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Aphasia in acute stroke

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ABSTRACT

Aphasia is a language impairment due to a brain lesion, usually in the left hemisphere, and is a common symptom in acute stroke. The aims of this thesis were to evaluate aphasia in acute stroke patients, to assess spontaneous language recovery, to evaluate the test instruments, to evaluate the efficacy of drug treatment, and speech and language therapy for recovery of aphasia, and to assess the possibility to reliable identify depression in aphasic patients.

The patients were gathered from three study populations. The first study population was a cohort of consecutive acute stroke patients where we assessed the incidence of aphasia, morbidity and mortality. The second study population was included in a randomized placebo controlled trial (RCT) to evaluate the efficacy of moclobemide, a MAO-A inhibitor, on aphasia recovery, where we also evaluated the possibility to identify depression in aphasic patients. The third study population is an ongoing RCT to evaluate the efficacy of early speech and language therapy (SLT) for acute aphasic stroke patients

Aphasia was present in one third of our acute stroke patients. The aphasic patients had three times higher short-term mortality than the non-aphasics. Long-term mortality was twice as high in the aphasic patients. Patients with aphasia had more severe strokes than those without aphasia, and the communication deficit in itself made the patient more disabled. Aphasic patients had longer hospital stay, and required more rehabilitation resources than other stroke patients. Cerebral emboli and atrial fibrillation were almost twice as common in aphasic patients as in non-aphasics. Indeed, in every patient with aphasia and an ischemic stroke an embolic source should be looked for. There was a considerable spontaneous recovery and most of the recovery took place within the first month. The initial degree of aphasia predicted the final stage. The aphasia instruments used: Norsk Grunntest for Afasi and Amsterdam-Nijmegen Everyday Language Test showed an important consistency in the three studies. The degree of aphasia measured according to these tests can predict complete recovery. Patients with mild aphasia in the acute stage will recover completely to a high extent. Treatment with moclobemide showed no improvement of the degree of aphasia beyond that of placebo. A randomized controlled trial on early SLT for acute stroke patients has been found feasible to perform with the design and methods used.

Two thirds of acute aphasic stroke patients, with all types of aphasia, could be reliably investigated for depression according to DSM-IV criteria within the first weeks after stroke onset. With the help of proxy, almost all could be diagnosed. There was a trend for more depression in patients with emotionalism at baseline. In stroke patients some depression symptoms occur irrespective of an ongoing depression. Hence, depression may possibly be over-diagnosed in the individual stroke patient with aphasia.

Keywords: Acute stroke, aphasia, atrial fibrillation, depression, drug treatment, prognosis, speech and language therapy

Sammanfattning på svenska

Afasi är en språkstörning till följd av en fokal hjärnskada, oftast i vänster hjärnhalva. Afasi är ett vanligt symtom vid akut stroke, och medför ofta det största lidandet för patienten.

Syftet med de studier som ligger till grund för denna avhandling har varit att undersöka frekvensen av afasi vid akut stroke, och skillnader mellan strokepatienter med och utan afasi avseende dödlighet, sjuklighet och förbättring. Vi har studerat hur använda testinstrument kan följa förbättring och hur väl de kan prognostisera tillfrisknande. I en randomiserad, kontrollerad studie har vi undersökt effekten av behandling med moclobemide, ett antidepressivt läkemedel, på återhämtningen. Möjligheten att identifiera depression hos afatiska patienter har studerats. En pågående randomiserad, kontrollerad studie skall försöka ge svar på om tidig, intensiv logopedträning förbättrar restitutionen av afasi efter akut stroke.

Våra studier visar afasi hos en tredjedel av de akuta strokepatienterna. Dödligheten hos afasipatienterna var dubbelt så hög som bland övriga strokedrabbade. Förmaksflimmer var dubbelt så vanligt hos afatiska patienter som hos övriga strokepatienter. Afasipatienterna hade allvarligare stroke vilket innebar längre vårdtider och större rehabiliteringsbehov. En betydande spontan språklig förbättring skedde, särskilt under de första veckorna efter akut stroke. Efter 3 månader var förbättringen mer blygsam. Vid 18 månader hade 24 % av afasipatienterna tillfrisknat, 43 % hade kvarstående afasi och 21 % hade avlidit. Graden av afasi i akutskedet hade avgörande betydelse för prognosen. Förståelsen var den del av språket som återhämtade sig först. De testmetoder vi har använt, en standardmetod för typ och grad av afasi och ett funktionellt kommunikationstest, visade att man kan följa förbättring med båda metoderna, och att de redan i akutskedet kunde förutsäga vilka som blir helt återställda. Förbättringsgraden i de båda testen var parallell. Standardtestet för afasi förefaller vara mest lämpligt i akutskedet.

Försök att öka återhämtningen vid afasi med moklobemid, ett antidepressivt läkemedel som ökar halten av serotonin, noradrenalin och dopamin i hjärnan visade ingen skillnad på afasirestitution jämfört med placebo. Moklobemid gav inte heller någon ökad frekvens biverkningar. Afasiresitutionen var i denna studie samma som spontanförbättring när den mättes vid sex månader. Vi har visat att man kan bedöma depression hos afasipatienter. Afasi är således inget hinder för att deltaga i studier rörande depression.

En studie avseende tidig språklig träning vid afasi hos akuta strokepatienter pågår. Vi visar att en sådan studie är möjlig att genomföra och att den kan belysa det eventuella värdet av att påbörja språklig träning snarast efter insjuknandet.

Resultaten av våra undersökningar kan bidra till en bättre selektion av patienter och val av lämplig tidpunkt för optimal rehabilitering efter akut stroke.

LIST OF PUBLICATIONS

This thesis is based on the following original papers, which will be referred to by their Roman numerals:

I **Laska A C**, Hellblom A, Murray V, Kahan T, von Arbin M.
Aphasia in acute stroke and relation to outcome.
J Intern Med 2001;249:413–422

II **Laska A C,** von Arbin M, Kahan T, Hellblom A, Murray V.
Long-term antidepressant treatment with moclobemide for aphasia in acute stroke patients: A randomised, double-blind, placebo controlled study.
Cerebrovasc Dis 2005;19:125–132

III **Laska A C,** Kahan T, Hellblom A, Murray V, von Arbin M.
A randomized controlled trial on early speech and language therapy in acute stroke patients. Design and methods.
Submitted

IV **Laska A C**, Bartfai A, Hellblom A, Murray V, Kahan T.
Clinical and prognostic properties of standardized and functional aphasia assessments.
J Rehabil Med 2007;39:00-00

V **Laska A C,** Mårtensson B, Kahan T, von Arbin M, Murray V.
Recognition of depression in aphasic stroke patients.
Cerebrovasc Dis 2007;24: 00-00

ABBREVIATIONS

ADL	Activity of daily living
AF	Atrial fibrillation
ANELT	Amsterdam-Nijmegen Everyday Language Test
CBF	Cerebral blood flow
CGI-S	Clinical global impression of severity
Coeff	Coefficient in Norsk Grunntest for Afasi
CT	Computed tomography
D	Depressed
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Ed.
ECG	Electrocardiogram
ICH	Intracerebral hemorrhage
IST-3	The third International Stroke Trial
LET	Language Enriched Therapy
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO	Monoamine oxidase
MRI	Magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
Non-D	Not depressed
NGTA	Norsk Grunntest for Afasi
PSD	Post-stroke depression
RCT	Randomized controlled trial
RBMT	Rivermead behavioral memory test
ROC	Receiving operating curve
SD	Standard deviation
SEM	Standard error of the mean
SLT	Speech and language therapy
SSS	Scandinavian Stroke Scale
SSSS	Scandinavian Stroke Supervision Scale
SU	Stroke Unit
TOAST	Trial of ORG 10172 in acute stroke treatment
TIA	Transient ischemic attack
WAB	Western Aphasia Battery
WAIS-R-NI	Wechsler Adult Intelligence Scale-Revised- Neuropsychological Instrument
WHO	World Health Organization

CONTENTS

INTRODUCTION

Aphasia is a language impairment due to a brain lesion, often in the left hemisphere (1). Aphasia is a common symptom in acute stroke with an incidence in earlier studies between 21 – 38 % (2-4). The language impairment affects both spoken and written language. The communication difficulty due to aphasia, is above all a dysfunction of verbal communication, while non-verbal communication may be spared. Speech is the mechanical aspect of communication. A right hemisphere lesion can partly affect both non-verbal and verbal communication (5, 6). Approximately 99 % of all right-handed individuals are said to have language function in the left hemisphere (7).

