Journal of Stroke and Cerebrovascular Diseases 34 (2025) 108142

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Aphasia profiles and trajectories in acute ischemic stroke: An observational study

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ARTICLE INFO

Keywords:
Acute stroke
Aphasia
Rehabilitation
Women

ABSTRACT

Background: In acute ischemic stroke (AIS), neuropsychological deficits and their long-term impact are insufficiently studied. We studied pure aphasic AIS patients, their short-term aphasiological course, predictors of persisting aphasia, and their outcome.

Methods: In the ASTRAL Registry, we assessed all pure aphasic AIS patients from 2003-2019, and reviewed their neuropsychological examination performed after 3-10 days. We identified factors associated with persistent significant aphasia in the subacute phase, and predictors of unfavourable functional outcome at 3 months (mRS≥2), using multivariate analyses (MVA).

Results: Among 4513 consecutive AISs, 131 (2.9 %) had pure aphasia at admission. Eighty-one had a good quality neuropsychological examination and were analysed further (median age 76.3yrs; 44.4 % female; 6.2 % left-handed; 27.2 % treated by acute revascularization). Of these, 28.4 % still had significant aphasia in the subacute phase. Persistent aphasia was independently associated with cardioembolic (OR 13.6, 95 %CI 2.6-70.8) or atheromatous (OR 16.0, 95 %CI 1.9-132.1) stroke mechanisms, and with an executive function deficit on neuropsychological examination (OR 10.5, 95 %CI 2.0-54.4). At 3 months, female gender (OR 4.2, 95 %CI 1.2-15.3) and significant aphasia in the subacute phase (OR 12.0, 95 %CI 3.3-43.6) predicted an mRS≥2.

Conclusion: Pure aphasia was present in 2.9 % of all AIS patients and resolved in three-quarters in the subacute phase. Persistent aphasia was associated with embolic stroke mechanisms and concomitant executive function impairment, and poor 3 months outcome, with female gender and enduring subacute aphasia. These data may help with prognostication, management and rehabilitation planning.

Key message: Pure aphasic ischemic stroke is rare and most recover spontaneously within days, and persistent subacute aphasia is associated with defined embolic stroke mechanisms, and concomitant executive dysfunction. Unfavourable functional outcome at 3 months is present in women and if there is persistent subacute aphasia.

Background

Acute ischemic stroke (AIS) carries high short- and long-term burdens for patients, their next of kin, the health care system and the society. Much of the impact of stroke comes from stroke-related cognitive, behavioural and emotional problems,[1] but these are insufficiently considered in current research.[2] A systematic approach to studying these problems may help to detect, predict, prevent and treat them more effectively, both before and after a stroke.[3]

Knowledge is scarce on the profile and course of aphasia in acute stroke patients, in particular with regards to underlying stroke mechanisms, the impact of other cognitive variables and early outcome. Studies have shown a role of orientation at hospitalisation discharge[4] and activities of daily living,[5] but the role of pure aphasia in long-term independence is not well documented.[6] Particularly, knowledge of the initial aphasia profile associated with longer term language impairment and the overall clinical outcome.

The aim in this project is to define patients' profile in aphasia due to AIS, and to understand the variability of clinical trajectories. To concentrate on the aphasic element, we focused retrospectively on

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.108142
Received 12 February 2024; Received in revised form 16 October 2024; Accepted 13 November 2024
Available online 27 November 2024

patients with pure aphasia as admission symptom.

Methodology

We used data from The Acute STroke Registry and Analysis of Lausanne (ASTRAL), containing since 01.01.2003 all acute ischemic stroke patients admitted to the stroke unit and/or intensive care unit of Lausanne University Hospital (CHUV) within 24 hours of last-well time, as published previously.[7]

Clinical data collected in ASTRAL

Stroke physicians and study nurses collect a large range of parameters in a prespecified manner in ASTRAL during the acute hospital stay, and completed after discharge. The data include demographics, medical history and cardiovascular risk factors, current medications, clinical symptoms and examination, process-oriented data, stroke localization, stroke severity (NIHSS) on admission and in the first 7 days (day 1 is the first day of admission), comorbidities, vital signs and metabolic and hematologic parameters in the acute and subacute phase. In addition, acute and subacute multimodal brain imaging, acute recanalization treatments and arterial recanalization, stroke mechanism, discharge medication and patient disposition, clinical outcomes at 3 and 12 months including living situation and stroke recurrences are also detailed.

