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BRIEF COMMUNICATION

Cognitive functioning in patients with a small infarct in the brainstem

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Abstract

Earlier findings in patients with a small supratentorial white matter infarct demonstrated subtle impairments of cognition. This is in line with reported difficulties in regaining premorbid level of functioning in daily life activities, even though any physical neurological deficits are no longer present. Either a "bystander effect" of adjoining gray matter or a long distance effect through hypometabolism or other neurochemical changes might underlie these impairments. To find the best explanation, a group of 17 patients with a lacunar infarct in the brainstem was neuropsychologically evaluated and compared with a closely matched control group. The patients demonstrated significantly impaired task performance on a constellation of neuropsychological tasks that was very similar to the findings previously found in patients with a supratentorial lacunar infarct (Boston Naming Test, TEA visual elevator, category fluency, Trailmaking Test). We conclude that a small white-matter infarct may affect cognitive functioning in a nonspecific way independently of its location. (*JINS*, 2003, *9*, 490–494.)

Keywords: Brainstem, Small infarct, Neuropsychology, Cognitive impairment

INTRODUCTION

In about 25% of cases, ischemic strokes concerns a lacunar infarct. This type of stroke is most often caused by obstruction of a small deep perforating artery in the brain. The resulting small infarcts occur most often in the deep nuclei of the brain, the deep cerebral white matter, or the pons. The clinical features of a lacunar infarct can be categorized into at least 20 different syndromes, characterized by one or more of the following neurological deficits: weakness, sensory loss, ataxia, and dysarthria (Fisher, 1991). None of these syndromes is associated with cognitive dysfunction. It has been well established that the physical outcome of a lacunar stroke is favorable in comparison with other types of stroke (Clavier et al., 1994). Less attention has been directed towards behavioral and cognitive outcome, despite anecdotal reports on emotional lability, a reduction in quality of life and cognitive disorders (de Haan et al., 1995).

In an earlier study, we evaluated neuropsychological functioning in a group of patients with a lacunar stroke confined to the internal capsule, the corona radiata or the centrum semiovale (Van Zandvoort et al., 1998). As expected, none of these patients showed substantial neuropsychological impairment. It was, however, remarkable that as a group, the patients demonstrated decreased performance on a constellation of five demanding neuropsychological tasks (language, concept-shifting, abstraction, incidental memory, verbal fluency) compared to a well-matched control group. These subtle cognitive disturbances add credence to the complaints commonly heard from patients that "things are not as easy as they used to be" and "I am tired after activities that used to be automatic or effortless." Furthermore, the observed neuropsychological impairments cannot be explained by a single cognitive domain nor do they reflect a general cognitive decline. They do, however, restrict the capacity to regain full premorbid performance.

In a follow-up study we found that the same pattern could be discerned 6 months after initial examination. This finding showed that the mild cognitive impairments were consistent over time (Van Zandvoort et al., 2001). A case study

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of a patient who was neuropsychologically evaluated before and after a small infarct in the right corona radiata provided additional evidence that a single supratentorial lacunar can be associated with cognitive impairments (Van Zandvoort et al., 2000). After his stroke he presented with subtle cognitive changes in a constellation of tasks similar to the previously discerned pattern. The subtle impairments in cognitive functioning after a small deep infarct may result from a lesion of adjoining gray matter or to a distance effect *via* hypometabolism or other biochemical changes underlying the cognitive anomalies. Neurochemical abnormalities associated with the occurrence of an ischemic infarction, even of a small infarct, can be much more more extensive than the structural damage (Basso et al., 1987; Ferro et al., 1984; Kwan et al., 1999; Lanfermann et al., 1995; Metter et al., 1985). Moreover, distance effects of an infarct may be independent of its site. Clinical observations suggest that the effects appear even in patients with a lacunar infarct confined to the brainstem. In one-half of the patients with a small brainstem infarct good physical outcome is associated with persistent limitations in daily life activities (Chua & Kong, 1996; Malm et al., 1999; Nelles et al., 1998). Moreover, cognitive impairments may prevent patients' return to work or regular daily activities despite apparent recovery to premorbid level (Malm et al., 1999). Despite the extensive evidence about the role of the brainstem in sleep, dreaming, arousal, and vigilance (Sturm et al., 1999), the brainstem probably does not directly influence cognitive functioning. Because of this and the poor outcome in patients with large brainstem strokes, research on neuropsychological functioning after a brainstem stroke is lacking.

