ACUTE CONFUSIONAL STATE (DELIRIUM)
Clinical studies in hip-fracture and stroke patients

by

Yngve Gustafson

Umeå 1991
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ABSTRACT

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Acute confusional state (ACS) or delirium according to DSM-III-R holds a central position in the medicine of old age. ACS is a common and sometimes the only symptom of diseases and medical complications in the elderly patient.

The aim of this study was to elucidate ACS in patients with femoral neck fractures and patients with acute stroke with regard to frequency, predictors, possible pathogenetic mechanisms, associated complications, assessment and documentary routines and the clinical outcome for the patients. An intervention program to prevent postoperative ACS based on our results was developed and evaluated.

The main findings of the study were high frequencies of ACS in elderly patients with femoral neck fractures (61 %) and in patients with acute stroke (48 %). The main risk factors for ACS in patients with femoral neck fractures were old age, diseases and drug treatment interfering with cerebral cholinergic metabolism. There was no link between anaesthetic technique and ACS but the connection between peroperative hypotension, early postoperative hypoxia and ACS was close.

In stroke patients the degree of extremity paresis and old age were independent ACS risk factors. ACS was commonly associated with post stroke complications such as myocardial infarction, pneumonia, urinary infection and urinary retention. In stroke patients there was a close connection between high hypothalamic-pituitary-adrenal axis (HPA-axis) activity and ACS. High HPA-axis activity and disturbances in the cerebral cholinergic system may be two important ACS mechanisms.

A correct diagnosis is a prerequisite for proper treatment of ACS and its underlying causes. In the orthopaedic wards both physicians and nurses diagnosed and documented ACS poorly and therefore associated complications were insufficiently treated.

The intervention program for postoperative ACS, aimed mainly at protecting the cerebral oxidative metabolism and thereby the cerebral cholinergic metabolism which is especially sensitive to hypoxia. Postoperative complications associated with ACS were also treated. The intervention resulted in reduced frequency, duration and severity of postoperative ACS and in shorter orthopedic ward stay for patients with femoral neck fractures.

Key words: Acute confusional state, delirium, elderly, stroke, femoral neck fractures, acetylcholine, cortisol.
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ABBREVIATIONS

ACS = Acute confusional state

ADL = Activities of daily living

C.I. = Confidence interval

CNS = Central nervous system

CT = Computed tomography

DEX = Dexamethasone

DSM-III = Diagnostic and statistical manual of mental disorders (third edition)

DSM-III-R = Diagnostic and statistical manual of mental disorders (third edition-revised)

DST = Dexamethasone Suppression Test

GA = General anesthesia

HPA axis = Hypothalamic-pituitary-adrenal axis

IL = Interleukin

MMSE = Mini mental state examination

PAI = Plasminogen activator inhibitor

RA = Regional anesthesia

RAS = Reticular activating system

TIA = Transitory ischemic attack
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A correct diagnosis is a prerequisite for proper treatment of ACS and its underlying causes. In the orthopaedic wards both physicians and nurses diagnosed and documented ACS poorly and therefore associated complications were insufficiently treated.
The intervention program for postoperative ACS, aimed mainly at protecting the cerebral oxidative metabolism and thereby the cerebral cholinergic metabolism which is especially sensitive to hypoxia. Postoperative complications associated with ACS were also treated. The intervention resulted in reduced frequency, duration and severity of postoperative ACS and in shorter orthopedic ward stay for patients with femoral neck fractures.

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INTRODUCTION

HISTORY
Acute confusional state (ACS) or delirium was one of the first mental disorders described in the literature. About 2500 years ago, Hippocrates described ACS as a mental disorder of physiologic origin in a different terminology though. Several of his observations are still relevant, for example "When a delirium or raving is appeased by sleep, it is a good sign" and "Difficulty of breathing and delirium in continual fevers are mortal". Greek and Roman writers used the term phrenitis which refers to both diaphragm and mind. The soul or seat of life was considered to be in the diaphragm and the disruption of the union between mind and senses was suggested as the cause of phrenitis. This view on ACS as a disruption of the integrative system of mental functioning is in line with modern perspectives on the pathophysiology of ACS. For a review of the history of ACS see the monograph by Lipowski (Lipowski 1990).

The literature from the 19th century contains excellent clinical descriptions of ACS. One of them made by Savage in 1887 proposes a multifactorial approach to ACS because "there are several predisposing causes which may have been in operation for a long time, as well as one or more exciting causes which may have been in action for much shorter periods" (Savage 1887).

