

Cognitive impairment is common in infratentorial infarct

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Thesis

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<p>Bakgrund och syfte: Kognitiv nedsättning är ett välkänt fenomen efter supratentorial infarkt, däremot är dess prevalens och svårighetsgrad i samband med infratentoriala infarkter oklar. Vi jämförde frekvensen och prognostiska värdet av domän-specifika kognitiva underskott efter supratentoriala och infratentoriala infarkter.</p> <p>Metoder: I en konsekutiv kohort med patienter intagna till Helsingfors Universitetssjukhus som drabbats av sin första stroke någonsin (N=244), hade 37 patienter en infratentorial infarkt. En neuropsykologisk undersökning tog plats 3 månader efter infarkten och innehöll en undersökning av 9 kognitiva domäner. Patienterna undersöktes även beträffande funktionshinder 15 månader efter infarkten. Förekomsten av kognitiva nedsättningar jämfördes med Pearson chi-square test. Associationen mellan kognitiv nedsättning och funktionshinder vid 15 månader post-stroke analyserades med logistisk regression.</p> <p>Resultat: Ingen statistiskt signifikant skillnad kunde observeras i förekomsten av kognitiv nedsättning i patienter med supra- vs infratentoriala infarkter. Sammanlagt hade 73% av patienter med infratentorial infarkt och 82.1% av patienter med supratentorial infarkt nedsättning i minst ett kognitivt domän. Patienter med nedsättning i 3 eller flera kognitiva domäner var 42.3% i infratentorialgruppen och 47.3% i supratentorialgruppen. I infratentorialgruppen hade endast nedsättning av visuospatiala funktioner (OR 9.0, 95%CI 1.3-62.5, p=0.027) en association med funktionshinder vid 15 månader post-stroke. I supratentorialgruppen hade domänerna visuospatiala funktioner (OR 2.9, 95% CI 1.5-5.7, p=0.001) och exekutiva funktioner och uppmärksamhet (OR 2,9, 95%CI 1.5-5.8, p=0.002) en association med funktionshinder vid 15 månader post-stroke.</p> <p>Slutsats: Kognitiva underskott är lika vanliga vid infratentorial och supratentorial infarkt, och det är viktigt att känna igen detta för att nå möjligast bra rehabilitation.</p>			
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Tiivistelmä – Referat – Abstract

Background and purpose: Cognitive impairment is a common and well-known consequence of supratentorial infarct, but its prevalence and severity after infratentorial infarct is unclear. We compared the frequency and prognostic value of domain-specific cognitive deficits after supratentorial and infratentorial infarct.

Methods: In a consecutive cohort of first-ever stroke patients (N=244) admitted to Helsinki University Hospital, 37 patients had an infratentorial infarct. Patients were assessed by a neuropsychologist 3 months post-stroke in 9 cognitive domains, and functional disability was assessed at 15 months. Frequencies of cognitive deficits were compared using the Pearson chi-square test. The association between cognitive deficits and functional disability at the 15-month follow-up was analysed using logistic regression.

Results: There was no significant difference between the frequency of cognitive deficits in patients with infratentorial vs supratentorial infarct. Altogether 73% of patients with infratentorial infarct and 82.1% of patients with supratentorial infarct had impairment in at least one cognitive domain, and 42.3% in the infratentorial group and 47.3% in the supratentorial group had deficits in 3 or more cognitive domains. In the infratentorial group, only visuoconstructional and spatial functions showed at least a convincing trend of association with functional disability at 15 months (OR 9.0, 95%CI 1.3-62.5, p=0.027). In the supratentorial group, both executive functions and attention (OR 2.9, 95%CI 1.5-5.8, p=0.002) and visuoconstructional and spatial functions (OR 2.9, 95%CI 1.5-5.7, p=0.001) showed this association.

Conclusion: Cognitive deficits are as common in infratentorial as in supratentorial infarct, and it is important to recognize them to meet the needs of rehabilitation.

Avainsanat – Nyckelord – Keywords

Stroke; Brain stem infarction; cerebellar infarction; cognitive functions

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1 Introduction

In the past, the cerebellum was thought to be a purely sensory-motoric centre. This function is well known and has been extensively documented and studied. The typical clinical picture in cerebellar infarct includes symptoms such as dizziness, nausea and vomiting, unsteady gait, and headache (1).