Stroke etiology

According to the Swedish national stroke register (Riks-Stroke), the etiology of stroke in Sweden is intracerebral hemorrhage (ICH) in 12 %, thrombosis in 62 %, and cerebral emboli in 26 % (8). In our stroke unit (SU) at Danderyd University Hospital, 12 % of stroke patients have ICH, 59 % thrombosis, and 29 % cerebral emboli. International studies of stroke subtypes show ICH in 20 %, thrombosis in 60 %, and embolic stroke in 20 % (9, 10). The mean age of patients in those international studies is ten years lower than the mean age (75 years) in acute stroke patients in Sweden.

Atrial fibrillation

Atrial fibrillation (AF) constitutes the main part of the etiology behind cerebral emboli, and increases with age. AF is present in 25 % in first ever ischemic stroke patients and is associated with higher mortality (11), and higher stroke recurrence (12). Stroke associated with AF is more severe than ischemic stroke due to other etiologies (11, 13). The Framingham Study showed that ischemic stroke associated with AF has twice as high mortality as non atrial fibrillation stroke, and functional deficit is more severe in the survivors (14). One earlier study has shown that 40 % of the ischemic stroke patients with Wernicke's aphasia had emboli (15). Among TIA patients with AF, aphasia was observed more frequently than in patients without AF (16). It is thought that the heart may be the source of large emboli, which can impact on the large cerebral arteries and lead to severe neurological deficits. Microemboli from carotid artery disease can easily migrate through the large cerebral arteries, to become lodged in the small vessels, resulting in mild neurological deficits. Cardiac emboli lodge equally in the anterior and posterior divisions of the middle cerebral artery. Patients without cardiac emboli have higher frequency of deep, subcortical infarcts (17).

Mortality in acute stroke, within the first month, is at present less than 15 % in Sweden (Riks-Stroke). The highest mortality rate, 30 %, is seen in patients with intracerebral hemorrhage (8). Of acute aphasic patients followed for one year, 27 % died (18).

In 2005 discharge destination from acute hospitals, for stroke patients in Sweden, was home in 50 %, geriatric or neurological rehabilitation in 17 %, nursing home 18 % and death in 11 % (8). In our SU, the corresponding percentage was 58, 20, 15, and 6 %,

respectively. Mean hospital stay in acute hospitals in Sweden is 13 days, and in our SU 7 days (8).

Aphasia assessment

Many different instruments for the formal testing of aphasia are available. Assessment of aphasia is for diagnostic purposes, while measurement of the degree of aphasia is necessary to evaluate outcome of treatment, and to estimate prognosis. Standardized aphasia tests like the Western Aphasia Battery and Boston Diagnostic Aphasia Examination (19, 20) classify the type of aphasia, and measure the degree of aphasia. All standardized aphasia tests measure speech fluency, comprehension, naming and repetition; some of them also reading and writing. The sum of the three main variables defines the degree of aphasia. The tests are performed by a speech pathologist. According to some authors (21) standardized aphasia tests are less suitable to assess functional recovery.

The degree of aphasia can also be assessed by functional communication tests. These tests may be assessed both by speech therapists and significant others (22, 23). The neurological impairment tests like the Scandinavian Stroke Scale (SSS) (24) and the National Institute of Health Stroke Scale (25) usually have one item for language impairment. The type of aphasia can be grouped as fluent – non fluent, or impressive – expressive, or according to lesion location posterior – anterior. Fluent types of aphasia are: Wernicke, conduction, transcortical sensory, and anomic. Non fluent types are: global, Broca, and transcortical motor. In fluent aphasias the lesion is located posteriorly, in non fluent more anterior. In global aphasia there is usually a large lesion involving both anterior and posterior parts of the arteria cerebri media area.

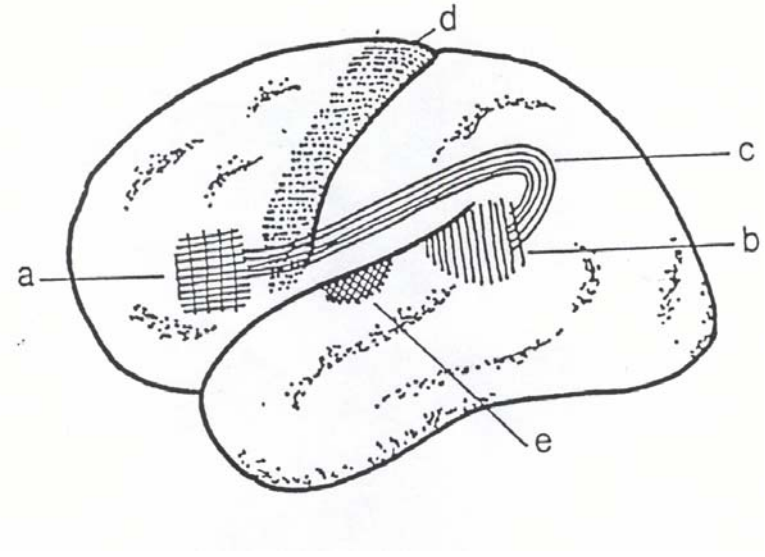

Figure 1. Left hemisphere a) Broca's area, b) Wernicke's area, c) fasciculus arcuatus, d) motorcortex, e) auditory cortex

The impairment of the different parts of the language in relation to the types is shown in Table I. Global and unclassified aphasias account for 50 % of the aphasic syndromes in the acute stage, whereas the classic aphasias are less frequent (26). The non fluent (anterior) type of aphasia is often accompanied by hemiparesis, while patients with fluent aphasia (posterior) often have no paresis (Fig.1). The fluent aphasic patient might be interpreted as confused in the emergency department. Fluent aphasias are seen in older patients and non fluent in younger age (27, 28).

Table I. Schematic illustration of classification of types of aphasia

Type of aphasia	Fluency	Comprehension	Naming	Repetition	
Global	+++	+++	+++	+++	**NON FLUENT**
Broca	+++	+	++	++	
Transcortical motor	+++	+	+	+	
Mixed non fluent	++	+	++	++	
Wernicke	+	+++	+++	+++	**FLUENT**
Transcortical Sensory	+	+++	+++	+	
Conduction	+	+	+	+++	
Anomic	+	+	++	+	
Mixed fluent	+	++	++	++	

+ = mildly impaired or normal
++ = moderately impaired
+++ = severely impaired

Recovery

There is a considerable spontaneous recovery of aphasia with time. The greatest improvement takes place within the first months after stroke onset (2, 29-31). The final state depends to a high extent on the initial degree of aphasia (18, 29, 32, 33). Stroke severity also predicts outcome (18, 34). Patients with mild language impairment show excellent outcome, whereas impairment in patients with global aphasia remains severe. There may be exceptional cases, such as global aphasics, who show remarkable recovery (32). Age appeared to show a reverse correlation with recovery rates, i.e. younger patients recovered better (32, 33, 35). Complete recovery of aphasia in survivors of acute stroke patients may be seen in around one fourth (2, 32). Fluent aphasics have the most rapid recovery in the first 6 months after stroke, whereas the non fluent aphasics recover more between 6 to 12 months (36).

Evolution in aphasia is the change in type of aphasia during recovery (Figure 2). The amount of patients with evolving aphasias is around 50 % (32, 37).

