was performed only in a selected group of patients, we assessed the prevalence of vascular lesions by means of Doppler ultrasounds. NLTIAS had a higher frequency of obstructive lesions of the symptomatic neck vessel than LTIAS; among patients without embolicgenic heart disease, only three out of 43 LTIAS had pathological Doppler findings, as opposed to 13 of 41 NLTIAS (OR = 6-19; 95% CI 1-50–23-51; p = 0-009). Overall, patients with NLTIAS had a 4-5 times higher prevalence of cardiac or arterial sources of thromboembolism than LTIAS (p = 0-0001).

Data on follow up are presented in table 2, and the figure shows the Kaplan-Meier survival curves for major vascular events and their combinations. Since patients with LTIAS were on average younger than those with NLTIAS, and a greater proportion of them had taken antithrombotic drugs, results of survival curve analysis have been adjusted as HR after adjusting for age and for treatment with antithrombotic drugs. Prognosis of LTIAS was significantly more favourable with regard to vascular mortality and to all considered combinations of major events; overall mortality was likewise lower in this group (HR = 5-2; 95% CI 1-5–18-1; p = 0-01). LTIAS also had a lower incidence of strokes, which were less often disabling or fatal than those experienced by NLTIAS (table 2). A multivariate regression analysis including, besides type of TIA, all variables listed in table 1 identified three independent prognostic factors associated with occurrence of stroke or death, namely non-lacunar type of TIA (HR = 2-55, 95% CI 1-12–6-82; p = 0-02), diabetes (HR = 2-68; 95% CI 1-09–6-52; p = 0-03), and embolicgenic heart disease (HR = 2-55; 95% CI 1-06–6-12; p = 0-03).

Discussion
Recruitment of patients at the emergency room is unusual in studies on TIA, yet it helped to obviate some potential drawbacks of our investigation. Firstly since most patients presented without having been previously examined by a physician, it probably reduced the referral bias inherent to hospital based studies. In fact, the age and sex distribution of our population and the prevalence of vascular risk factors were more similar to those observed in a community recruited...
cohort than to those of hospital referred populations. Secondly, history could be obtained shortly after the attack, allowing early prospective differentiation of lacunar from non-lacunar episodes, not biased by results of subsequent examinations. Finally, emergency room evaluation enabled us to include patients in the study within 24 hours of symptom onset and thus to identify events manifesting very soon after TIA, thereby enhancing completeness of follow up, as illustrated by occurrence of four strokes during the first week. On the other hand, none of our patients had experienced amaurosis...
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fugax, a condition which may harbour a better prognosis than do TIA of the brain, as these patients were first evaluated by an ophthalmologist and only later referred to the neurologist. The criteria for diagnosis of LTIA, which ensure an excellent degree of reliability among different observers, were similar to those of Kappelle et al.8 who in addition included in this subgroup patients with symptoms restricted to one body part. Hankey and Warlow adopted stricter criteria, as they required involvement of all three body parts or, in patients with brachiofacial or brachioocular symptoms, that the whole of each body part was affected, information which may be difficult to ascertain from history. Moreover, they considered only right handed patients with left hemispheric TIA who had attempted to speak during the episode, thus allowing them to evaluate occurrence of aphasia. While these criteria increased the sensitivity of the diagnosis of lacunar TIA syndrome, they also reduced its field of applicability to only 26.5% of the authors' original TIA population. At variance with the two abovementioned studies we did not exclude patients with TIA in a vertebralbasilar distribution, since lacunar syndromes may result from brainstem lesions, and because there is no definite evidence that posterior circulation TIAs have a peculiar pathogenesis and prognosis. Moreover, as we wanted to verify whether clinical history alone could identify a pathogenetically and prognostically homogeneous subgroup out of an unselected population with TIA, we did not reclassify our patients according to CT scan results. In fact, 44% of our patients with "positive" CT scan had clinically silent lesions, implying also that appropriately sited lesions may be mistakenly associated with occurrence of TIA. It is nonetheless remarkable that the proportion of concomitant CT lacunar infarcts among our LTIA (75%) and NLTIAS (40%) were equal to those observed by Kappelle et al.8

Our study demonstrates that cardiac and arterial sources of thromboembolism are associated with the occurrence of NLTIAS. The same features characterise non-lacunar strokes.35-37 Reports on the long-term outcome of stroke agree that patients with lacunar ischaemic stroke syndromes have a more benign prognosis than those with other stroke subtypes.35,37 Our study indicates that the same holds true for LTIA. Furthermore, results of our multivariate regression analysis demonstrate that lacunar TIA represents an independent prognostic variable, which remains significantly associated with a favourable outcome even if other risk factors are considered. Again, the same findings apply to lacunar ischaemic stroke.7