In the past three decades, documentation on the cerebellum's role in cognitive functions has been emerging, and the interest is growing (2).

Schmahmann and co-authors (3) proposed the concept of "cerebellar cognitive affective syndrome" (CCAS) in the late 1990s based on their studies. The syndrome is characterized by variable degrees of disturbance in executive functions (planning, set-shifting, verbal fluency, abstract reasoning, and working memory), difficulties with spatial cognition including visual-spatial organization and memory, personality change with blunting of affect or disinhibited and inappropriate behavior and language deficits including agrammatism and dysprosodia. Several studies have also suggested certain topographic infratentorial areas, mainly the posterior cerebellum, to be responsible for distinct cognitive functions, since lesions in these areas have been shown to associate with cognitive impairments (4–8).

Despite the possible severity of this syndrome, there have been only a limited number of studies regarding cognitive deficits in isolated infratentorial infarcts (Table 1). The studies have been heterogeneous regarding neuropsychological test batteries, the timing of post-stroke assessment, different definitions of cognitive impairment and other methodological differences. Besides the cohort studies, the documentation consists of case reports (9–11) and studies with very small patient groups (5,12).

As the focus has traditionally been on recovery from motor and clinical symptoms after stroke, the more subtle cognitive deficits can remain undetected or be overlooked. Considering the effects that cognitive decline can have on the quality of life, daily functioning, occupational abilities and even long-term survival (13), it is important to recognize a potential pattern of cognitive deficits in patients with infratentorial infarcts, to meet the needs of rehabilitation.

In this study, we compared the frequency of diverse neuropsychological deficits between patients with first-ever infratentorial infarct and patients with first-ever supratentorial infarct. Further, we investigated the association between cognitive deficits at 3 months post-stroke and functional dependence at the 15-month follow-up.

Table 1. Studies on cognitive deficits after infratentorial infarcts.

Study	Country	Number of patients	Location of stroke based on	Mean/median age	First-ever stroke %	Female sex %	Low education <6 years %	Hypertension %	Diabetes %	Myocardial infarct %	Current smoking %	Patients with stroke %
Malm et al. 1998	Sweden	24	MRI/CT	37	-	50	-	-	-	-	-	100
Schmahmann 1998	USA	20	MRI/CT/ SPECT/PET	48	-	40	- ¹	-	-	-	-	65 ⁴
Neau et al. 2000	France	15	MRI/CT/ SPECT	57	-	40	- ²	-	-	-	-	100
Kalashnikova et al. 2005	Russia	25	MRI/CT	52	-	56	-	-	-	-	-	100
Hokkanen et al. 2006	Finland	26	MRI/CT	47	-	19	- ³	-	-	-	-	100
Our study	Finland	37	MRI/CT	71	100	49	30	60	22	24	49	100

¹ Mean education 13.9 years; ² Mean education level was 3.9 ± 1.7 (range 2 to 7), using the classification of Barbizet & Duizabo (14);

³ Mean education 13 years; ⁴ Thirteen patients suffered a stroke, three had postinfectious cerebellitis, three had cerebellar cortical atrophy, and one had a midline cerebellar tumor resected.

2 Materials and methods

2.1 Patients

The study procedure and the characteristics of the patients have been described in full previously (15).

In summary, the patients included were all Caucasian with suspected stroke admitted to Helsinki University Central Hospital (n=1622) between 1 December 1993 and 30 March 1995, aged 55-85 years and living in Helsinki. Only patients with ischemic stroke were included; thus, patients suffering from intracerebral (n=229) or subarachnoid hemorrhage (n=69) were excluded. Altogether 642 patients met the inclusion criteria and were invited to a baseline visit 3 months post-stroke. Out of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%), and three were lost (0.5%) due to undefined causes. Finally, 486 (246 men, 240 women) of the living patients were included in the final cohort. Out of these, 409 (84.2%) participated in neuropsychological examinations. Patients with severe aphasia and thus unable to participate in the neuropsychological examination were excluded together with those who had severe sight or hearing disabilities or a reduced level of consciousness.