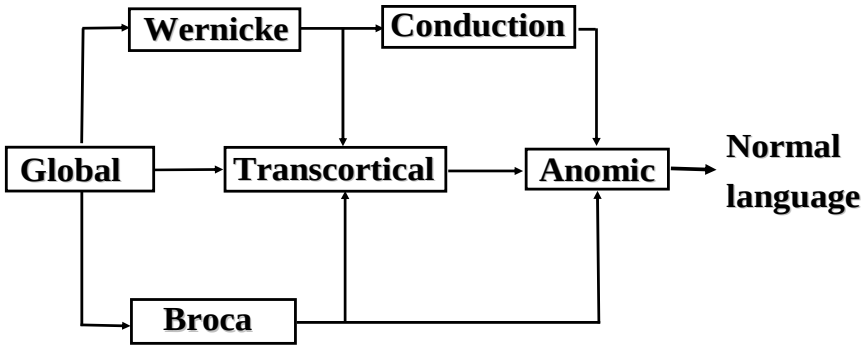

Figure 2. Evolution in aphasia (38)

Recovery mechanism

Patients who have recovered completely from previous aphasia, almost always present with aphasia when a recurrent stroke occurs, even though it might be in the right hemisphere. This could depend on new damage to language areas, or damage to areas that compensate for earlier stroke (35, 39). Studies of regional cerebral blood flow (rCBF) have shown an increase in blood flow to homologue right language areas, which is in favour of a brain reorganisation during recovery (40), (41). Recent studies with repeated functional magnetic resonance imaging (fMRI) suggest that brain reorganization during language recovery proceeds in three phases: a strongly reduced activation of remaining left language areas in the acute phase is followed by an up-regulation with recruitment of homologue language zones, which correlates with language improvement. In the chronic phase a normalization of activation is observed, possibly reflecting consolidation in the language system (42). Very little is known about the pathophysiology of improvement in the later chronic stage.

Gender

Sex is not a determinant of aphasia in stroke, and no gender difference was found in the anterior-posterior distribution of lesions (18, 26, 27). There is no relation between gender and degree of aphasia or type of aphasia (27), and no significant gender differences regarding recovery have been found (18, 32, 43).

Other cognitive impairment

Acute stroke patients with aphasia often have other cognitive impairments in addition to the language impairment. These additional deficits have prognostic implications and may

render difficulties for the patient to participate in testing and therapy. Cognitive recovery is associated with the initial degree of deficit, and is negatively related to increasing age (44).

Pharmacological interventions

There is an increased interest in the development of drugs to promote functional recovery after stroke. Experimental work over the past decades indicates that pharmacologic intervention to enhance recovery may be possible in the subacute stage, days to weeks post-stroke. Amphetamine, the most studied drug, has been shown to promote recovery of function in animal models (45). In a study of Martinsson et al, however, increased intensity of physiotherapy in combination with dexamphetamine during the first week after stroke onset did not affect short- or long-term functional outcome in a small sample of patients with severe stroke. To note is that the recruitment of 32 patients in the study took four years (46). However, in another randomized controlled trial a single dose of levodopa was given in combination with physiotherapy within the first months after stroke onset and enhanced motor recovery in patients with hemiplegia (47).

The primary goal for aphasia rehabilitation is to improve functional communication. As a major symptom of stroke, aphasia may share common physiological and neurochemical features with other stroke manifestations, such as supranuclear motor paresis and central sensory loss. Pharmacotherapy aimed at stroke rehabilitation through direct effects on the central nervous system may thus be assumed to work in a similar way in language recovery as in sensory-motor recovery. The nootropic agent piracetam was evaluated on its effect on aphasia recovery. It showed effect in one of the subtests, but these improvements were not maintained after the cessation of piracetam treatment (48). The Cochrane review of 2001 on pharmacological treatment for aphasia included studies evaluating six different drugs. Two studies used dopamine agonist, no other drugs directly enhancing neurotransmitter activity were used. The only drug for which there was any evidence of benefit was piracetam, but the evidence was weak, and there were concerns about its safety. It was not possible to conclude whether piracetam was more effective than SLT in treating aphasia after stroke (49).

Moclobemide is a reversible and selective inhibitor of the MAO-A isoenzyme. Clinical studies and meta-analysis have confirmed the efficacy of moclobemide in the treatment of depressive disorders (50, 51). It is shown to have similar efficacy as tricyclic antidepressant and selective serotonin reuptake inhibitors (52). Its lack of adverse anticholinergic, cardiovascular, cognitive and psychomotor effects makes moclobemide a particularly useful option in the elderly and in patients with cardiovascular disease (53).

Speech and language therapy

Speech and language therapy (SLT) is almost unanimously considered to be the mainstay of aphasia treatment. However, over the past decades there has been much debate whether SLT for aphasia is really effective, mainly because analyses of clinical outcome have yielded mixed results. In the Cochrane review in 1999 on SLT for aphasia following

stroke, the main conclusion was that SLT could not be shown to be clearly effective nor clearly ineffective (54). A more recent review of studies from 1998 to 2002 could identify three RCT of good quality supporting the recommendation that patients with aphasia should receive SLT (55). Later studies have shown that intensive SLT over a short period of time can provide better outcome than less intensive regimens over a longer period (56). However, almost all patients in these studies had chronic aphasia, i.e. duration of more than three months after stroke onset. New therapies like constraint-induced therapy, i.e. suppressing non-verbal communication in favour of verbal communication, and transcranial magnetic stimulation to language areas have shown positive outcome for treatment target item with variable generalisation of improvement to other language domains (57, 58). So, while aphasia treatment in the chronic phase does help, it does not attain enough. The therapy's aspirations are generally too modest for patients and families, and the failing rapidity and extent of gains from existing approaches keep patients frustrated and disappointed. Notable, SLTs are time consuming, difficult to implement and expensive.

Aphasia and depression

Depression is a well-known complication after stroke. One third of all patients may suffer from post-stroke depression (PSD) during the first year (59). The incidence may be higher in aphasic stroke patients (60, 61). Studies have shown that patients with non fluent aphasia have a higher incidence of PSD than other aphasics (62, 63). Anatomically, the lesion in non fluent aphasic patients is usually located in the frontal pole of the left hemisphere. Earlier studies suggest a relationship between a left hemisphere lesion and mood disorders (60, 61) supported in one systematic review (64) and contradicted in another (65). Depression in aphasic patients could be due to the inability to communicate, which leads to social isolation, and is likely to be associated with depressive reactions (66), and may be one of the emotionally most burdening neurological deficits. Since assessments of mood disorders are based on questionnaires, randomized controlled trials of PSD have excluded most aphasic patients (63, 67, 68). Some specific instruments for assessing depression in aphasic patients are being developed but are not ready for common use (69-71).

The influence of antidepressant drug treatment on the outcome of stroke patients is still an open issue. Tricyclic antidepressant drugs have been shown to relieve PSD, but their usefulness is limited because of frequent adverse events. A systematic review of pharmacological therapies showed that antidepressants reduced mood symptoms but had no clear effect on producing a remission of diagnosable depressive illness. Further, there was no definitive evidence that antidepressants prevent depression or improve recovery after stroke (68).

Post stroke pathologic crying is a distressing condition in which episodes occur in response to minor stimuli without associated mood changes. RCTs show that selective serotonin reuptake inhibitors have been effective in the treatment of pathologic crying and emotionalism (72, 73).

Language is one of the most complex of human cognitive functions and neither the nature of human language nor the brain mechanism for producing or receiving it are fully understood. This prompted us to investigate the mechanism of aphasia in acute stroke patients, its recovery and prognosis. The assessment of aphasia is of great importance and we have evaluated different methods. Drug treatment to increase recovery after stroke has been tried, though not yet with satisfactory effect. This inspired us to evaluate yet another drug on aphasia restitution. SLT may be effective in the chronic stage but is far from enough, and we investigate if early SLT may help patients in recovery from aphasia.

AIMS OF THE PROJECT

- To evaluate the incidence of aphasia in acute stroke patients, and the frequency of different types of aphasia.
- To study the difference between aphasic and non-aphasic patients with regard to morbidity, mortality, and functional outcome.
- To assess spontaneous recovery in aphasia and evolution in aphasia.
- To measure the capacity of the test instruments to assess the degree of aphasia, the changes over time, and to predict outcome.
- To evaluate the efficacy of a pharmacological treatment for recovery of aphasia.
- To evaluate the efficacy of early speech and language therapy in acute stroke patients.
- To assess the possibility to identify depression in aphasic patients.

PATIENTS AND METHODS

Study populations

The patients were gathered from three study populations. Every patient had suffered an acute stroke and was treated in the stroke unit (SU) at Danderyd University Hospital. The patients constituted or were screened from consecutive, unselected acute stroke patients. In the observational study (I) (74), 106 consecutive, unselected acute stroke patients were studied. The aphasic patients in this material plus another 83 aphasic patients were included and followed- up at three, six, and 18 months. In a randomized placebo-controlled double-blind trial (II) (75), 89 patients were included and treated for six months and followed-up after one year. In an ongoing, randomized, controlled trial (III), so far 80 patients have been included and treated for three weeks and followed-up after six months (76),. Patients or relatives gave their informed consent, orally in I and written in II and III. In Paper IV the patients were collected from Study I and II. Paper V contains the same study population as in Study II.