The validity of the lacunar hypothesis relating lacunar ischaemic stroke syndromes to small vessel disease has been questioned on the assumption that their pathogenetic and prognostic features are not peculiar but simply those of "small strokes".24 Our finding that these same features characterise a similar subgroup among patients with TIA, who by definition experience complete resolution of symptoms within 24 hours, supports the validity of the lacunar hypothesis. We therefore suggest transposition of the term "lacunar" from its original pathological setting25 to a clinical one, to designate attacks which manifest with specific patterns of signs or even symptoms. Although it cannot be excluded that, in a given patient, an LTIA is due to thromboembolism from arterial or cardiac sources, the low prevalence of stenosis of the symptomatic neck vessel and of embolicgenic heart disease observed among patients with LTIA, resembling those reported in asymptomatic individuals of similar age,26,27 is consistent with the possibility that these abnormalities represent general markers of atheroembolism rather than factors involved in the pathogenesis of the attack. Careful history taking, a simple and widely applicable method not dependent on sophisticated technologies, thus allows identification of a subgroup of patients with TIA who may benefit from a distinct diagnostic and therapeutic approach and who should be considered separately in studies on the natural history and treatment of this condition.

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The first description of idiopathic progressive bulbar palsy

Furukawa has recently recounted the lesser known contributions to clinical neurology of Sir Charles Bell who first described the numb chin syndrome and the phantom phenomena in his book on the nervous system. We would like to report an account of a patient with progressive bulbar palsy (PBP) who was referred to Bell, is included in the same book and predates the writings of Duchenne de Boulogne, who is usually credited with the first descriptions.

The patient’s details are contained in a letter to Bell from Robert RW Robinson, of Preston, England, dated 21 July 1825. He asked for advice about “an unmarried lady, nearly seventy years of age, who has enjoyed uninterrupted good health up to the present illness.” He states:

From the first of her complaint to the present moment she has been free from headache (sic) and from pain, numbness, or debility of the limbs. The vision and hearing are natural; the appetite good; the bowels regular, and the sleep natural. ... Some few months ago she had some difficulty in using the tongue and in expressing particular words. This difficulty has gradually increased, and now she cannot pronounce the tongue, or even move it. She has lost her speech altogether. The tongue itself is soft and pulpy; but it retains its sense of taste and feeling. The deglutition is impaired and occasionally she is distressed with a sense of suffocation, in attempting to swallow food, which she is now obliged to do with great care. She cannot hack up any thing from the throat, nor draw any thing from the posterior nares by a back draught. The features of the face are quite natural, and the skin retains its feeling. The saliva occasionally flows from the mouth."

Bell noticed the similarity between this patient’s condition and the syndrome observed in a dog after section of the lower cranial nerves and concluded that the patient was suffering from “a paraesthetic affection of the ninth nerve” and noted that the “function of the fifth nerve had been preserved.” Unfortunately no follow up or necropsy results are available to tell us if the disease became more widespread, neither is there any information about the deep tendon reflexes, as this physical sign was not introduced into the neurological examination until 1875. Bell advised nauseating medicines and leeches under the mastoid, amongst other remedies.

This description would rival any modern case report for conveying clearly the clinical signs, the important negative features for the diagnosis and the disability resulting from this tragic affliction. We would argue that this patient’s illness, which combines anarthria, impaired deglutition and tongue movement with palsy, probably with mixed upper and lower motor neuron signs, is due to idiopathic PBP, one of the modes of presentation of motor neuron disease and which may occasionally remain confined to the bulbar region. Given the advanced disease, a brainstem tumour seems unlikely in the absence of sensory signs and if the bulbar palsy was due to myasthenia gravis, ocular and limb symptoms would be expected.

Bell’s observations were common but little is known of the referring physician. Robinson was born in Lancashire and graduated Doctor of Medicine at Edinburgh on 12 September 1800. He was president of the Royal Medical Society, founded in 1734 by a group of medical students after the successful acquisition of a fresh body for dissection. The founders initially met in taverns “... with the intention that a dissertation in English or Latin on some medical subject ... should be composed and read” and later meetings were attended by Charles Darwin. There is no evidence that Robinson had an earlier interest in neurology as he obtained a doctorate based on a urological subject (Dispanatura medica inaugurali de vesicea, urethraeque morbis). He became a Licensiate of the College of Physicians (London) in 1807 and returned to his native Lancashire where he was an influential member of the board of management of the Preston Dispensary, founded in 1809. Unfortunately 169 years after his original account, the etiology of PBP remains obscure.

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