For this study, out of the 409 stroke patients, those with no previous strokes were included (n=244). Out of these, there were 37 patients with isolated cerebellar or pons infarct, without any supratentorial infarcts involved.

2.2 Imaging and neuropsychological assessment

Patients underwent an extensive evaluation including brain CT at admission to the hospital, later brain MRI, structured medical, neurological and laboratory evaluations and survey of risk factors. Previous infarcts were determined from the medical history and brain CT and MRI. Also, a person close to the patient was interviewed, when possible.

Clinical and neuropsychological assessments were carried out 3 months post-stroke. Impairment within nine cognitive domains was determined according to age-appropriate normative data from a random healthy population. Patients in the two groups were assessed by a neuropsychologist on average 105 (SD 14.8) days post-stroke. The test regime included 19 established cognitive tests grouped into nine cognitive domains (Table 2)(16). Almost all the patients in infratentorial infarct group were able to complete the neuropsychological test battery (1 missing in memory function, 2 in arithmetic). In the supratentorial infarct group, there was 8-29 missing results per domain. Missing data in the cognitive tests occurred mainly due to the inability of patients to complete the entire test battery. The valid n-count in each of the tested cognitive domains is reported in Table 4.

2.3 Statistics

The frequencies of cognitive deficits in the patients with an infratentorial infarct were compared with those with supratentorial infarct using the Pearson chi-square test. The potential association between cognitive deficits and functional disability at the 15-month follow-up was analyzed using logistic regression and controlling for age, sex and low education. IBM SPSS Statistics version 25 was used.

Table 2. Neuropsychological test battery (Jokinen et al. 2015)

Executive functions and attention

Trail making test, parts A and B

Stroop test, color naming and interference

Wisconsin card sorting test

Verbal fluency, phonemic and semantic

Digit span, forward and backward

Memory

WMS-R logical memory, story A, immediate and delayed recall

WMS-R visual reproduction, immediate and delayed recall

Fuld object memory evaluation, 10-item learning test, 5 trials and delayed recall

Visuoconstructional and spatial functions

WAIS-R block design

Figure copying test

Clock drawing test

Abstract thinking

WAIS-R similarities

Aphasia

Token test

Boston naming test

Boston diagnostic aphasia examination, overall speech evaluation

Reading and writing

Samples

Arithmetic

Arithmetic operations

Neglect

Bells test

Agnosia

Poppelreuter

Table 3. The association between infratentorial infarct and demographic factors/risk factors.

Variable	Supratentorial infarct			Infratentorial infarct			Statistics
	Valid n	Mean/n	SD/%	Valid n	Mean/n	SD/%	p-value
Age	207	70.2	7.7	37	71.1	7.8	0.525
Female sex	207	102	49.3	37	15	40.5	0.327
Low education (<6 years)	204	60	29.4	37	6	29.7	0.969
Severe stroke (mRS 3-5)	207	73	35.3	37	12	32.4	0.739
Smoking (current or former)	204	92	45.1	37	18	48.6	0.690
Myocardial infarction	207	37	17.9	37	9	24.3	0.356
Hypertension	207	96	46.4	37	22	59.5	0.142
Diabetes	207	51	24.6	37	8	21.6	0.693

3 Results

The study included a total of 244 first-ever stroke patients, of whom 37 had an infratentorial infarct and the rest had a supratentorial infarct (Table 3). The mean age was 70.3 ± 7.7 years, 48.0% (17 of 244) were female, and 27.0% (66 of 241) had a low level of education (<6 years).

There were no significant differences between patients with infratentorial and supratentorial infarct regarding demographic and risk factors (Table 3).

The most common post-stroke cognitive deficits in both groups were memory, visuoconstructional and spatial functions, and executive functions and attention (Table 4). Less common cognitive deficits were abstract reasoning, reading and writing, arithmetic skill and aphasia. Very few patients suffered from agnosia and neglect in the supratentorial infarct group and none in the infratentorial infarct group, which is logical since they are predominantly hemispheric domains.

3.1 Cognitive deficits

No statistically significant difference was found between patients with infratentorial and supratentorial infarct regarding the frequency of cognitive deficits (Table 4).