For outcome results, we calculated the delta-mRS at 3 months in order to correct for pre-stroke handicap for group A patients (see below) as delta-mRS = mRS at 3 months – pre-hospitalisation mRS. Negative delta-mRS values were set to zero, and delta-mRS for patients who died was set to "6", independently of the pre-hospitalisation mRS. For this study with patients with an isolated language deficit, we considered a delta-mRS at 3 months $\leq$1 as a favourable outcome, and $\geq$2 an unfavourable outcome.

Neuropsychological data collected in the ASTRAL-NEUROPSY module

About half of the patients in ASTRAL undergo a structured neuropsychological exam in the subacute phase. The criteria for requesting neuropsychological testing in AIS in our centre are 1) supratentorial or cerebellar stroke with neuropsychological deficits seen on bedside examination by a neurologist, or 2) supratentorial or cerebellar stroke in a patient capable of driving or being employed. For this study, we did a retrospective analysis of data from all selected patients with isolated aphasia at admission (according to the admitting neurologist or neurologist in training) who also underwent neuropsychological testing in the subacute phase (days 2 to 10) during the period 01/01/2003 to 31/12/2019. Educational level was divided into three categories (none/mandatory school only, which are 11 years in Switzerland = until age 16 or completion of professional skill, which is education after secondary school, apprenticeship and the third category highschool or university) We grouped them in mandatory only vs postgrade, which is any education after age 16 that has been completed. We evaluated pre-existing dementia based on history-taking from the patient and/or a knowledgeable person representing the patient, past cognitive assessment, and abnormalities on the current cognitive exam not sufficiently explained by the localization or extent of the prevailing stroke.

We excluded the following patients based on neuropsychological grounds: absence of formal neuropsychological testing during acute hospitalisation within 10 days, and/or testing considered insufficient for analysis, i.e. when less than two of the five main cognitive domains (executive function, language, praxia, gnosia, memory- complete list of tests in supplementary file 3) could be assessed to decide whether a deficit is present or not. Patients with pre-existing dementia[8] and patients with moderate or severe cognitive sequelae from previous stroke[9] and other neurological diseases were also excluded. Reasons for absent or insufficient neuropsychological assessment were documented.

We searched for existing cognitive deficits during the neuropsychological evaluation using a structured neuropsychological examination partially adapted to the patient's age, clinical question and capacity to collaborate. This exam included normative testing (also known as "standardized" tests), non-normative testing (non standardized tests for which only the clinical performance of the patient is assessed) and clinical observation. If several tests were available for one domain, the examining neuropsychologist chose the most appropriate test for the current clinical setting, and added others if needed to decide if a significant deficit was present. We tested orientation and attention before testing the five main cognitive domains. The formal neuropsychological evaluation routinely assessed and recorded current emotional findings, which we noted as present if recorded in the neuropsychological report and absent, if not recorded or detected. Emotional findings were categorised into anxiety, depressive symptoms, delirium, paranoid ideas, hallucinations, mania euphoria, emotional lability or incontinence, anhedonia, or emotional detachement..For executive functions, we used non-verbal tests such as graphic programmation or gesture sequences if comprehension was impaired

We used the tests to classify a neuropsychological item and domain as dysfunctional or not. Specifically, for aphasia evaluation, we used the BARD, Boston Naming Test, verbal fluency test, three step comprehension, picture-word and sentence association tests (TICS), sentence completion (Boston lecture) and automatic writing and writing after dictation.

We then classified deficits as present, absent or as "not tested/insufficient testing" as appropriate. When normative tests were used, z-values less than 1.65 times (equivalent to the 5th percentile) of the standard deviation were generally considered as significant. If formal testing of an item was not possible or incomplete, an obvious deficit on clinical observation was also classified as a dysfunction of this item. If an item could not be tested sufficiently by quantitative or direct clinical observation, this domain was recorded as "not tested/insufficient testing".