Our SU is a well established unit with specially trained staff, team-members from different occupations, and a defined treatment program. The routine program of the SU includes computed tomography of the brain, a standard electrocardiogram (ECG), regular assessments of neurological deficit and vital signs, laboratory tests, and ultrasound investigation of the carotid arteries and the heart, magnetic resonance imaging of the brain, as needed, as well as assessment of all team members, as needed. Information of demographic data and risk factors are collected. Every patient in the studies was included in this routine program. Patients are discharged to their homes, to geriatric rehabilitation, to neurological rehabilitation or to nursing homes, as appropriate.

Methods

The etiology of stroke was defined as thrombosis, cardiac emboli. intracerebral hemorrhage, and undetermined stroke in accordance with the International Classification of Diseases (77). In III the ischemic strokes were classified according to the TOAST-criteria (78) and the Oxfordshire classification of stroke (79). Atrial fibrillation or sinus rhythm was collected from the ECG at admission. Neurological deficits were assessed according to Scandinavian Stroke Supervision scale (SSSS) (80), which is a development from SSS (24) in I and II, and according to National Institute of Health Stroke Scale (NIHSS) (25) in III. Activity of Daily Living (ADL) was assessed according to Katz Index (81) in I and according to Barthel Index (82) in II and III. The reason for changing method in assessing neurological deficit and ADL was that the methods used in I was the method used by all researchers in our SU at that time. In the following studies, we made a successive adjustment to the predominant international standard.

Assessment of aphasia

All aphasia assessments were performed by a speech pathologist. The two tests, as described below, were performed in random order. Both tests were well validated and available in Swedish.

Standardized test

Norsk Grunntest for afasi (NGTA) (83) is based on the Boston terminology and similar to the Western Aphasia Battery (19). NGTA measures fluency, comprehension, naming and repetition, as well as writing and reading. The sum of the total score of three main variables yields the aphasia coefficient (Coeff). Coeff is a measure of the severity of language impairment and constitutes the degree of aphasia. In I and III, where the aphasic patients were tested very early after stroke onset, we used a shorter, adjusted version, representative of the entire NGTA (83). The short version is performed in 10–15 minutes. In II the entire NGTA was used, which takes 30–45 minutes. The Coeff has a range of 0–59 in the short version, and 0–217 in the entire NGTA. Percentile values give each patient's raw score for the variables naming, repetition and comprehension in relation to the score of the whole group of these aphasics. The relation between the percentile value of three parameters and fluency estimated from spontaneous speech gives the type of aphasia. The NGTA recognizes that some aphasic patients actually have a mixture of two or more aphasia syndromes. These patients are therefore classified as mixed non fluent or mixed fluent. Fluent aphasias are: Wernicke, conduction, transcortical sensory, anomic and mixed fluent. Non fluent aphasias are: global, Broca, transcortical motor and mixed non fluent. Unclassified type of aphasia means that the aphasic patients are accurately tested but the different language variables give values that do not fit into any of the aphasia types. A battery of "yes and no" capability questions from the comprehension part of the NGTA was selected to secure depression diagnosis. Evolution of aphasia was defined as a change in type of aphasia during the course of recovery. This was assessed among patients who were tested on more than three occasions and who improved.

Functional test

Amsterdam-Nijmegen Everyday Language Test (ANELT) (84) is a measure of verbal communication ability and was used to assess the degree of aphasia. In this functional test the understandability of the patients' message and the intelligibility of the utterance are each rated on a 5-point scale, where 1.0 indicates the most severe degree of aphasia. Each parallel test consists of ten items, and takes in all about 15 minutes to perform. The items are constructed as scenarios of familiar daily life situations, e.g. calling a doctor, or talking to a sales clerk. The test starts with two training tasks to ensure that the patient understands the idea of the test. The ANELT understandability score indicates the severity of the communication disability, and is a measure of the degree of aphasia. Since patients in I with an initial score between 4.0 and 5.0 had a high rate of complete spontaneous recovery, such patients were excluded in II. In I and III, a score of 0 was given when the patient, due to severe aphasia, was incapable of taking instructions and/or producing an answer.

The Token test was used to discriminate aphasia during follow-up (85). The version used has a range of 0-36, and the cut-off was set at 30 to define aphasia. The Token test was performed in I.

Complete recovery was defined as full score in both the NGTA and the ANELT tests, a Token test score of more than 30, and normal language in the opinion of both the patient and the speech pathologist.

Other tests

The diagnosis of major and minor depression was made in accordance with DSM-IV criteria for depression, and the DSM-IV research criteria, respectively (86). DSM-IV diagnosis is based on questions demanding "yes" and "no" answers. The feasibility of administering the DSM-IV was assessed in the group of patients capable of correctly answering the "yes" and "no" battery from the comprehension test, as well as in the whole study population including patients needing assistance of relatives and/or staff.

Attempts were made to interview all patients using the Montgomery-Åsberg Depression Rating Scale (MADRS) (87), a 10-item structured interview where a score of 6 per item represents the most severe degree. The score of 10 was used as cut-off point to suspect a depression (73). The patients were also assessed according to the Clinical Global Impressions Rating Scale for Severity (CGI-S) technique (88), applied by the same person at every visit, based on each patient's appearance and on information from relatives and/or staff. The utilised version of the CGI-S contains seven grades of illness. The cut-off point for suspecting a depression was set between 1 and 2.

Emotionalism was defined as increased tearfulness and pathological crying beyond control as reported by the patient. The assessment was completed by observations made by relatives and staff. The answers were treated as a dichotomous variable (occurring/non-occurring).

In II a neuropsychological test battery was performed, primarily to exclude patients with dementia, consisting of the following tests: Token test, Boston naming test, Rivermead Behavioural Memory Test (RBMT) pictures, faces and orientation, memory, and four subtests of the WAIS-R-NI, and apraxia tasks (89). Reasons for not carrying out the test were too severe aphasia, too tired patients, or administrative problems. Patients with a low score (n=3) on the date and orientation of the RBMT were classified as demented.

Treatment methods

In II, patients were randomized to receive double-blind oral treatment with the reversible monoamine oxidase (MAO)-A inhibitor moclobemide or placebo within three weeks of stroke onset. The treatment was either moclobemide supplied in capsules of 150 mg, or identical-looking placebo capsules. The initial dose was two capsules taken in the morning. After one week the dose was increased with one capsule taken after lunch, and after one month the dose was increased again to two capsules in the morning and two

after lunch. Patients were seen at one, three and six months of study drug treatment for vital signs, compliance, and adverse events. After six months drug treatment was stopped and patients were seen again at seven, and 12 months.

In III, the included patients were stratified into three groups according to the result of the NIHSS, and then randomized by draw of a consecutive sealed envelope to receive early intensive SLT or no SLT (control) for three weeks. The SLT treatment was Language Enrichment Therapy (LET) (90) and was carried out by a few trained, independent, non-testing speech pathologists. The therapy contained three sessions of 15 minutes per day for 15 weekdays, i.e. three weeks. The LET program consists of exercises in comprehension and naming in a hierarchic edified program. When the patient was discharged from the SU, the therapy continued where the patient stayed with one daily session of 45 minutes.

Statistical methods

Data are presented as mean values ± SEM, and median with 25^{th} and 75^{th} quantiles, as appropriate. Contingency tables were evaluated by χ^2-test, or in case of small expected frequencies by Fisher's exact test. Comparisons between groups were made using student's *t*-test, one-way analysis of variance, or by Mann-Whitney. The Wilcoxon signed rank test was used when comparing groups with skewed distributions. For multivariate regression analyses, multivariate analysis of variance was used. A probability value (p) of < 0.05 was considered to be statistically significant. Likelihood ratios were also calculated (91).

In II the primary efficacy variable was regression of aphasia from baseline to six months, as measured by ANELT. The study was dimensioned to detect a difference of 0.75 in ANELT between the two treatment groups and an estimated SD of 0.6. The coefficient of variation for ANELT was estimated a maximum of 80 %, the level of significance at 5 % and the power at 80 %. These conditions required 30 evaluable patients in each treatment group. To compensate for premature withdrawal during the treatment, 45 patients were to be included in each treatment group.