Table 4. The association between infratentorial infarction and cognitive deficits.

Variable	Supratentorial infarct			Infratentorial infarct			Statistics
	Valid n	Mean/n	SD/%	Valid n	Mean/n	SD/%	p-value
Memory functions	187	106	56.7	36	20	55.6	0.900
Abstract reasoning	178	45	25.3	37	10	27.0	0.825
Executive functions and attention	184	85	46.2	37	15	40.5	0.528
Aphasia	199	62	31.2	37	8	21.6	0.244
Agnosia	190	7	3.7	37	0	0.0	0.236
Visuoconstructional and spatial functions	198	102	51.5	37	16	43.2	0.356
Neglect	184	18	9.8	37	0	0.0	0.047
Reading and writing	186	58	31.2	37	10	27.0	0.616
Arithmetic	181	32	17.7	35	6	17.1	0.939

In general, the frequency of cognitive impairment was high in both groups: 73% of patients with infratentorial infarct and 82.1% of patients with supratentorial infarct had impairment in at least one cognitive domain. Moreover, cognitive deficits often occurred as multiple domain deficits at the same time. Altogether, 42.3% in the infratentorial group and 47.3% in the supratentorial group had deficits in 3 or more cognitive domains.

3.2 Association with functional disability at the 15-month follow-up

The three most common domain-specific cognitive deficits (memory functions, executive functions and attention, and visuoconstructional and spatial functions) were analyzed one by one for a potential association with functional disability (modified Rankin Scale, mRS = 2–5) at the 15-month follow-up, using logistic regression and controlling for age, sex and low education.

In the infratentorial infarct group, only visuoconstructional and spatial functions showed at least a convincing trend of association with functional disability at the 15-month follow-up (OR 9.0, 95% CI 1.3-62.5, $p=0.027$).

In the supratentorial infarct group, both executive functions and attention (OR 2.9, 95% CI 1.5-5.8, $p=0.002$) and visuoconstructional and spatial functions (OR 2.9, 95% CI 1.5-5.7, $p=0.001$) showed an association with functional disability at the 15-month follow-up. Memory functions also showed a trend towards a similar association, but this did not reach significance (OR 1.9, 95% CI 1.0-3.8, $p=0.053$).

4 Discussion

Our study demonstrates that the frequency of cognitive deficits in patients with infratentorial infarct was as high as in patients with supratentorial infarct.

The three most common domain-specific deficits were memory functions, executive functions and attention, and visuoconstructional and spatial functions, which is in line with previous studies (3,7,17–19). Otherwise, direct comparison with previous studies is difficult due to differences in neuropsychological test batteries, the timing of post-stroke assessment, the definition of cognitive impairment and other methodological differences.

Visuoconstructional and spatial functions seemed to associate with functional disability at 15 months post-stroke in both groups, and in addition, executive functions and attention showed an association in the supratentorial group. This latter association could not be separately demonstrated in our study for infratentorial infarct, probably due to the small group size.

Our study also demonstrated that patients who suffer from post-stroke cognitive deficits often have problems in several different areas of cognition. This could be an indication of the complex involvement of infratentorial areas in cognitive functions.

Cognitive deficits may remain undetected by medical staff, especially in the case of infratentorial infarcts. Our study underlines the importance of cognitive screening when treating these patients. The widely used MMSE test has been shown to be a poor indicator of cognitive deficits (16). Although Montreal Cognitive Assessment (MoCA) is somewhat more sensitive (20), neuropsychological examination is the golden rule, especially when assessing milder impairment.

A limitation in this study was the small number of patients, which has also been a challenge in previous studies on the subject. In addition, the infratentorial lesion locations were not analyzed separately. Therefore, our analysis did not give detailed information on which locations in the infratentorium may be responsible for cognitive functions. The strength of this study was that all the patients, both the infratentorial and supratentorial infarct group, were taken from the same patient sample and were assessed with identical methods. The compared groups were also similar regarding demographic factors and there was no distraction from earlier infarcts, as all patients were verified first-ever stroke sufferers.