Radiological data collected in ASTRAL

We assessed acute brain imaging at admission, mostly CT-based, for the ASPECTS[10] score to indicate the extent of early ischemia in strokes involving the middle cerebral artery territory. Perfusion-imaging and imaging of cervical and cerebral arteries was performed in most patients. Repeat brain CT or MRI was done at approximately 24 hours of hospitalisation in patients receiving acute recanalization treatment and in others when clinically indicated.

Analyses and statistical methods

Patients were grouped according to their hyperacute aphasia status on neurological evaluation in the emergency room into:

- hyperacute Group A = only pure aphasia as symptoms (= Language deficit without other neurological deficits);
- hyperacute Group B = aphasia plus other neurological deficits;
- hyperacute Group C = only other deficits (without aphasia).

Within Group A, based on language neuropsychological testing (see tests above) in the subacute hospitalisation phase, patients' aphasia findings were then grouped as follows:

1) Subgroup 1 = Persistent significant aphasia (persistent language deficit with at least one impaired score at naming test[11])
2) Subgroup 2 = language impairment but no strict aphasia defined by a strictly normal naming tests but impairment at repetition, comprehension or fluency
3) Subgroup 3 = No aphasia or other language impairment.

In the first analysis, we studied associations with favourable aphasiology outcome at subacute neuropsychological evaluation. We compared patients with no significant aphasia (subgroups 2&3) with patients with continued significant aphasia (subgroup 1). After univariate analysis (Analysis 1a- Table 1), we performed a multivariate analysis (Analysis 1b– Table 2) using as dependent variable significant aphasia and as independent variables all those significant in the univariate analysis and adjusting for executive function deficit, non-lateralised attention tasks, educational level, age, gender and NIHSS at admission. Significance level was set at p<5 %

In the second analysis (Analysis 2, Table 2), we assessed factors associated with a favourable long-term functional outcome in patients with initial pure aphasia (all group A). We adjusted this outcome for common confounders such as educational level, NIHSS at admission, gender, age, executive function deficit, non-lateralized attention deficit, presence of significant aphasia in the subacute phase, stroke mechanism, ASPECTS score on initial CT and presence of significant arterial findings on the admission angio-CT. Similar to analysis 1, all significant variables found in the univariate analysis were automatically included in the multivariate analysis. (Analysis 2 - Table 2). This study was conducted under the auspices of the ethical standards committee humans of the canton de vaud (CER-VD). Because of the retrospective nature of this study, the committee approved the use of data from ASTRAL for scientific purposes without requiring individual informed consent.

Results

During the study period, 4513 stroke patients were admitted to our stroke centre. Of these, 1538 patients presented with aphasia and another neurological deficit, and 81 presented with pure aphasia (hyperacute phase) as initial and only symptoms and also had a good-quality neuropsychological exam in the subacute phase (see Fig. 1). Those were included in the analyses. Their median age was 76.3 years; 6.2 % of the patients were left-handed and 44.4 % were females. The median NIHSS was 2, and 27.2 % received hyperacute recanalization therapy (intravenous thrombolysis or mechanical thrombectomy). In the subacute phase, 28.4 % still had significant aphasia (subgroup 1).

The univariate analysis 1a can be studied with selected results in Table 1. In the multivariate analysis (Table 2) we found that patients with cardioembolic (OR 13.60, 95 % CI 2.62-70.76, p = 0.2 %) or atherosclerotic (OR 15.99, 95 % CI 1.93-132.12, p = 1.0 %) stroke, and patients with executive function impairment (OR 10.54, 95 % CI 2.04-54.42, p = 0.5 %) had higher odds of having significant aphasia in the subacute phase than patients without these variables.

In the second analysis (Analysis 2) looking at the dichotomized (≥2) delta-mRS at 3 months, multivariate analysis showed that female patients (OR 4.2, 95 %CI 1.18-15.27, p =2.7 %) and patients with significant aphasia in the subacute phase (OR 11.99, 95 %CI 3.30-43.57, p < 0.5 %.) more often had an unfavourable outcome.