In the present study, we assessed the cognitive status of a group of patients with a stroke confined to the brainstem (medulla oblongata and pons) in order to test the hypothesis that the same subtle cognitive impairments as observed in patients with a supratentorial lacunar stroke are present in this patient group. Support for this hypothesis would argue against the alternative explanation of a bystander effect in gray matter as an explanation for the cognitive decline after a lacunar infarct. In addition, the observation of cognitive impairment after brainstem lesions has implications for clinical practice.

METHODS

Research Participants

Patients with a small infarct confined to the brainstem area were identified among the consecutive acute stroke patients referred to the stroke unit of the University Medical Center Utrecht in the period from 1998 to 1999. Patients were selected on the presence of the clinical symptoms of a nondisabling brainstem stroke (Rankin score = 3) diagnosed by a senior neurologist (L.J.K.). A lacunar infarct in the brainstem area (pons and medulla oblongata) had to be visible on a CT scan or MR image (see Figure 1). Patients with other relevant brain abnormalities, such as disproportionate white matter abnormalities or prior ischemic lesions, were excluded. Furthermore, patients had to be able to undergo the testing procedure of 1-$\frac{1}{2}$ hr during their stay in the hospital, by means of a purpose-designed neuropsychological test battery in the Dutch language. In order to be selected for the study, patients had to be no older than 80 years, right handed, free of medical history with respect to ischemic episodes or other conditions that affect cognitive functioning, and have no history of psychiatric disorders or alcoholism. For each patient, a control subject closely matched with respect to age, gender and education was included. Control persons were recruited from the general population by means of advertisements in local newspapers. The study protocol was approved by the ethics committee of the hospital (WHO standard) and all patients signed an informed-consent form.

Procedure and Measures

The testing procedure was identical for patients and controls. First, they were interviewed by means of a semistructured interview including questions about details of the onset associated with the stroke, their (premorbid) occupation and/or daily life activities, their medical history, level of education, the possible presence of symptoms affecting physical, cognitive and/or emotional well-being (Van Zandvoort et al., 1998, 2001). Subsequently, patients were evaluated neuropsychologically by means of a test battery that had proved to be sufficiently sensitive to detect subtle cognitive disturbances in patients with supratentorial small deep infarct patients (Van Zandvoort et al., 1998). The battery included the following standardized neuropsychologi-

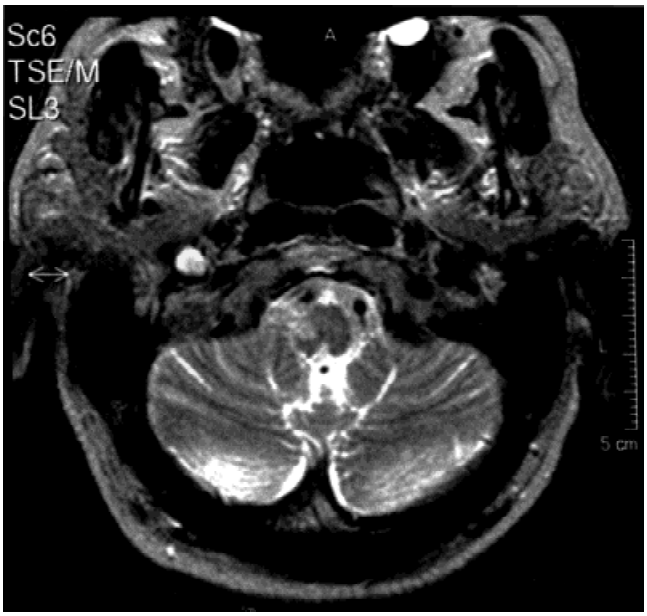

Fig. 1.

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cal tasks covering the major cognitive domains of language: Boston Naming Test, Verbal Fluency–letter (UNCA), and Category Test (*animals* and *professions*). For measuring attention and executive functioning, the Digit Span, Visual Elevator and Lottery subtests of the Task for Everyday Attention (TEA), Trailmaking Test A and B and interference score (TMT), WAIS similarities were used. Visual–perceptual and construction abilities were tested by means of the Rey-Osterrieth Complex Figure Copy. To assess memory the Corsiblock Span and Rey-Osterrieth complex figure delayed recall were used. The complete procedure took 1.5 hr. All interviews and neuropsychological examinations were performed by the same person (M.v.Z.).