TERMINOLOGY
ACS is one of the most common and important forms of psychopathology in the elderly (Lipowski 1989). ACS is perhaps the most frequent presenting symptom of disease in the medicine of old age (Hodkinson 1976, Lipowski 1989). The study of ACS has been plagued by terminological confusion obstructing research, nursing and medical care, as well as communication and education in the field. In Table 1 some of the synonyms of ACS used in the literature are presented. The lack of uniform terminology would have been a minor problem if consistent diagnostic criteria had been used. The use of DSM-III and DSM-III-R criteria for delirium has made it possible to compare research results (APA 1980, APA 1987). For reasons discussed under diagnostic criteria we have chosen to use the term Acute Confusional State (ACS) in this study.
<table>
<thead>
<tr>
<th>Acute brain dysfunction</th>
<th>Metabolic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute brain failure</td>
<td>Organic confusion</td>
</tr>
<tr>
<td>Acute brain syndrome</td>
<td>Pharmacotoxic psychosis</td>
</tr>
<tr>
<td>Acute cerebral insufficiency</td>
<td>Phrenitis</td>
</tr>
<tr>
<td>Acute cognitive disorder</td>
<td>Phrensy</td>
</tr>
<tr>
<td>Acute confusion</td>
<td>Postanesthetic delirium</td>
</tr>
<tr>
<td>Acute confusional insanity</td>
<td>Postoperative confusion</td>
</tr>
<tr>
<td>Acute organic brain syndrome</td>
<td>Postoperative delirium</td>
</tr>
<tr>
<td>Acute organic psychosis</td>
<td>Postoperative insanity</td>
</tr>
<tr>
<td>Acute organic reaction</td>
<td>Postoperative psychosis</td>
</tr>
<tr>
<td>Acute organic syndrome</td>
<td>Pseudodementia</td>
</tr>
<tr>
<td>Acute psychoorganic syndrome</td>
<td>Pseudosenility</td>
</tr>
<tr>
<td>Agitated confusion</td>
<td>Reversible cognitive dysfunction</td>
</tr>
<tr>
<td>Agitated delirium</td>
<td>Reversible dementia</td>
</tr>
<tr>
<td>Brain dysfunction</td>
<td>Reversible madness</td>
</tr>
<tr>
<td>Cerebral insufficiency syndrome</td>
<td>Reversible toxic psychosis</td>
</tr>
<tr>
<td>Clouded state</td>
<td>Senile delirium</td>
</tr>
<tr>
<td>Confusion</td>
<td>States of excitement</td>
</tr>
<tr>
<td>Confusional state</td>
<td>Subacute befuddlement</td>
</tr>
<tr>
<td>Delayed psychosis</td>
<td>Symptomatic psychoses</td>
</tr>
<tr>
<td>Deliria of fever</td>
<td>Toxic confusion</td>
</tr>
<tr>
<td>Delirious state</td>
<td>Toxic confusional state</td>
</tr>
<tr>
<td>Delirium</td>
<td>Toxic delirious reaction</td>
</tr>
<tr>
<td>Delirium nervosum</td>
<td>Toxic delirium</td>
</tr>
<tr>
<td>Dysergastic reaction</td>
<td>Toxic encephalopathy</td>
</tr>
<tr>
<td>Emergency delirium</td>
<td>Toxic-infectious psychoses</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Toxic psychosis</td>
</tr>
<tr>
<td>Exogenous psychosis</td>
<td>Transient behavioural syndrome</td>
</tr>
<tr>
<td>Infective exhaustive psychosis</td>
<td>Transient cognitive disorder</td>
</tr>
<tr>
<td>Intensive care syndrome</td>
<td>Vascular psychotic organic brain syndrome</td>
</tr>
</tbody>
</table>
DIAGNOSTIC CRITERIA

DSM-III criteria for delirium (APA 1980) are:
A. Clouding of consciousness (reduced clarity of awareness of the environment), with reduced capacity to shift, focus and sustain attention as to environmental stimuli.
B. At least two of the following:
   1. perceptual disturbance, misinterpretations, illusions, or hallucinations
   2. speech at times incoherent
   3. disturbance in the sleep-wakefulness cycle, with insomnia or day-time drowsiness
   4. increased or decreased psychomotor activity
C. Disorientation and impaired memory (if possible to test).
D. Clinical features developing over a short period of time (usually hours or days) and tending to fluctuate during the course of a day.
E. Evidence, from the history, physical examination or laboratory tests of a specific organic factor judged to be etiologically related to the disturbance.

In 1987 the DSM-III-R was published as a revision of the DSM-III. DSM-III-R criteria for delirium (APA 1987) are:
A. Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverates answer to a previous question).
B. Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech.
C. At least two of the following:
   1. reduced level of consciousness, e.g., difficulty in keeping awake during examination
   2. perceptual disturbances: misinterpretations, illusions, or hallucinations
   3. disturbance in sleep-wake cycle with insomnia or daytime sleepiness
   4. increased or decreased psychomotor activity
   5. disorientation to time, place, or person
   6. impaired memory, e.g., inability to learn new material, such as the names of several unrelated objects after five
minutes, or to remember past events, such as the history of the current episode of illness
D. Clinical features developing over a short period of time (usually hours or days) and tending to fluctuate during the course of a day.
E. Either (1) or (2):
   1. evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) that can be etiologically related to the disturbance
   2. in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by a nonorganic mental disorder, e.g., manic episode accounting for agitation and sleep disturbance.

The DSM-III and DSM-III-R criteria for delirium are essentially the same. The difference is an altered hierarchy which makes no difference in substance. When we have applied DSM-III-R criteria on patients previously assessed as acutely confused according to DSM-III, no diagnosis has been changed.
Unfortunately DSM-III and DSM-III-R criteria (E) do not accept psycho-social factors as etiological for delirium. However, in most cases of delirium, there are several contributing risk factors and triggering factors for delirium and therefore it is difficult to distinguish between organic and psychological mechanisms for delirium. A multifactorial approach to delirium is necessary in assessment as well as in treatment. Jolley summarizes the basic mechanisms producing the ACS as one: "in the elderly it is usual for many factors to contribute a little, rather than one factor to contribute the whole" (Jolley 1981). In most cases there are probably psychosocial factors acting as risk factors or contributing triggering factors. This is particularly true of patients with dementia. Regarding ACS as a threshold phenomenon, it is obvious that the demented patient who has reduced cerebral spare capacity can develop ACS from minor strain. We have no instrument to differentiate between the biochemical disturbance in the brain caused by psycho-social factors and those caused by organic/metabolic factors. As the etiology of delirium in most cases is multifactorial we have chosen to use the term Acute Confusional State (ACS) in this study. However, the DSM-III and DSM-III-R criteria for delirium are fulfilled in all aspects in
patients classified as being in an acute confusional state (ACS) in all the papers.

Another problem with the DSM-III and DSM-III-R criteria is that the diagnosis is sometimes technically difficult in a single given situation due to two criteria, namely rapid onset and fluctuating symptoms. The fulfilment of these criteria demands an observation of a fluctuating course or that relatives or caregivers can report a rapid onset and a fluctuating course. In clinical practice, when in doubt, it is necessary to make a provisional ACS diagnosis and immediately assess the patient for potential causes.

**CLINICAL FEATURES**

In ACS the highest integrative functions of the brain, such as perception, processing and retrieval of information are disorganized (Geschwind 1982). This makes the acutely confused patient more or less incapable of thinking and acting in a rational and goal-directed manner (Lipowski 1990).