In the future, it will be important to study larger cohorts of infratentorial infarct patients, preferably patients with similar specific infarct locations. A uniform test battery of

cognitive functions should be used in order to obtain comparable results. It is important to recognize a potential pattern of cognitive deficits in patients with infratentorial stroke, to meet the needs for rehabilitation.

References

1. Edlow JA, Newman-Toker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. *Lancet Neurol.* 2008 Oct 1;7(10):951–64.
2. Schmahmann JD. The cerebellum and cognition. Vol. 688, *Neuroscience Letters.* 2019. p. 62–75.
3. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Vol. 121, *Brain.* 1998.
4. Schmahmann JD. Disorders of the Cerebellum: Ataxia, Dysmetria of Thought, and the Cerebellar Cognitive Affective Syndrome. *J Neuropsychiatry Clin Neurosci.* 2004 Aug;16(3):367–78.
5. Exner C, Weniger G, Irle E. Cerebellar lesions in the PICA but not SCA territory impair cognition. *Neurology.* 2004 Dec 14;63(11):2132–5.
6. Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM. Evidence for distinct cognitive deficits after focal cerebellar lesions. *J Neurol Neurosurg Psychiatry.* 2004 Nov;75(11):1524–31.
7. Hokkanen LSK, Kauranen V, Roine RO, Salonen O, Kotila M. Subtle cognitive deficits after cerebellar infarcts. *Eur J Neurol.* 2006 Feb 1;13(2):161–70.
8. Stoodley CJ, MacMore JP, Makris N, Sherman JC, Schmahmann JD. Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke. *NeuroImage Clin.* 2016;12:765–75.
9. Vokaer M, Bier JC, Elinx S, Claes T, Paquier P, Goldman S, et al. The cerebellum may be directly involved in cognitive functions. *Neurology.* 2002 Mar 26;58(6):967–70.
10. Paulus KS, Magnano I, Conti M, Galistu P, D’Onofrio M, Satta W, et al. Pure post-stroke cerebellar cognitive affective syndrome: A case report. *Neurol Sci.* 2004;25(4):220–4.
11. Nakamoto FK, Tsutsumiuchi M, Maeda H, Uesaka Y, Takeda K. Neurocase The Neural Basis of Cognition Memory impairment following right cerebellar infarction: a case study. 2014;
12. Hoffmann M, Watts A. Cognitive dysfunction in isolated brainstem stroke: A neuropsychological and SPECT study. *J Stroke Cerebrovasc Dis.* 1998 Jan 1;7(1):24–31.
13. Oksala NKJ, Jokinen H, Melkas S, Oksala A, Pohjasvaara T, Hietanen M, et al. Cognitive impairment predicts poststroke death in long-term follow-up. *J Neurol. Neurosurg. & Psychiatr.* 2009 Nov 1;80(11):1230 LP – 1235.
14. Barbizet, J; Duizabo P. *Abrégé de Neuropsychologie.* Paris: Masson, 1985.
15. Pohjasvaara T, Erkinjuntti T, Vataja R, Kaste M. Dementia Three Months After Stroke. *Stroke.* 1997 Apr;28(4):785–92.
16. Jokinen H, Melkas S, Ylikoski R, Pohjasvaara T, Kaste M, Erkinjuntti T, et al. Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur J Neurol.* 2015 Sep;22(9):1288–94.
17. Malm J, Kristensen B, Karlsson T, Carlberg B, Fagerlund M, Olsson T. Cognitive impairment in young adults with infratentorial infarcts. *Neurology.* 1998 Aug

- 1;51(2):433–40.
18. Neau J-P, Anillo EA, Bonnaud V, Ingrand P, Gil R. Neuropsychological disturbances in cerebellar infarcts. *Acta Neurol Scand*. 2000 Dec 1;102(6):363–70.
 19. Kalashnikova LA, Zueva Y V., Pugacheva O V., Korsakova NK. Cognitive Impairments in Cerebellar Infarcts. *Neurosci Behav Physiol*. 2005 Oct;35(8):773–9.
 20. Dong Y, Sharma VK, Chan BP-L, Venketasubramanian N, Teoh HL, Seet RCS, et al. The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci*. 2010 Dec 15;299(1–2):15–8.