RESULTS

Seventeen patients with a first-time small infarct in the brainstem were included. In all cases the ischemic lesion could be confirmed by CT scan or MR imaging. In Table 1, patient characteristics, clinical symptoms and lesion location are summarized. Testing took place as soon as the patient was able to sit up independently and was likely to be free from nausea or dizziness for at least 1.5 hr. The mean interval between stroke onset and testing was 11.2 (7.1) days post stroke. At the moment of examination, all patients were on oral antithrombotic medication, 4 were on antihypertensive medication, and 1 patient had well-controlled insulin-dependent diabetes mellitus. Seventeen closely matched healthy volunteers served as a control group. They did not significantly differ with respect to age [*M*: 60.1 (11.6) *vs.* 60.3 (12.6)], level of education according to Hochstenbach et al. (1998): [*M*: 4.6 (1.1) *vs.* 4.7 (1.4)], or gender (male: female ratio was 13:4 and 13:4 for the patient and control groups, respectively).

Patients reported to be more easily emotional (Mann-Whitney $U = 51.0$, $p = .001$) and had more complaints about fatigue (Mann-Whitney $U = 76.5$, $p = .02$) as compared to the control subjects. Furthermore, patients had no more complaints about memory, attention, and feelings of gloominess than the control subjects. None of the patients showed a catastrophic reaction pattern or presented with pathological laughter or crying, features which can be found after a brainstem stroke (Kim & Choi-Kwon, 2000).

For statistical analyses, mean performance scores on the 13 neuropsychological tasks were calculated for both groups. First, an overall multivariate analysis of variance (MANOVA) was performed with tests (the 13 neuropsychological tasks) as within-group variable and group (patients *vs.* controls) as between-group variable. This analysis demonstrated a significant overall group effect [$F(1,32) = 31.5$, $p < .001$], indicating that the patients performed worse than the control group on the neuropsychological tasks in general. The interaction of Tests × Group also reached significance [$F(1,12) = 9.4$, $p < .001$], indicating that patients were not equally impaired on the separate neuropsychological tasks. This was further investigated by means of *post-hoc* ANOVAs on the 13 individual neuropsychological tasks (see Table 2).

We corrected for multiple testing by restricting alpha by means of a Bonferroni correction The analyses demonstrated five significantly discriminating tasks in which the patients showed a lower performance than the control group. The patients had more trouble in finding the correct words on the Boston Naming Test [$F(1,32) = 12.7$, $p = .001$] and were slower on the TEA Visual Elevator [$F(1,32) = 23.8$,

Table 1. Characteristics, neurological symptoms and lesion location of the patients

No.	Age	Gender	Education*	Days post stroke	Neurological symptoms	Lesion location
1	56	m	6	12	Dizzy, nausea	Medulla oblongata
2	54	m	4	13	Wallenberg, dysarthria, dysphagia, dizzy, arm paresthesia	Medulla oblongata
3	75	m	4	5	Dysarthria, dysphagia, dizzy, hemiparesis, arm paresthesia	Pons
4	55	m	4	17	Dysarthria, dizzy, leg paresis	Pons
5	50	m	6	14	Dysarthria, dizzy, hemiparesis	Pons
6	64	f	5	9	Hemiparesis	Pons
7	67	m	4	5	Dysarthria, dysphagia, dizzy, paresthesia, diplopia	Medulla oblongata
8	75	m	6	18	Dysarthria, dizzy, hemiparesis, paresthesia	Pons
9	32	f	5	16	Dysarthria, dysphagia, hemiparesis, leg parethesia, Horner syndrome	Medulla oblongata
10	45	m	4	6	Dysarthria, dizzy, hemiparesis, leg paresthesia	Pons
11	66	f	4	8	Dysarthria, hemiparesis	Pons
12	77	m	4	11	Dysarthria, hemiparesis	Pons
13	66	m	4	4	Dysarthria, hemiparesis	Pons
14	57	m	6	5	Diplopia	Pons
15	67	f	2	7	Dysarthria, hemiparesis, paresthesia, nausea	Pons
16	62	f	5	13	Dysarthria, hemiparesis	Pons
17	57	m	5	10	Dysarthria, hemiparesis	Pons