The essential features of ACS are the reduced ability to maintain the attention paid to external stimuli and to appropriately shift attention to new external stimuli; the disorganized thinking resulting in reduced clarity of speech that appears rambling, fragmentary, disjointed, irrelevant or incoherent. The syndrome also includes a reduced level of consciousness, sensory misinterpretations, disturbances in the sleep-wake cycle and increased or reduced psychomotor activity. The patient is usually disorientated to time, place, situation and/or person. The onset is often rapid and the course fluctuates in a typical manner and the duration is short, at least if the etiologic factor/factors is/are treated (Lipowski 1989, DSM-III, DSM-III-R).

ACS may appear in three clinical variants: 1. a hyperactive variant, characterized by psychomotor over-activity; 2. a hypoactive variant, characterized by reduced psychomotor activity and apathy; 3. a mixed variant which shifts rapidly between hyperactive and hypoactive behaviour (Lipowski 1990). Many studies, old studies in particular, have focused mainly on ACS with an agitated, restless and disturbing symptomatology. The hypoactive, sometimes stuporous type may be misdiagnosed by the clinician and the necessary assessment of its cause is thus not performed.
DIFFERENTIAL DIAGNOSIS

ACS may simulate many types of mental disorders in the elderly. In most cases the differential diagnosis concerns dementia (Lipowski 1982). The two syndromes often coincide which sometimes makes a distinction between them difficult. ACS in a patient not assessed previously makes it impossible to diagnose dementia as the ACS symptoms interfere with the proper assessment of dementia. Both diagnoses are given only when there is a definite history of pre-existing dementia. In most cases the typical rapid onset, fluctuating course, disturbed attention and clouding of consciousness make the ACS diagnosis simple. When there is uncertainty a provisional ACS diagnosis must be made and a consequent assessment of underlying diseases must be performed. In time the proper diagnosis will appear.

In some cases depression with cognitive impairment and psychotic symptoms may also cause diagnostic problems. Schizophrenia, schizophreniform disorders and other acute psychoses may appear with hallucinations, delusions and disordered thinking (Daniel 1985). In an elderly patient with cognitive impairment due to pre-existing diseases these diagnoses can cause diagnostic problems. Table 2 presents the typical symptoms of the syndromes or diseases that can cause diagnostic problems, constructed and modified after the DSM-III-R (APA 1987) and the monograph made by Lipowski (Lipowski 1990).
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ACS</th>
<th>DEMENTIA</th>
<th>DEPRESSION</th>
<th>ACUTE FUNCTIONAL PSYCHOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial onset</td>
<td>&gt;60</td>
<td>&gt;60</td>
<td>All ages</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Onset</td>
<td>Minutes-hours</td>
<td>Months</td>
<td>Weeks</td>
<td>Days-Weeks</td>
</tr>
<tr>
<td>Course</td>
<td>Fluctuating</td>
<td>Stable</td>
<td>Fluctuating</td>
<td>Stable</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours-weeks</td>
<td>Months-years</td>
<td>Weeks-months</td>
<td>Weeks-months</td>
</tr>
<tr>
<td>Consciousness</td>
<td>Reduced</td>
<td>Clear</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td>Emotions</td>
<td>Fear, agony</td>
<td>Indifferent</td>
<td>Discomfort</td>
<td>Various depending upon type</td>
</tr>
<tr>
<td>Awareness</td>
<td>Fluctuating</td>
<td>Normal</td>
<td>Normal</td>
<td>May be disordered</td>
</tr>
<tr>
<td>Alertness</td>
<td>Fluctuating</td>
<td>Normal</td>
<td>Usually normal</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Attention</td>
<td>Globally disordered</td>
<td>Usually normal</td>
<td>Usually normal</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Cognition</td>
<td>Globally disordered</td>
<td>Normally</td>
<td>Normal or fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td>Orientation</td>
<td>Impaired fluctuations</td>
<td>Impaired</td>
<td>Usually</td>
<td>Normal</td>
</tr>
<tr>
<td>Memory</td>
<td>Impaired</td>
<td>Impaired</td>
<td>May be</td>
<td>May be</td>
</tr>
<tr>
<td>Thinking</td>
<td>Disorganized</td>
<td>Impaired abstraction</td>
<td>Normal</td>
<td>Often disordered</td>
</tr>
<tr>
<td>Perception</td>
<td>Distorted</td>
<td>Often normal</td>
<td>Normal</td>
<td>Sometimes disturbed</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Visual and/or auditory</td>
<td>Absent</td>
<td>Absent</td>
<td>Predominantly auditory</td>
</tr>
<tr>
<td>Delusions</td>
<td>Fleeting un-systematized</td>
<td>Absent</td>
<td>Absent</td>
<td>Sustained and systematized</td>
</tr>
<tr>
<td>Psychomotor activity</td>
<td>Increased decreased shifting</td>
<td>Normal</td>
<td>Normal or slightly decreased</td>
<td>Varies depending on type of psychosis</td>
</tr>
<tr>
<td>Speech</td>
<td>Incoherent</td>
<td>Dysphasia</td>
<td>Normal</td>
<td>Normal, slow or rapid</td>
</tr>
<tr>
<td>Sleep-Wake cycle</td>
<td>Disturbed often reversed</td>
<td>Normal or fragmented</td>
<td>Sometimes disturbed</td>
<td>Sometimes disturbed</td>
</tr>
<tr>
<td>Involuntary movements</td>
<td>Asterixis or tremor</td>
<td>Often absent</td>
<td>Absent</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Physical illness</td>
<td>Present</td>
<td>Usually</td>
<td>Usually</td>
<td>Absent</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Often present</td>
<td>Usually absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Awareness of symptoms</td>
<td>Unaware</td>
<td>Unaware or conceals &quot;Near miss&quot;</td>
<td>Highlights disabilities</td>
<td>Usually unaware</td>
</tr>
<tr>
<td>Answers</td>
<td>Wrong</td>
<td>and conceals</td>
<td>I don’t know</td>
<td>Usually correct</td>
</tr>
<tr>
<td>EEG</td>
<td>Abnormal</td>
<td>Normal in early phase</td>
<td>Normal</td>
<td>Usually normal</td>
</tr>
</tbody>
</table>
Different diagnostic ACS criteria and various patient populations in clinical studies have resulted in incidence and prevalence rates from 0.7 - 80% (Liston 1982, MacDonald 1989, Lipowski 1990). In older studies of cognitive impairment in the elderly, few authors have made any distinction between dementia and ACS. Even fewer authors describe ACS in patients with dementia. The results of recent studies on the frequency of ACS in different patient groups are summarized in Table 3.