Receiver operating characteristic (ROC) curves were constructed by a plot of the sensitivity to predict a complete recovery by (1-sensitivity) for each value of the Coeff and ANELT, which is a graphical representation of the relationship between false positive and true-positive rates. The relationship was evaluated as the area under the curve.

In III the primary outcome is the difference in the degree of aphasia between the SLT treated group and the control group measured by the ANELT understandability score at three weeks. Secondary measure of outcome is the difference in the recovery rate in Coeff between the two groups at three weeks. A difference on the ANELT scale of 1.0 was considered clinically relevant, whereas 0.5 was considered too small to be clinically relevant. The power was set at 90 % and the two-sided level of significance at 5%. To secure that a true clinically relevant difference was not to be missed we used a difference

of 0.75, which would require 52 patients in each group. In order to compensate for premature withdrawals during the treatment phase a total number of 125 patients are to be included in the study. The primary analysis will be according to intention-to-treat.

All analyses were carried out with JMP®, version 3.1 and 5.1 (SAS Institute Inc., Cary, NC. USA).

RESULTS

In consecutive, unselected patients with acute stroke, 33 % had aphasia. The incidence of aphasia among first ever strokes was 28 %. The etiology of the stroke in the consecutive group was: Intracerebral haemorrhage (ICH) 9 %, thrombosis 58 %, cerebral emboli 29 % and undetermined 4 %. The distribution of the etiology in the studies is shown in Table II.

Table II Baseline characteristics for the three study populations

Study population	**I**	**II**	**III**
Number of patients	119	89	80
Age, years, median	77	76	80
Gender, % male	54	56	44
Etiology			
ICH, %	8	14	-
Thrombosis, %	60	48	60
Emboli, %	28	37	40
Neurologic deficit			
SSSS, median (6-27)	14	12	-
NIHSS, median (0-27)	-	-	8
Aphasia			
Coeff, median	34	84	18
ANELT, median	1.7	1.2	1.1
Fluency, %	65	43	-

Among consecutive stroke patients in I the short term mortality was 11 % in the aphasic group, as compared to 3 % in the non-aphasic. Long term (18 months) mortality was 36 % among the aphasic patients, as compared to 16 % in the non-aphasics.

Atrial fibrillation

Atrial fibrillation (AF) was found in 42 % of the consecutive aphasic patients. The frequency of atrial fibrillation according to the ECG at admission was 26 % in I, and 32 % in III.

Inclusion

The median time from stroke onset to inclusion in the study was for I, II, III, 5, 18, and 3 days, respectively. See figure 3.

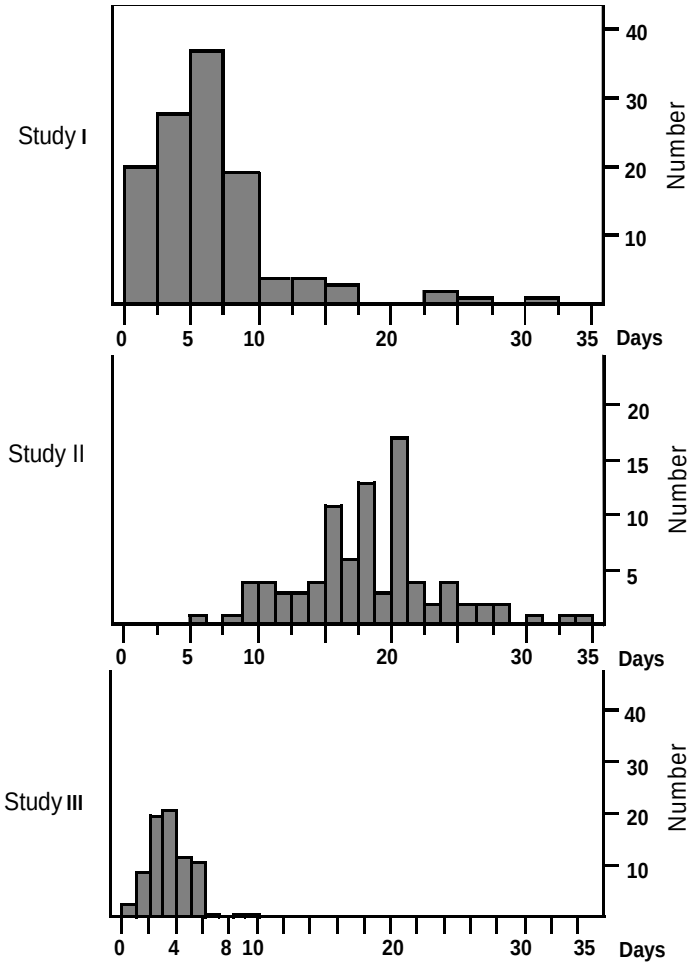

Figure 3. The number of included patients per day in the three studies.

Hospital stay

The mean duration of hospital stay in the SU for the aphasic patients in III was 11 days. Patients were discharged in 35 % to their homes, in 39 % to geriatric rehabilitation and 18 % to neurological rehabilitation, 8 % were discharged to nursing homes. Corresponding figures in I were 51, 35, 5, and 8 %, respectively.

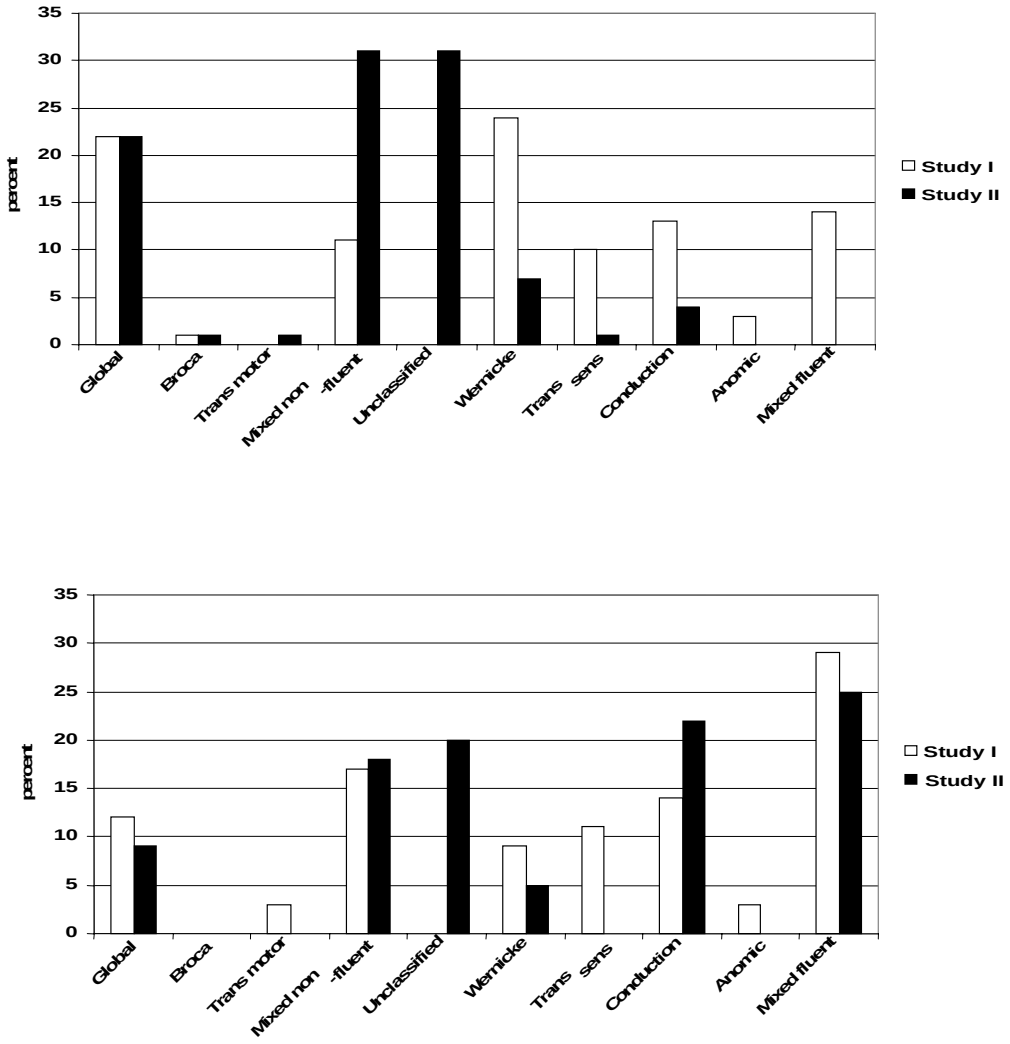

Figure 4. The different types of aphasia in acute stroke patients from I and II at baseline (upper panel) and at 6 months (lower panel).