Discussion

In a consecutive series of purely aphasic AIS patients with 27.2 % receiving acute recanalization therapy, we found a rapid regression of aphasia in three quarters of them. Persistent disabling aphasia in the subacute phase was associated with atherosclerotic and cardioembolic stroke mechanisms, and with additional executive dysfunction on neuropsychological examination. Poorer long-term functional outcome was more frequent in patients with persistent aphasia in the subacute stroke phase and in female patients.

In patients with AIS presenting with pure aphasia, the rapidly resolving symptoms in the subacute phase (small language deficits or no residual symptoms in three-quarters of patients and total regression in one-third) is similar to previous studies.[12,13] This is probably explained by the high rate of spontaneous arterial recanalization related to only-distal occlusions in the vascular tree, stroke size thus not large enough to cause more than purely aphasic deficits. Secondly, acute recanalization therapy reduces cognitive stroke deficits very effectively and rapidly.[14] Thirdly, patients with low NIHSS scores (median NIHSS at admission = 2) are more likely to recover rapidly from their deficits, with or without revascularization,[15] which is also true for patients with small acute stroke lesions[16] (mean final infarct volume of 2.3 cm^3 in our population). In addition the relatively the high level of education (17 % university level, 40 % above mandatory education) might increase the cognitive reserve and; thereby, the fast recovery in our patients.[17] Finally, there is a possibility of selection bias due to our definition of “significant aphasia” based on the Boston naming test, as motor aphasia seems to have the best prognosis for improvement[18]

Persistent aphasia in the subacute period was significantly associated with atheromatous or cardiac stroke origin. As the two types of stroke are typically embolic, cortical damage is more likely than in micro-angiopathic or rare stroke mechanisms. This was already shown in a Swiss population in a previous study.[19] This emphasizes the need for monitoring secondary prevention compliance, atrial fibrillation, but also mild stroke symptoms in the patients’ follow-up.

The fact that executive function is independently associated with persistent aphasia probably speaks to its important role in compensating for other cognitive deficits. Both executive function and (motor) aphasia rely on large cognitive networks that are strongly interdependent within the frontal lobe.[20] Executive dysfunction is the most common cognitive deficit after stroke,[21] and probably preexistent to stroke due to the chronic vascular profile of stroke patients[22] (the average age was relatively old), which impairs the functioning of the frontal lobe.[23] Patients known to have executive dysfunction before the stroke may therefore be expected to have a more protracted and incomplete recovery from aphasia, with or without dedicated neurorehabilitation.

Interestingly, age did not correlate with persistence of aphasia, contrary to previous analyses,[24] 24 but studies are not unanimous on this topic.[25]

Our study is the first to investigate overall prognosis in purely aphasic stroke patients, and it shows the negative influence of persistent subacute aphasia on comprehensive long-term function. In general stroke patients, such an association was already described,[26] suggesting common recovery mechanisms between motor function and aphasia impairments.[27] Better knowledge of the early course of aphasia may help to determine focused neuro-rehabilitation programs.[28] The optimal timing of speech therapy[29] remains a subject of debate,[30] some saying it should take place later in the patient’s recovery course.[31]

We found female gender to be associated with a worse functional outcome at 3 months in our population. We[31,32] and others have repetitively found poorer functional outcome in women; the reason for this observation remains speculative, but is not solely explained by higher age or pre-stroke disability.[33] Recent studies have also shown that the onset to door time is longer in women,[34] a meta analysis has suggested that baseline differences play a role[35,36] (such as vascular risk factors, stroke etiology, lower use of thrombolysis), and they face more challenges as they recover in the post-stroke daily life.[37,38]

The strengths of this study are its focus on purely aphasic patients, the detailed neuropsychological assessment in the subacute stroke phase and the use of multivariate analyses for several clinical outcomes. Limitations of our work are its retrospective nature, its non-continuous recruitment as subacute neuropsychological testing could not be performed in all aphasic patients (early transfer, lack of collaboration, severe multi-domain aphasia, logistical reasons). The hyperacute assessment of language was performed by neurologists (some in training) using the NIHSS methodology rather than by a neuropsychologist. The absence of systematic neuropsychological long-term follow-up forced us to use functional independence (mRS) as the outcome. Finally, imaging (ASPECTS) was based on imaging in the hyperacute phase, whereas formal aphasia testing was done in the subacute phase.