### TABLE 3. FREQUENCY OF ACS IN RECENT STUDIES ON ELDERLY PATIENTS.

<table>
<thead>
<tr>
<th>POPULATION Setting</th>
<th>Age</th>
<th>Pat. (N)</th>
<th>ACS (%)</th>
<th>Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>General hospital medicine</td>
<td>≥60</td>
<td>99</td>
<td>56</td>
<td>Chisholm</td>
<td>1982</td>
</tr>
<tr>
<td>General hospital medicine</td>
<td>≥70</td>
<td>173</td>
<td>30</td>
<td>Gillick</td>
<td>1982</td>
</tr>
<tr>
<td>General hospital medicine</td>
<td>≥65</td>
<td>282</td>
<td>21</td>
<td>Erkinjuntti</td>
<td>1987**</td>
</tr>
<tr>
<td>General hospital medicine</td>
<td>All ages</td>
<td>133</td>
<td>15</td>
<td>Thomas</td>
<td>1988**</td>
</tr>
<tr>
<td>Medical intensive care</td>
<td>≥60</td>
<td>71</td>
<td>38*</td>
<td>Foreman</td>
<td>1989**</td>
</tr>
<tr>
<td>Nonintensive medical care</td>
<td>≥65</td>
<td>80</td>
<td>30</td>
<td>Rockwood</td>
<td>1989**</td>
</tr>
<tr>
<td>General hospital medicine</td>
<td>≥75</td>
<td>146</td>
<td>40</td>
<td>Bucht</td>
<td>1990**</td>
</tr>
<tr>
<td>Nursing home</td>
<td>≥75</td>
<td>203</td>
<td>65</td>
<td>Bucht</td>
<td>1990**</td>
</tr>
<tr>
<td>Home for the aged</td>
<td>≥75</td>
<td>196</td>
<td>25</td>
<td>Bucht</td>
<td>1990**</td>
</tr>
<tr>
<td>Home care</td>
<td>≥75</td>
<td>172</td>
<td>25</td>
<td>Bucht</td>
<td>1990**</td>
</tr>
<tr>
<td>General medicine</td>
<td>≥70</td>
<td>235</td>
<td>20*</td>
<td>Johnson</td>
<td>1990**</td>
</tr>
<tr>
<td>General medicine</td>
<td>≥70</td>
<td>229</td>
<td>22*</td>
<td>Francis</td>
<td>1990**</td>
</tr>
</tbody>
</table>

* Patients with dementia excluded

** ACS diagnosed according to DSM-III or DSM-III-R criteria
POSTOPERATIVE ACS

Postoperative or postanesthetic confusion has been given a lot of interest in the literature. As early as in 1887 George Savage carefully described 'postoperative insanity' based on his clinical experience and proposed possible etiologies (Savage 1887). A farsighted review of post-operative psychoses, risk factors and organic features such as 'endocrine upsets, changes in chemistry and nutritional disturbances' was written in 1938 by Milton Abeles (Abeles 1938).

Postoperative confusion has been reported to occur after different types of surgery such as cataract surgery (Summers 1979, Burrows 1985), prostatectomy (Ghoneim 1988), hip-fracture surgery (Morse 1771, Williams 1979), pelvic floor repair (Chung 1987) and cardiovascular surgery (Morse 1969, Morse 1971). For review on postoperative confusion see Whitaker 1989. In Table 4 the frequency of postoperative ACS in recent studies are summarized.

Postanesthetic confusion has been associated with different types of premedication and/or anesthetic agents such as alcohol, belladonna, fentanyl and halothane (Savage 1887, Simpson 1976).

TABLE 4. FREQUENCY OF POSTOPERATIVE ACS IN RECENT STUDIES

<table>
<thead>
<tr>
<th>Patient sample</th>
<th>Age</th>
<th>Pat. (N)</th>
<th>ACS (%)</th>
<th>Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective hipsurgery</td>
<td>All ages</td>
<td>60</td>
<td>12*</td>
<td>Hole</td>
<td>1980</td>
</tr>
<tr>
<td>General surgery</td>
<td>≥65</td>
<td>100</td>
<td>14</td>
<td>Millar</td>
<td>1981</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>≥60</td>
<td>170</td>
<td>52*</td>
<td>Williams</td>
<td>1985a</td>
</tr>
<tr>
<td>Hip-fracture (Intervention)</td>
<td>≥60</td>
<td>57</td>
<td>44*</td>
<td>Williams</td>
<td>1985b</td>
</tr>
<tr>
<td>General surgery</td>
<td>All ages</td>
<td>92</td>
<td>42*</td>
<td>Dieckelmann</td>
<td>1989</td>
</tr>
<tr>
<td>Elective orthopaedic surgery</td>
<td>≥60</td>
<td>46</td>
<td>26*</td>
<td>Rogers</td>
<td>1989**</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>≥60</td>
<td>35</td>
<td>43</td>
<td>Brännström</td>
<td>1989**</td>
</tr>
<tr>
<td>Hip-fracture (6 months survivors)</td>
<td>≥65</td>
<td>536</td>
<td>23</td>
<td>Magaziner</td>
<td>1990</td>
</tr>
</tbody>
</table>

* Patients with dementia excluded
** ACS diagnosed according to DSM-III or DSM-III-R criteria
ACS IN STROKE PATIENTS