Recovery

Recovery over time, measured as mean values at each visit for ANELT and Coeff, is shown in figure 5. In I 66 % of the aphasic patients had fluent aphasia at baseline, while in II, where those with the mildest degree of aphasia (ANELT 4.0 – 5.0) were not included, 44 % had fluent aphasia. At six months patients with fluent type of aphasia reached a significant higher level of language function measured by Coeff and ANELT ($p<0.01$ for both) in both I and II. Recovery rate, as measured as the difference between the degree of aphasia at baseline, and at six and 18 months, respectively, showed in univariate analysis that the initial degree of aphasia was negatively correlated to the recovery rate ($p<0.01$ in I and II), i.e. the better the initial degree of aphasia, the less the

recovery rate. The recovery rate was equal for fluent and non fluent type of aphasia measured by both Coeff and ANELT. In study II patients with ICH had a higher recovery rate. In stepwise multivariate regression analysis, including age, etiology, neurological deficit, type of aphasia, and initial degree of aphasia as measured both by Coeff and ANELT, the initial degree of aphasia and ICH were significantly related to recovery rate ($p<0.05$). Age and global type of aphasia were negatively correlated to recovery rate, but did not reach significance in the multiple regression analysis. The final stage of the degree of aphasia, i.e. ANELT and Coeff at the stage of six and eighteen months, were both significantly related to the initial degree of aphasia in univariate analysis, which means the higher the initial degree, the higher the final degree. In a stepwise multiple regression analysis the initial degree of aphasia was positively, and type of aphasia (global and Wernicke) negatively related to the final degree of aphasia ($p<0.05$).

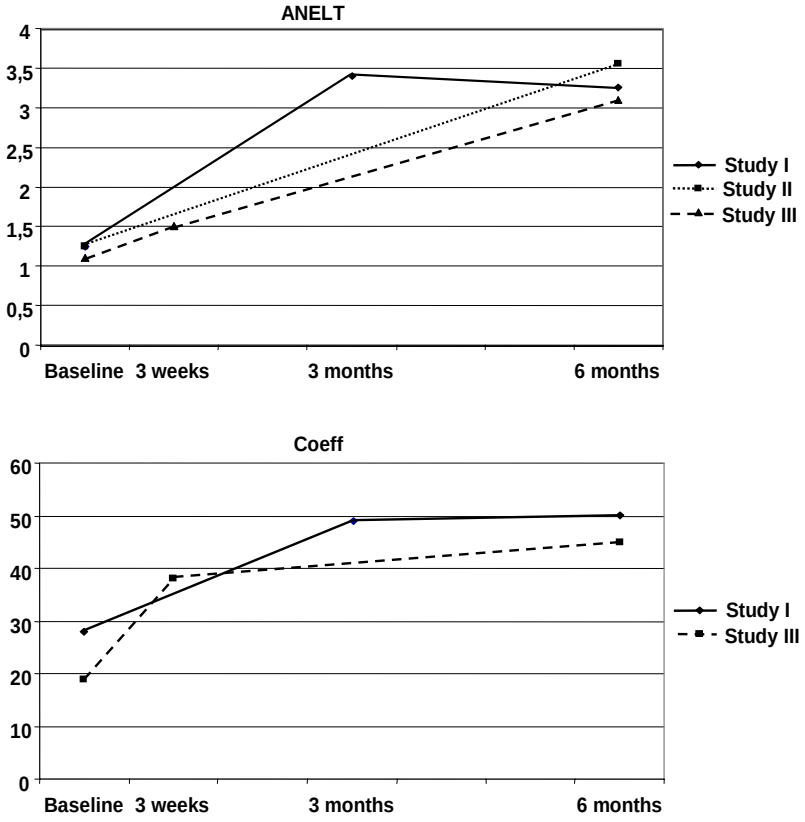

Figure 5. Degree of aphasia as measured by ANELT (upper panel) and Coeff (lower panel) at baseline, 3 weeks, 3 months and 6 months.

Evolution

Evolution of aphasia was observed in 34 of the 63 patients (54 %) in I who could be tested at least three times during 18 months and who improved. Evolution was not affected by age or gender. Wernicke's aphasia was more frequent among those whose

aphasia evolved than among those where it did not (47% vs.15 %; p=0.01). Evolution was not found to be related to the initial degree of aphasia measured with ANELT.

Predicting prognosis

The initial degree of aphasia could predict outcome. In I, 28 aphasic patients (24 %) recovered completely by 18 months. Among patients with Coeff ≥ 49 at baseline, 22 patients recovered completely, and among patients with ANELT ≥ 3.5 at baseline, 22 patients also recovered completely. See Figure 6. Except for two patients, these were the same persons. In a multivariate analysis including Coeff, ANELT, type of aphasia, age and comprehension, ANELT was the only variable that predicted complete recovery ($p<0.05$). Patients with aphasia at baseline still had aphasia at 18 months in 43 % of the survivors, but usually in a milder form.

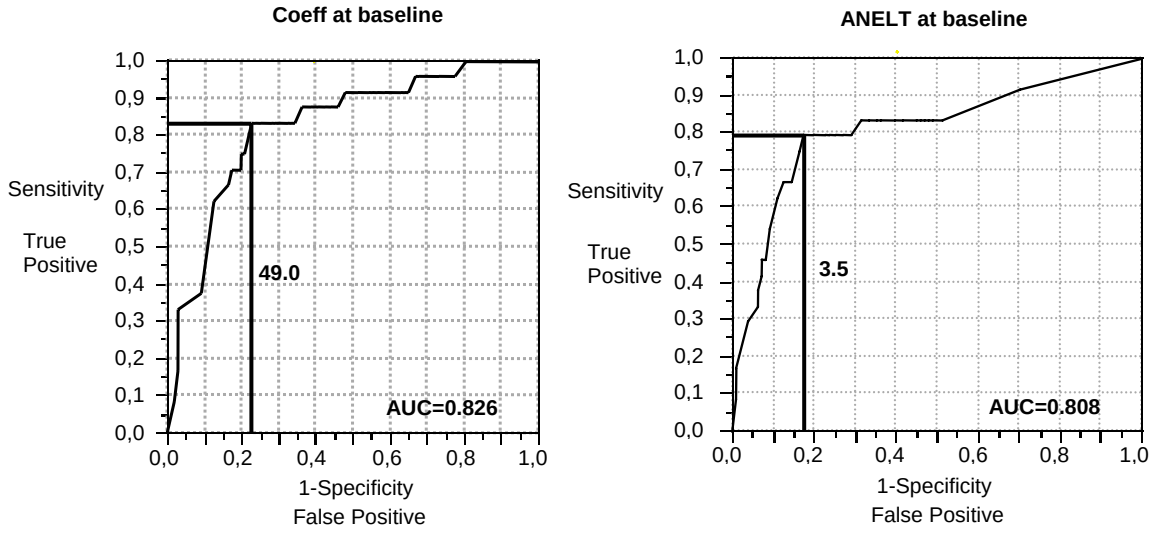

Figure 6 Receiver operating characteristic curves for (Coeff) and for (ANELT) show the sensitivity and specificity to predict complete recovery of aphasia.

Neuropsychological tests

Neuropsychological tests could be carried out in 37 patients in II. Multivariate analyses, including Coeff and ANELT at baseline, age, RBMT/picture and face, Block span total, forward, and backward, showed that Coeff at baseline, Block span total, forward, and backward, were related to recovery, measured by Coeff 0-6 months ($p<0.0001$, $p=0.06$, $p<0.01$, and $p=0.07$, respectively). For the recovery measured by ANELT 0-6 months, we found Coeff and ANELT at baseline, and RBMT/picture and face related ($p=0.01$, $p<0.0001$, $p<0.01$, and $p=0.05$, respectively).