Table 1
Analysis 1a.

Variable	None / Non Significant Aphasia (N=58)	Significant Aphasia (N = 23)	Total (N = 81)	OR	OR - 95 % CI	p-value
Age, years	76.3 (12 %)	77.2 (21.3 %)	76.3 (13.4 %)	0.99	0.95 - 1.03	0.67
Gender (female)	27 / 58 (46.6 %)	9 / 23 (39.1 %)	36 / 81 (44.4 %)	0.74	0.28 - 1.97	0.54
Private insurance	27 / 58 (46.6 %)	4 / 23 (17.4 %)	31 / 81 (38.3 %)	0.24	0.07 - 0.80	0.02
AIS Mechanism (TOAST)						
Atherosclerotic	5 / 57 (8.8 %)	4 / 22 (18.2 %)	9 / 79 (11.4 %)	REF		
Cardio-embolic	23 / 57 (40.4 %)	16 / 22 (72.7 %)	39 / 79 (49.4 %)	0.87	0.20 - 3.75	0.85
Undetermined	26 / 57 (45.6 %)	1 / 22 (4.5 %)	27 / 79 (34.2 %)	0.05	0.00 - 0.53	0.01
Other	3 / 57 (5.3 %)	1 / 22 (4.5 %)	4 / 79 (5.1 %)	0.42	0.03 - 5.71	0.51
NIHSS at admission	2.0 (2.0)	4.0 (3.5)	2.0 (3.0)	1.24	1.01 - 1.51	0.03
Subacute orientation, rehab.	6 / 58 (10.3 %)	10 / 23 (43.5 %)	16 / 81 (19.8 %)	6.67	2.05 - 21.71	<0.01
Delta mRS at 3m						
-1 or 0	30 / 56 (53.6 %)	5 / 22 (22.7 %)	35 / 78 (44.9 %)			
1	18 / 56 (32.1 %)	4 / 22 (18.2 %)	22 / 78 (28.2 %)	1.33	0.32 - 5.62	0.69
2 +	8 / 56 (14.3 %)	13 / 22 (59.1 %)	21 / 78 (26.9 %)	9.75	2.68 - 35.53	<0.01
mRS at 12m						
0 - 2	41 / 47 (87.2 %)	17 / 22 (77.3 %)	58 / 69 (84.1 %)			
3 +	6 / 47 (12.8 %)	5 / 22 (22.7 %)	11 / 69 (15.9 %)	2.01	0.54 - 7.48	0.29
Acute CT ASPECTS+ Acute MRI ASPECTS (median)	10.0 (1.0)	10.0 (2.0)	10.0 (1.2)	0.67	0.46 - 0.98	0.04
Acute CTA Significant Pathology+ MRA (ischemic)	18 / 52 (34.6 %)	9 / 17 (52.9 %)	27 / 69 (39.1 %)	2.13	0.70 - 6.45	0.18
Education						
None / only Compulsory schooling	23 / 58 (39.7 %)	9 / 17 (52.9 %)	32 / 75 (42.7 %)	REF		
Apprenticeship / professional skill completed	26 / 58 (44.8 %)	4 / 17 (23.5 %)	30 / 75 (40.0 %)	0.39	0.11 - 1.45	0.16
Highschool / University	9 / 58 (15.5 %)	4 / 17 (23.5 %)	13 / 75 (17.3 %)	1.14	0.28 - 4.64	0.85
Pre-existing Cognitive Deficit	3 / 54 (5.6 %)	1 / 21 (4.8 %)	4 / 75 (5.3 %)	0.85	0.08 - 8.66	0.89
Pre-existing Psychiatric Disease	4 / 58 (6.9 %)	3 / 23 (13.0 %)	7 / 81 (8.6 %)	2.02	0.42 - 9.86	0.38
Current Emotional Findings	8 / 58 (13.8 %)	5 / 23 (21.7 %)	13 / 81 (16.0 %)	1.74	0.50 - 6.00	0.38
Non-Fluent	1 / 57 (1.8 %)	5 / 23 (21.7 %)	6 / 80 (7.5 %)	15.56	1.70 - 142.05	0.01
Acalculia						
no	42 / 58 (72.4 %)	4 / 23 (17.4 %)	46 / 81 (56.8 %)			
yes	12 / 58 (20.7 %)	12 / 23 (52.2 %)	24 / 81 (29.6 %)	10.50	2.86 - 38.56	<0.01
not tested	4 / 58 (6.9 %)	7 / 23 (30.4 %)	11 / 81 (13.6 %)	18.37	3.71 - 91.04	<0.01
Gestual Apraxia						
no	48 / 58 (82.8 %)	12 / 23 (52.2 %)	60 / 81 (74.1 %)			
yes	8 / 58 (13.8 %)	9 / 23 (39.1 %)	17 / 81 (21.0 %)	4.50	1.43 - 14.12	0.01
not tested	2 / 58 (3.4 %)	2 / 23 (8.7 %)	4 / 81 (4.9 %)	4.00	0.51 - 31.37	0.18
Short-Term Memory						
no	49 / 57 (86.0 %)	9 / 23 (39.1 %)	58 / 80 (72.5 %)			
yes	8 / 57 (14.0 %)	1 / 23 (4.3 %)	9 / 80 (11.2 %)	0.68	0.08 - 6.12	0.73
not tested	0 / 57 (0.0 %)	13 / 23 (56.5 %)	13 / 80 (16.2 %)	NA	NA - NA	NA
Long-Term Memory						
no	32 / 57 (56.1 %)	2 / 23 (8.7 %)	34 / 80 (42.5 %)			
yes	24 / 57 (42.1 %)	7 / 23 (30.4 %)	31 / 80 (38.8 %)	4.67	0.89 - 24.50	0.06
not tested	1 / 57 (1.8 %)	14 / 23 (60.9 %)	15 / 80 (18.8 %)	NA	NA - NA	NA
Executive Function Impairment	33 / 58 (56.9 %)	17 / 19 (89.5 %)	50 / 77 (64.9 %)	6.44	1.36 - 30.48	0.02
Non-Lateralised Attention Deficit	31 / 56 (55.4 %)	13 / 17 (76.5 %)	44 / 73 (60.3 %)	2.62	0.76 - 9.04	0.12