ACS in stroke patients has never been studied prospectively in a representative sample of stroke patients. There are a few retrospective studies (de Reuck 1982, Dunne 1986), several studies on selected patients with different types and localisation of their strokes (Mullally 1982, Schmidley 1984, Mori 1987, Garcia-Albea 1989) and several case reports (Horenstein 1967, Medina 1974, Mesulam 1976, Medina 1977, Levine 1982, Graff-Radford 1984, Santamaria 1984, Price 1985, Balter 1986, Bogousslavsky 1988, Devinsky 1988). It is difficult to apply DSM-III or DSM-III-R criteria on retrospective study samples and a retrospective approach is likely to lead to an underestimation of ACS. In one retrospective study, using DSM-III criteria for ACS, 150 of the 450 (33%) patients with cerebral infarctions were disorientated or "confused" upon presentation, and 112 of the 211 (53%) with spontaneous brain hemorrhage were disorientated or "confused" (Dunne 1986). In a study of patients with right middle cerebral artery infarction, 25 out of 41 (61%) were judged to be acutely confused (Mori 1987). ACS has been reported to be more common in patients with right hemisphere lesions than in patients with left hemisphere brain lesions (Dunne 1986). In different case reports, ACS has been associated with cerebrovascular lesions affecting a large variety of specific locations such as right middle cerebral artery infarctions, left posterior infarctions, medial temporo-occipital infarction, after infarctions of the hippocampal region, the fusiform and lingual gyri or in the thalamus (Horenstein 1967, Medina 1974, Medina 1977, Mesulam 1976, Mullally 1982, de Reuck 1982, Levine 1982, Schmidley 1984, Graff-Radford 1984, Santamaria 1984, Price 1985, Dunne 1986, Mori 1987, Bogousslavsky 1988, Devinsky 1988, Garcia-Albea 1989). ACS has also been described in patients with multiple small cerebral infarctions (Balter 1986). However, the definition of ACS differs between various studies, and only one retrospective study used the DSM-III criteria (Dunne 1986).

PREDISPOSING ACS FACTORS

A multifactorial approach considering the patient’s previous diagnoses, medication and psycho-social capacity is necessary in the assessment of ACS (Arie 1981). There are often one or more
preventable or treatable risk factors or triggering factors in elderly patients (Jolley 1981, Lipowski 1990). The literature contains an overwhelming number of case reports but few systematic analyses of risk factors and potential triggering mechanisms for ACS. The following is a summary of factors reported to increase the risk for ACS:


Gender: Most studies report a similar ACS frequency in men and women (Judge 1977, Lipowski 1990). However, in three studies a higher ACS frequency has been reported among men (Simon 1963, Kay 1972, Seymour 1983).


Previous stroke: Stroke has also been reported to be a predisposing and triggering factor for ACS (Flint 1956, Lipowski 1990).

Cardiac disease: Several cardiac diseases are reported to predispose to ACS (Wolff 1935, Flint 1956, Morse 1969a, Morse 1969b, Varsamis 1978).

Depression increases the patient’s vulnerability (Gold 1988a, Gold 1988b) and increases the risk for ACS (Wolff 1935, Morse 1969a, Morse 1969b, Varsamis 1978). Other preoperative psychological states, e.g. anxiety, has also been reported to predict the postoperative psychological course (Abraham 1961, Varsamis 1978). Impaired hearing is an important ACS risk factor according to several studies (Hodkinson 1973, Judge 1977).

Impaired vision has also been reported to be an ACS risk factor (Hodkinson 1973, Judge 1977, Lipowski 1990).

Drugs: Treatment with many different groups of drugs, drugs with anticholinergic effects in particular, has been reported to increase

**ANESTHETIC TECHNIQUE AND HIP-SURGERY**

The incidence of hip-fracture is rapidly increasing in all the western world (Jensen 1980b, Nickens 1983). Old age is an important risk factor for hip fractures but explains only a minor part of the increase (Zetterberg 1982). Anesthesists would like to select an anesthetic technique resulting in minimal postoperative morbidity for the old and vulnerable patient with a fracture of the femoral neck (Covert 1989). General anesthesia is reported, in older studies, to cause more complications in elderly patients than regional anesthesia (McLaren 1978). A general opinion in the literature before 1980 was that general anesthesia was complicated with more adverse cerebral effects than regional anesthesia (Gauthier 1963). Gauthier on the other hand reported a similar morbidity and mortality rate after spinal anesthesia and general anesthesia. In Table 5 some randomized studies on hip surgery are summarized. Neither general nor regional anesthesia are convincingly supported by the results regarding mortality or postoperative cognitive functioning.
### TABLE 5. GENERAL ANESTHESIA (GA) VERSUS REGIONAL ANESTHESIA (RA).

<table>
<thead>
<tr>
<th>Patient sample</th>
<th>N</th>
<th>GA or RA better for postop cognition</th>
<th>Difference in mortality</th>
<th>Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip-fracture</td>
<td>55</td>
<td>-</td>
<td>GA&gt;RA</td>
<td>McLaren</td>
<td>1978</td>
</tr>
<tr>
<td>Hip-replacem.</td>
<td>60</td>
<td>RA better than GA</td>
<td>No</td>
<td>Hole</td>
<td>1980</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>100</td>
<td>-</td>
<td>No</td>
<td>McKenzie</td>
<td>1980</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>60</td>
<td>-</td>
<td>No</td>
<td>White</td>
<td>1980</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>132</td>
<td>-</td>
<td>No</td>
<td>Davis</td>
<td>1981</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>169</td>
<td>-</td>
<td>No</td>
<td>Wikström</td>
<td>1982</td>
</tr>
<tr>
<td>Hip-replacem.</td>
<td>30</td>
<td>GA=RA</td>
<td>No</td>
<td>Rîls</td>
<td>1983</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>150</td>
<td>-</td>
<td>GA&gt;RA</td>
<td>McKenzie</td>
<td>1984</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>40</td>
<td>GA=RA</td>
<td>No</td>
<td>Bigler</td>
<td>1985</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>578</td>
<td>-</td>
<td>No</td>
<td>Valentin</td>
<td>1986</td>
</tr>
<tr>
<td>Hip-fracture</td>
<td>538</td>
<td>-</td>
<td>No</td>
<td>Davis</td>
<td>1987</td>
</tr>
<tr>
<td>Hip-replacem.</td>
<td>105</td>
<td>GA=RA</td>
<td>No</td>
<td>Ghoneim</td>
<td>1988</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip or knee replacem.</td>
<td>146</td>
<td>GA=RA</td>
<td>No</td>
<td>Jones</td>
<td>1990</td>
</tr>
</tbody>
</table>