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Table 2. Mean neuropsychological test performance for the patients and the control group and level of significance on *post-hoc t* tests

Task	Patient mean (*SD*)	Control mean (*SD*)	Significance ($\alpha = .04$)
Boston Naming Test	166.4 (9.3)	175 (4.7)	*
Digit span total	11.9 (2.8)	13.8 (3.2)	
Corsiblock span	5.2 (0.8)	5.1 (0.6)	
TEA visual elevator time	5.3 (1.1)	3.7 (0.9)	*
Category fluency	32.3 (7.5)	42.5 (7.2)	*
Letter fluency	35.1 (8.7)	43.1 (11.9)	
TEA lottery	9.5 (1.3)	9.7 (0.7)	
Rey-o copy	34.6 (1.9)	35.2 (1.4)	
Rey-o immediate recall	21.4 (6.2)	25.0 (5.6)	
Rey-o delayed recall	21.7 (6.1)	23.7 (5.0)	
TMT–A	53 (23)	35 (13)	*
TMT–interference	1.05 (0.41)	0.6 (0.3)	*
WAIS–Similarities	17.5 (4.9)	21.2 (3.2)	

$p < .001$]. Also patients came up with fewer words in a given semantic category [Category Fluency, *animals* and *professions*: $F(1,32) = 17.2$, $p < .001$]. Patients were slower on the TMT–A than controls [$F(1,32) = 9.7$, $p = .004$] and they had more trouble with concept-shifting, as indicated by the interference score on the TMT [$F(1,32) = 13.5$, $p = .001$]. This effect cannot only be attributed to the influence of motor impairment as in which motor impairment is controlled for in the interference score. The other seven tasks did not show a difference in performance between the two groups.

DISCUSSION

We examined neuropsychological function in 17 patients with a first-time lacunar stroke in the brainstem and compared their performance with that of 20 closely matched healthy controls by means of a test battery that has been shown to be sensitive to subtle cognitive changes. The patients as a group performed worse than the control group. Additional analyses demonstrated that we were not dealing with a general decline in cognitive function, as performance was intact on the majority of the tasks. Moreover, the finding that the patients had a normal attention span (as measured by the digit span) and intact sustained attention (as indicated by the Lottery subtest of the TEA) showed that the revealed impairments in neuropsychological function after a small brainstem infarct cannot be attributed to a reduced level of arousal or alertness. The absence of disturbances in attention argues against the influence of noncognitive processes that are frequently reported to confound the interpretation of neuropsychological function after brainstem damage (Steckler et al., 1994). The same argument holds for an account of performance decrements due to a decrease in concentration or motivation associated with being unexpectedly hospitalized. The possible influence of motor impairment was controlled for when necessary (e.g., in the Trail Making Test). Although no signs of fatigue or emotionality were observed during the testing procedure, patients reported to be more easily aroused emotionally and had more complaints about fatigue. This was to be expected in patients who have recently had a stroke. We cannot fully exclude the influence of both emotionality and fatigue on cognitive function in our patients, but it is not likely that this influence alone can account for the impaired performances. In spite of the overall intact performance, in five tasks the patients demonstrated impaired performance, namely, in the Boston Naming Test, the Verbal Fluency, the TEA–Visual Elevator, the TMT–A, and the TMT interference score. The similarity of the neuropsychological impairments and subjective complaints of these subjects to the findings we reported earlier for patients with brainstem stroke or with a supratentorial small deep infarct suggests a similar structural basis in both groups. This supports our contention that a small infarct can have a detrimental effect on cognitive functioning irrespective of the location of the ischemic event. The explanation in terms of bystander involvement of gray matter in supratentorial lacunar strokes can be ruled out in patients with infarcts confined to the brainstem. We argue that a lacunar infarct may have indirect effects through hypometabolism or other neurochemical changes. To assess the pathophysiology of this mediated effect is beyond the scope of the current study, but it is a necessary next step in further research. In conclusion the findings in this study suggest that a small white-matter infarct, independently of its location, affects cognitive function in a nonspecific way.

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