In II 25 % of the patients could give their own written informed consent, in III 27%. The ability to give written informed consent was related to the severity of the stroke and the degree of aphasia ($p< 0.001$ for both).

Effect of drug treatment

In II the two treatment groups displayed balance for baseline characteristics except for a lower level of ADL and a higher degree of neurological deficit in the placebo group. There were no differences between the two treatment groups in baseline language characteristics except for more unclassified types of aphasia in the moclobemide group. At six months there was no difference in types of aphasia between the two groups. There was a significant improvement in the degree of aphasia from baseline Coeff median 84, and ANELT median 1.2 to six months Coeff median 184 and ANELT median 3.6 ($p<0.001$ for both).Hence, there was no difference between the treatment groups in these primary outcomes. Multivariate regression analysis, taking the baseline differences between the two arms into account, showed that the degree of aphasia at six months was not influenced by active substance treatment. In all, 66 patients completed the study drug therapy and 85 % of them maintained the doses according to protocol without difference between the two treatment arms. At six months 23 patients had discontinued study medication, but 76 of the 89 patients could be tested at six months.

Feasibility of DSM-IV diagnosis of depression

For all patients in II, including those in need of assistance from relatives and/or staff, feasibility to diagnose according to DSM-IV was 82, 90, 99 and 100%, at baseline, one, three, and six months, respectively. Sixty-three patients were capable to correctly answer "yes" and "no", according to NGTA (70% of the study population). Sixty of these 63 patients could be diagnosed according to DSM-IV, and were used as the reference group at baseline and onwards. The possibility to undertake a DSM-IV interview was related to the degree of aphasia, as measured by ANELT and Coeff ($p<0.01$). It was least in patients with the severe global and mixed non fluent types of aphasia. The possibility to undertake the DSM-IV was also related to the degree of comprehension ($p<0.001$). The DSM-IV symptom generally most difficult to understand and answer for the aphasic patient was number 7 (feeling of worthlessness/excessive guilt).

Feasibility of the depression rating scales

All 10 MADRS items could be completed by 76 % of all patients at baseline and by 90 % at six months. Among the 60 patients in the reference group 95, 93, 94, and 100 % were capable to complete all 10 items at baseline, and at one, three and six months, respectively. It was more difficult for the patients to accomplish a MADRS assessment than to participate in DSM-IV, especially for patients with global, mixed non fluent and Wernicke's types of aphasia. CGI-S could be evaluated in all patients at each visit. The assessment of a depression among patients needing proxy help was achieved at the expense of a lower validity.

Presence of depression and emotionalism

During the six-month treatment period minor depression was seen in 12 % of all patients and major depression in 12 %. Emotionalism was noted in 23 % of the patients at baseline and decreased during the study period. The cumulative occurrence of emotionalism during the treatment period was 38% in the moclobemide, and 41% in the placebo group. Emotionalism occurred more often among women (56 vs. 26%, $p<0.01$), and was associated with a more severe degree of neurological deficit ($p<0.05$), which was confirmed in multivariate analyses. The patients who had emotionalism at baseline tended to be more prone to develop depression during the study period ($p= 0.08$).

There was a trend towards more depression in patients with mixed non fluent aphasia ($p=0.10$). Major or minor depression was seen in 32% of the patients with mixed non fluent aphasia and in 14 % of those with unclassified aphasia.

Depression according to DSM-IV criteria occurred during the six months of treatment in 25% of the placebo patients and in 16% in the moclobemide group, i.e. no significant difference. During the six-month treatment period, minor depression affected one patient in the actively treated group and six patients in the placebo group, while major depression was equally distributed in the two groups (five and six, respectively).

A comparison at one month between patients reliably fulfilling the criteria for a depression (D) and those who did not (Non-D) revealed: by definition none of the two cardinal symptoms occurred among the Non-D. Of the other symptoms, weight loss (36% in D, 16% in Non-D); insomnia (50% in D, 33% in Non-D); loss of energy (25% in D, 20% in Non-D); and impaired concentration (27% in D, 19% in Non-D) occurred (all n.s.). At six months weight loss, insomnia, and loss of energy still occurred in more than 10% of the Non-Depressed patients.

GENERAL DISCUSSION

We confirm that aphasia is indeed common, one third of acute stroke patients have aphasia. A recent population based study showed that 30 % of first ever ischemic stroke patients had aphasia (92). For a correct aphasia diagnosis, the assessment must be done according to established tests and by a speech pathologist. The aphasia item in the different neurological impairment scales is not sufficient (4, 93). In the acute phase, aphasia will be over-diagnosed with neurological impairment tests because patients do not speak due to other neurological deficits. In the chronic phase, aphasia will be under-diagnosed because the questions are too simple to reveal mild language deficits.

Aphasia is a serious symptom. We show that the aphasic patients have three times higher short-term, in-hospital mortality than non-aphasics. The long-term mortality was twice as high in the aphasic patients, compared to the non-aphasic patients. Patients with aphasia have more severe strokes than those without aphasia, and the communication deficit in itself makes the patient more disabled. Consequently, patients with aphasia are discharged to their homes to a lesser extent than other stroke patients. They have a longer hospital stay and require in-hospital rehabilitation more often compared to patients without aphasia.

Cardiac emboli are almost twice as common as etiology among aphasic patients compared to other stroke patients. The frequency of atrial fibrillation is somewhat lower than that of cerebral emboli. The reason for this discrepancy is that the source of cardiac emboli may also be myocardial infarction, and that paroxysmal atrial fibrillation may be discovered during the hospital stay. Indeed, in every patient with aphasia and an ischemic stroke an embolic source should be sought.

In our studies, only one out of four patients was able to give written informed consent in the acute stage. Studies have shown that aphasia is the main reason for not getting consent from patients in acute stroke trials, other major reasons are old age and severe stroke. The responsibility for consent usually relies on relatives with potential inaccuracy of decision concerning the patient's wish or even conflict of interest (94). In a study from the IST-3 trial 83 % of the aphasics and 76 % of left hemisphere strokes had assent by relatives. The authors state that previously fit and active people who are affected by a severe stroke should surely have the opportunity to participate in research (95).

There is a considerable spontaneous recovery in acute aphasia and we showed that most of the recovery takes place within the first three months (I). Indeed, we could show that most of the recovery occurs within the first weeks (III). The aphasia tests show important consistency between the three studies, the mean values (Figure 5) being almost identical. The short version of NGTA was always possible to carry out, while half of the aphasic patients could not participate in the ANELT test within the first week of onset. After 3 – 4 weeks 75 % of them were able to carry out also the ANELT, which is more cognitive demanding. In II we did not include those with the mildest degree of aphasia, and being able to participate in ANELT was one of the inclusion criteria. Maybe as a consequence of this and the longer time after symptom onset, none of the patients in II recovered

completely. However, we have shown that the aphasia instruments can predict complete recovery, i.e. patients with mild aphasia in the acute stage will recover completely to a high extent. One fourth of the all aphasic patients recovered completely, which is in accordance with other authors (2, 32). These patients were tested within the first week, and the rate of complete recovery is of course dependent of at what time after the stroke onset the test is performed.

There was a high and consistent correlation between the NGTA and ANELT. In accordance with the Impairment and Disability Classification (96), NGTA measures language impairment, while ANELT measures functional communication, which is considered a measure of disability although ANELT is a verbal test. According to the more recent International Classification of Function both NGTA and ANELT are tests which involve body functions and activities (97). There is a difference between assessment of language impairment and how the individual gets along in a communicating world. The standardized aphasia tests focus on the language deficit, while functional communication tests measure what the patient can actually do. ANELT has been used to assess the functional communication but our results show that ANELT in several respects is similar to Coeff in the NGTA test. This type of correlation between a standardized and a functional test has also been shown by others (98). This is of interest since a standardized aphasia test is always feasible in acute stroke patients and NGTA was equally sensitive to improvement and able to predict outcome. Thus, a standardized test is sufficient in acute aphasic patients.