- = not assessed

### ACS AND CLINICAL OUTCOME

The mortality rate for patients developing ACS has been reported to be higher compared with that of patients who do not develop ACS (Bedford 1959, Roth 1959, Simon 1963, Rabins 1982, Liston 1982, Weddington 1982, Trzepacz 1985, Rockwood 1990, Francis 1990). ACS is probably underestimated as a risk factor contributing to death in many groups of patients (Weddington 1982).

In several studies prolonged ward-stay has been reported for patients who develop ACS (Glass 1977, Sheppeard 1980, Lamont 1983, Thomas 1988, Levkoff 1988, Brännström 1989, Rockwood 1990, Brännström 1991). The prolonged ward-stay is often associated with
many complications which are caused at least partly by the ACS. ACS has also been reported to be associated with poorer rehabilitation result (Magaziner 1990). The acutely confused patient is reported to be at the risk of being hospitalized as staff do not expect him to be able to manage on his own. This could contribute to prolonged dependency upon caregivers also after the ACS has been reversed (Brännström 1991). It has been shown that elderly patients’ mental impairment influences the nurse-patient interaction negatively. In confused patients the psychosocial interaction was particularly poor and the physical care was given priority (Armstrong-Esther 1986).

ACS patients have difficulties in cooperating with staff as they do not understand nor remember instructions. They often exhibit behaviour disturbances and/or act perilously demanding continuous supervision. The ACS-associated complications need to be attended to and often an acutely confused patient is probably incapable of experiencing thirst or hunger and even more incapable of satisfying these needs (Brännström 1989).

**ETIOLOGY AND PATHOGENESIS**

There are two major hypotheses about the pathogenesis and pathophysiology of ACS (Lipowski 1987). The first hypothesis suggests that a reduction in the cerebral metabolism and the consequent reduction in neurotransmitters, especially acetylcholine, contributes to the development of ACS (Blass 1979, Blass 1983). This hypothesis is supported by studies showing that the cerebral acetylcholine synthesis is especially sensitive to hypoxia and hypoglycemia (Gibson 1981, Hirsch 1984). A close link between ACS and anticholinergic activity has been reported by several authors (Itälä 1966, Tune 1981, Mondimore 1983, Miller 1988, Thienhaus 1990). ACS caused by anticholinergic medication can be reversed by means of physostigmine, a cholineesterase inhibitor (Green 1971, Aquilonius 1978). The second hypothesis suggests that ACS is a reaction to stress mediated by elevated plasma cortisol and its effects on the brain (Kraal 1962, Kraal 1975, Carpenter 1982, McEwen 1987, McEwen 1988). High cortisol levels have been suggested to affect the neuron function of the central nervous system (Sapolsky 1985, de Kloet 1987) and the cognitive function as a result of this (Micco 1980, Reus 1987, Issa 1990, Wolkowitz 1990). This may be
most pronounced in the hippocampus, where the number of glucocorticoid receptors is particularly high and thus compromising the cognitive function (Micco 1980, Gilad 1987, Joels 1989, Armanini 1990, Sapolsky 1990a). Glucocorticoids endanger hippocampal neurons probably by impairing their energy metabolism (Sapolsky 1986a). This is why glucocorticoids probably increase the neuronal vulnerability to hypoxia, ischemia and hypoglycemia. Supplementing with 'brain fuels' in animal models reduces the toxicity of glucocorticoids in the hippocampus (Sapolsky 1986a). It has also been reported that cortisol modulates cholinergic receptors in the subcortical limbic forebrain (von Euler 1990).

In several studies, ACS has been found to occur after hippocampal stroke (Medina 1974, Graff-Radford 1984, Santamaria 1984, Bogousslavsky 1988).

Acetylcholine is an important direct and indirect HPA-axis regulator (Gilad 1987, Calogero 1988). A close connection between stress, hippocampal cholinergic system, cognitive function and glucocorticoids has been demonstrated in animal models (Gilad 1987, Lai 1990). High cortisol levels have been reported to be associated with postoperative ACS 2-4 days after elective surgery (McIntosh 1985).

In most cases of ACS one or both of these mechanisms are involved in the development of the cognitive disturbances. Other mechanisms interfering with cerebral metabolism and transmitter activity may also be of importance such as the factors interfering with glutamate metabolism (Sapolsky 1990a). Protection of the cerebral oxidative metabolism and a reduction in stress mediated by high cortisol levels thus seem to be the most important possibilities in ACS prevention and treatment.

In Table 6, some suggested and/or documented etiological factors are presented, structured according to the two main hypotheses of ACS pathophysiology. Psycho-social factors, which have been suggested to contribute to or cause ACS, could act through the stress-cortisol system. Some psycho-social factors, which have been suggested to be risk factors and/or ACS triggering factors are presented in Table 6 under II B.
TABLE 6. SUGGESTED AND/OR DOCUMENTED ACS CAUSES IN THE LITERATURE. THE ACS CAUSES ARE STRUCTURED ACCORDING TO THE TWO MAIN HYPOTHESES OF ACS PATHOPHYSIOLOGY.

I. ACS MEDIATED MAINLY BY DISTURBANCES IN THE CHOLINERGIC FUNCTION OF THE BRAIN. (The acetylcholine synthesis is especially sensitive to disturbances in the brain energy metabolism, e.g. hypoxia, hypoglycemia. Disturbances in the cholinergic system is closely associated with cognitive disturbances).