Table 2
Analysis 1b & 2.

Variable	Odds	95 % LL	95 %UL	p-value
Analysis 1b				
Cardioembolic stroke mechanism	13.60	2.62	70.76	0.002
Atherosclerotic stroke mechanism	15.99	1.93	132.12	0.010
Executive Function impairment	10.54	2.04	54.42	0005
Analysis 2				
Gender (female vs male)	4.25	1.18	15.27	0.020
Aphasia	11.99	3.30	43.57	0.001

Conclusion

In this relatively large population of purely aphasic AIS patients, a standardized evaluation of the acute and subacute phases identified embolic (cardiac or atheromatous) stroke mechanisms and concomitant executive function impairment as independent predictors of persistent aphasia. Among multiple demographic, clinical and neuropsychological prognostic variables, we found that significant aphasia and female gender were associated with poor functional outcome at 3 months. These findings may be useful for clinicians, patients and families regarding prognostication, planning of early rehabilitation interventions and patient disposition and needs in the post-acute phase.

Fig. 1. Patient selection flow-chart

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

Olivier Bill: Writing – original draft, Validation, Project administration, Methodology, Investigation, Conceptualization. **Laurent Lievens:** Formal analysis. **Dimitris Lambrou:** Formal analysis, Data curation. **Ashraf Eskandari:** Software, Data curation. **Valerie Beaud:** Methodology, Formal analysis. **Patrik Michel:** Writing – review & editing, Validation, Supervision, Data curation.

Declaration of competing interest

The authors have no potential conflicts of interest with respect to research, authorship and publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.108142.

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