Pharmacological intervention with moclobemide did not improve the degree of aphasia beyond that of placebo, and the results were consistent for both Coeff and ANELT (II). This is, to the best of our knowledge, the only trial with an antidepressant drug in the treatment of aphasia. We chose moclobemide because it provides a general increase of neurotransmitter concentrations and has a more favorable side effect profile than other antidepressant drugs (53). However, it might yet not have given a sufficiently strong stimulus to central nervous system neurotransmission. The only drug stimulating neurotransmitter activity that has showed beneficial effect is amphetamine. Thus, dexamphetamine in addition to SLT facilitated recovery from aphasia in a small group of patients. In this trial, inclusion of 21 aphasic patients demanded more than four years (99). The long recruitment period is probably due to the many contraindications against dexamphetamine, and means that the use of dexamphetamine in poststroke aphasia should be restricted to highly selected patients. Most studies on pharmacological treatment for aphasic patients have been performed in conjunction with SLT, which may confound interpretation of the results. We did not combine the drug treatment with SLT in our study. We thought that both drug treatment and SLT need to be examined on their own in properly designed studies.

Reorganisation of the brain and the possibility to recover is greatest during the first weeks after onset. Hence, the main part of the spontaneous recovery takes place at this same time and there may be difficulties to show efficacy beyond the spontaneous recovery. Thus, the ongoing study on early SLT for acute aphasic patients is important. Another reason to perform a study as early as possible after stroke onset is partly to avoid the

potential ethical conflict due to the belief that SLT is essential for every individual aphasic patient in order to get full possibility to recover. Aphasic patients will routinely not receive SLT in acute SUs in Sweden. Weiller et al showed that there was a clear right hemisphere activation homotopic to the left hemisphere language zone (41). Repeated functional magnetic resonance imaging has shown an increased bilateral activation two weeks after onset of a stroke while in the chronic phase there is a re-shift to perilesional area in the left hemisphere (42). These findings indicate the importance of no other lesions but the index lesion in order to get maximal recovery. Accordingly, we only include first ever stroke and exclude patients with dementia. Of the four major components of the classic aphasic syndromes, comprehension usually shows the more rapid and complete recovery (100). The Language Enriched Therapy is based mainly on comprehension tasks and is an intensive therapy. As many studies have shown lately intensive SLT over short time is most efficient (101). Our study on early SLT for acute aphasic patients is feasible, and will clarify the potential value of early SLT in acute aphasic patients.

Two thirds of acute aphasic stroke patients with all types of aphasia could be reliably investigated for depression according to DSM-IV criteria within the first weeks after stroke onset, as long as a small battery of "yes/no" questions could be answered. With the help of proxy 82 % of all patients could be diagnosed. At three and six months the need for proxy help decreased and the possibility to diagnose a depression increased for the whole study group. At baseline, severity rating with the verbal MADRS was less feasible than DSM-IV, because MADRS is more verbally demanding than DSM-IV diagnosis, but feasibility for MADRS similarly increased over time. With the observational CGI-S, feasibility was 100 % at all times. The validity of the MADRS and CGI-S was higher in the "yes/no" capable group than when help of relatives or staff was needed. Accordingly, the need for help decreased over time, yielding an increase in validity. The use of significant others in the assessment of depression is seen in observational studies of aphasic patients (61, 102). MADRS and CGI have in one study been found equally sensitive to measure the efficacy of antidepressant treatment (103). To our knowledge there are no studies in aphasic patients on the validity of verbal methods.

The reluctance to include patients with aphasia in treatment trials may be attributed to the lack of knowledge of the feasibility of diagnostics and the fast increase in rating possibilities in aphasic stroke patients. Our findings seem to justify a new approach. At least two thirds of the aphasic patients can be included in controlled trials of PSD already in the acute phase. Basic demands are a reliable diagnosis of depression and that treatment effects are possible to assess by the same rating methods throughout. The type of aphasia is of importance for how soon after stroke onset the diagnosis may be made. Patients who could not be diagnosed according to DSM-IV were assessed as having more pronounced mood disorders on the CGI-S scale. We believe the correlation between the assessment methods and the DSM-IV diagnosis indicates that depression is not under-recognized.

The trend towards a higher occurrence of depression in patients with emotionalism at baseline has been observed also in other studies (104, 105). These findings provide

important clinical information in the acute setting, especially for patients who cannot be investigated by DSM-IV initially.

The 24% incidence of depression during the first six months may seem relatively low (60, 61). Hence, we identified a 12 % cumulated frequency of major depression, similar to previous findings in stroke patients (59). The patients with non fluent aphasia tended to have a higher incidence of PSD, which also has been found by others (63). Anatomically, the lesion in non fluent aphasic patients usually is located in the frontal pole of the left hemisphere. Earlier studies suggest a relationship between a left-hemisphere lesion and mood disorders (61), supported by one systematic review (64) although contradicted by another (65). Difficulties to identify and describe feelings with lesions in the right hemisphere could partly explain a higher rate of depression in patients with left hemisphere lesions (106). Depression in aphasic patients could be due to the inability to communicate, which leads to social isolation. This is likely to be associated with depressive reactions (66) and may be one of the emotionally most burdening neurological deficits. In stroke patients some depression symptoms occur irrespective of a depression diagnosis. Hence, depression may possibly be over-diagnosed in the individual stroke patient with aphasia.

In order to diminish the burden of aphasia, the most important issue is to minimize the lesion by optimal acute medical treatment. In the acute phase early mobilisation is important (107), probably also early SLT. Our trial will elucidate whether early SLT is effective in acute aphasic patients. These patients have a higher mortality and need longer hospital stay, and more rehabilitation resources than other stroke patients. We know now that patients with mild aphasia will recover spontaneously and completely to a high extent. Accordingly, the scarce speech therapist resources should not be directed towards this group of aphasic patients. No drug except for amphetamine, suitable only for a much selected group of stroke patients, in combination with SLT has yet shown to stimulate recovery. Depression is common in stroke patients, but might be over-diagnosed. We have found an interesting possibility to diagnose depression in a larger proportion already in the acute phase. Aphasic patients should be included in treatment trials on PSD. Prophylactic antidepressant therapy has not shown consistent efficacy, and should not be used except for patients with emotionalism, who were found to have a higher risk to develop PSD.

Future implications

Further research is required to find out if SLT for aphasic patients is effective, especially in the early stage. It will require RCTs large enough to have adequate statistical power. Such studies are warranted. The search for new drugs for treatment of aphasia will continue, and some of the tested drugs will be re-evaluated using methodologically improved RCTs. It appears equally important to identify in which patients and at what stage of the aphasia evolution process a specific pharmacological therapy may work. New drugs with properties to stimulate the reorganization of the brain, and hopefully other biological substances that may influence regeneration of the brain need to be evaluated. Speech and language therapy for the chronic aphasics has shown some effect,

though far from satisfactory. Further research on pharmacological treatment stimulating the brain in conjunction with SLT is warranted.

CONCLUSIONS

- Aphasia is seen in one third of acute stroke patients.

- Patients with aphasia have more severe strokes than other stroke patients, and the communication deficit in itself makes the patient more disabled. Aphasic patients have longer hospital stay, and require more rehabilitation resources.

- Aphasic patients have three times higher short-term mortality than non-aphasics. The long-term mortality is twice as high in aphasic patients as in non-aphasic patients.

- Cerebral emboli and atrial fibrillation are almost twice as common in aphasic stroke patients as in non-aphasics. In every patient with aphasia and an ischemic stroke an embolic source should be sought.

- The aphasia instruments: Norsk Grunntest for Afasi and Amsterdam-Nijmegen Everyday Language Test show consistent results.

- There is a considerable spontaneous recovery, which mainly takes place within the first weeks. The initial degree of aphasia predicts the final outcome. Patients with mild aphasia in the acute stage will recover completely to a high extent.

- Treatment with the antidepressant drug moclobemide does not improve the degree of aphasia beyond that of placebo.

- It is feasible to conduct a randomized controlled trial on early speech and language therapy for acute stroke patients.

- Two thirds of acute aphasic stroke patients can be reliably investigated for depression according to DSM-IV criteria within the first weeks after stroke onset. With the help of proxy, almost all of the acute patients can be diagnosed.

- There is a trend towards a higher occurrence of depression in patients with emotionalism at baseline.

- In stroke patients some depression symptoms occur irrespective of a depression diagnosis. Hence, depression may possibly be over-diagnosed in the individual stroke patient with aphasia.

- Aphasia in acute stroke is a serious symptom. The optimal therapeutic interventions remain, however, to be established. This warrants further studies.

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