<table>
<thead>
<tr>
<th>A. DISTURBED CEREBRAL OXYGENATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary diseases, e.g. pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td>2. Cardiac diseases, e.g. congestive heart diseases, pulmonary oedema, cardiac arrhythmia, myocardial infarction</td>
</tr>
<tr>
<td>3. Anaemia</td>
</tr>
<tr>
<td>4. Hypoperfusion, e.g. peroperative hypotension, hypovolemia</td>
</tr>
<tr>
<td>(bleeding, dehydration), ortostatism, aortic stenosis, ischemic brain disease, vasculitis, hyperventilation syndrome, disseminated intravascular coagulation, increased blood viscosity (e.g. polycytemia)</td>
</tr>
<tr>
<td>5. Carbon monoxide poisoning</td>
</tr>
<tr>
<td>6. Methemoglobinemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. DEPRIVATION OF ENERGY OR NUTRITIVE SUBSTANCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypoglycemia, e.g. insulin-coma, spontaneous (i.e.insulinoma, liver disease, starvation, cortisol deficiency), drug-induced (i.e.oral antidiabetics, haloperidol)</td>
</tr>
<tr>
<td>2. Cofactor deficiency, e.g. thiamine, niacine, pyridoxine, vitamin B12, vitamin E, vitamin C, folate</td>
</tr>
<tr>
<td>3. Hypoproteinemi</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. TOXIC DISTURBANCES IN THE CHOLINERGIC SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Drugs, e.g. neuroleptics, tricyclic antidepressants, cortisone, antihistamines, other drugs with anticholinergic effects</td>
</tr>
</tbody>
</table>

II. ACS AS A REACTION TO STRESS PROBABLY MEDIATED MAINLY BY HYPERCORTISOLISM. (Cholinergic neurons in hippocampus might be especially sensitive to hypercortisolism and glucocorticoids endanger hippocampal neurons by impairing their energy metabolism. Glucocorticoids probably thereby increase the damage to cholinergic neurons in the hippocampus induced by hypoxia or ischemia for instance).

<table>
<thead>
<tr>
<th>A. ORGANIC FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trauma, e.g. fractures, burns, contusions</td>
</tr>
<tr>
<td>2. Acute medical diseases, e.g. myocardial infarctions, congestive heart failure, acute stroke, deep vein thrombosis, pulmonary embolism</td>
</tr>
<tr>
<td>3. Acute surgical diseases, e.g. pancreatittis, cholecystitus, gastric ulcer</td>
</tr>
<tr>
<td>4. Diseases with hypercortisolism, e.g. Cushing’s syndrome</td>
</tr>
<tr>
<td>5. Urinary retention</td>
</tr>
<tr>
<td>6. Allergic reactions</td>
</tr>
<tr>
<td>7. Fecal impaction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. TREATMENT WITH CORTICOSTEROIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. PSYCHOSOCIAL FACTORS</td>
</tr>
<tr>
<td>1. Severe emotional stress, e.g. fatigue, pain, grief, anxiety, relocation</td>
</tr>
<tr>
<td>2. Secondary to psychiatric disorders, e.g. depression, mania, cycloid psychoses</td>
</tr>
<tr>
<td>3. Immobilization</td>
</tr>
<tr>
<td>4. Sensory deprivation, e.g. blindness, deafness</td>
</tr>
<tr>
<td>5. Sensory overload e.g. noise</td>
</tr>
<tr>
<td>6. Sleep deprivaion</td>
</tr>
</tbody>
</table>
III. OTHER METABOLIC OR TOXIC ACS-MECHANISMS DISTURBING THE BRAIN METABOLISM IN A MORE GENERAL WAY (Causes probably partly acting through previous mechanisms, hypoxia, hypoperfusion and/or otherwise disturbed transmitter metabolism partly caused by stressmediated hypercortisolism).

A. FEBRILE STATES
   1. Urinary infections
   2. Pneumonia
   3. Septical infections

B. HYPOTHERMIA
C. ENDOCRINE DISORDERS
   1. Pituitary disorders
   2. Hyper/hypothyreoidism
   3. Hyper/hypoparathyreoidism
   4. Addison's disease
   5. Pheochromocytoma

D. WATER AND ELECTROLYTE DISTURBANCES
   Different osmolality and electrolyte disturbances can cause ACS, e.g. hypo-osmolality (water intoxication), hyper-osmolality (nonketotic diabetic coma), hypo- and hypercalcaemia, hypo- and hyperkalemia, hypo- and hypernatremia, hypo- and hypermagnesemia, hypo- and hyperchloremia, hypo- and hyperphosphatemia

E. ACID-BASE DISTURBANCES
   1. Alkalosis/Acidosis

F. KIDNEY DISEASES
   1. Uraemia

G. LIVER DISEASES
   1. Liver precoma
   2. Porphyria

H. DRUGS
   Most drugs in toxic or therapeutic doses can cause ACS, e.g. penicillin, anticonvulsants, cardiac glycosides, sedative drugs, salicylates, analgetics, L-dopa, amantadine, selegiline, bromokriptine, cimetidine, timolol, anti-tumour agents, barbiturates

I. ALCOHOL
   1. Intoxication
   2. Withdrawal

J. POISONS
   Different poisons can cause ACS, e.g. paraldehyd, methyl alcohol, ethylene glycol, heavy metals, cyanide, bromid, insecticides

IV. OTHER CENTRAL NERVOUS DISORDERS (Causes probably partly acting through previous mechanisms, hypoxia, hypoperfusion and/or otherwise disturbed transmitter metabolism partly caused by stressmediated hypercortisolism).

A. HEAD TRAUMA
   1. Concussion
   2. Subdural hematoma

B. EPILEPSY
   1. Post-ictal state
   2. Seizure disorders

C. INFECTIONS
   Most cerebral infections can cause ACS, e.g. meningitis, encephalitis, neurosyphilis, borreliosis, cerebral abscess, toxoplasmosis, malaria

D. BRAIN TUMOURS
E. MULTIPLE SCLEROSIS
HIP-FRACTURE AND STROKE


Femoral neck fractures predominantly strike the old woman. As mentioned previously the incidence of hip fractures is rapidly increasing in all the western world (Zetterberg 1982, Jensen 1980b, Jensen 1980c, Nickens 1983, Falch 1985). In four of the papers ACS was studied in patients operated on for femoral neck fractures which is one of the most common operations among old people. The operation is usually rapid, and standardized and peroperative bleeding is rare. When studying the postoperative consequences of anesthetic technique it is important that the surgical procedure remains relatively constant.

In the United States alone there are 1.7 million stroke survivors at any given time (Grotta 1988). Patients with stroke are increasing in number in Sweden and represent the patient group consuming the highest percentage of hospital care (MFR 1986). Stroke patients like hip fracture patients have a high mean age but stroke is somewhat more common among men. The organisation of stroke care into non-intensive stroke units has improved the care and thereby the prognosis for stroke patients (Strand 1985, Eriksson 1987). The stroke unit in Medical Department 1 in Umeå was opened in 1978 and has been proved to be a good basis for research and for the development of stroke care (Strand 1985, Eriksson 1987).
AIMS OF THE STUDY

The aims of this study were:
- the elucidation of ACS in patients with femoral neck fractures and patients with acute stroke with regard to frequency, predictors, possible pathogenetic mechanisms, associated complications, assessments and documentary routines and the clinical outcome for the patients.
- the development and evaluation of an intervention program to prevent and treat ACS in patients operated on for femoral neck fractures.
PATIENTS

Paper I: One hundred and eleven consecutive patients 65 years old or older, with femoral neck fractures admitted to the Orthopaedic department of Umeå University Hospital between March 1983 and June 1984.

Paper II: Fifty-seven patients, lucid at admission, 65 years old or older, with femoral neck fractures, that could be randomized to receive either general or regional anesthesia and admitted to the Orthopaedic department of Umeå University Hospital between March 1983 and November 1984. Forty-five of the fifty-seven patients were also included in Paper I.

Paper III: One hundred and forty-five consecutive stroke patients of all ages admitted to the stroke unit of the department of Internal Medicine of Umeå University Hospital between April 1983 and December 1984.

Paper IV: Eighty-three selected stroke patients of all ages with supratentorial ischemic stroke admitted to the stroke unit of the department of Internal Medicine of Umeå University Hospital between June 1983 and March 1986.

Paper V: All patients in Papers I (N=111) and II (N=57) and two retrospective patient samples comparable with that of Paper I. The first retrospective control sample included: all patients 65 years old or older, irrespective of prefracture mental state, admitted to the Orthopaedic department of Umeå University Hospital during 1980 (N=66). The second retrospective control sample, with the same inclusion criteria was admitted to the department of General Surgery of Piteå County Hospital during 1980 and 1981 (N=68).

Paper VI: One hundred and three consecutive patients, 65 years old or older, with femoral neck fractures admitted to the Orthopaedic department of Umeå University Hospital between December 1986 and January 1988.
METHODS

ACS was diagnosed according to the DSM-III or DSM-III-R criteria for delirium (APA 1980, APA 1987), after clinical assessments including: 1. Pre-fracture/pre-stroke history checked through medical records and by means of interviews with the patients’ families or care-givers. 2. Behaviour on the ward assessed by direct patient observations and interviews with the staff. 3. Orientation, suspiciousness, emotions, depression, speech, delusions and hallucinations, recognition, motor function, sociability and changes in the patients’ mental function assessed and registered by means of the Organic Brain Syndrome Scale (Gustafson 1985, Hallberg 1989). 4. A Mini-Mental State Examination (MMSE) was made on admission and then once a week during the hospital stay for all patients included in the studies on stroke patients (Folstein 1975). MMSE was performed when considered necessary for the ACS diagnosis in the patients with femoral neck fractures.

All patients in this study were observed several times per day and assessments including tests and interviews were carried out on the first day of admission and then at several times during the patients’ hospital stay. All tests, interviews with patients, relatives and staff were carried out by the same physician (YG) in the studies on stroke patients and by three different raters in the studies on patients with femoral neck fractures. Before the start of the studies the three raters assessed ten patients to test the interrater reliability of the registration of the items included in the OBS-scale. The tests of these ratings were analyzed, and the agreement between the raters was above 90% in all ratings. While these studies were performed two of the raters collaborated in two other studies (Brännström 1989, Brännström 1991) using the same assessment routines. In both studies the agreement on the ACS diagnosis according to DSM-III, was above 95% between them.

In Paper I, all patients 65 years old or older, irrespective of prefracture mental state, operated on for femoral neck fractures with various anesthetic techniques, were studied regarding ACS frequency. In Paper II, patients lucid on admission were randomized to receive either general or regional anesthesia.
In Paper III the same methods, as in Paper I were used for stroke patients.
In Paper IV a selected sample of patients with supratentorial ischemic stroke was assessed with the dexamethasone suppression test (DST) and compared with a healthy control population.
In Paper V data from the review of medical records were compared with clinical studies from the care occasions, presented in Papers I and II. To find out whether the on-going clinical studies had influenced the physicians' and nurses' ACS documentation in their case-notes, two other retrospective case-note samples on the corresponding patient groups were studied.
The medical records were studied in order to find the noted ACS frequency and treatment, notes on its consequences and the nursing activities associated with these notes. In the study of the medical records, ACS criteria were explicit statements on ACS and/or documented symptoms or behaviour indicating ACS. The analysis of the records and the classification of patients were made independently by two of the authors of Paper V (BB, YG). There was 89% exact agreement between the authors regarding the diagnoses made from the case-note analyses. Every case of disagreement was subject to diagnostic discussions ending up in full agreement on the ACS and the dementia diagnoses.
The intervention program (Paper VI), was based on the results of our previous studies (Papers I and II). The intervention aimed at preventing postoperative ACS by protecting the patients cerebral oxidative metabolism which was achieved by the prevention of hypoxia and hypotension/hypo-perfusion. Patients who developed postoperative ACS were assessed and treated for associated complications. The intervention study could not be performed as a randomized study since the results of our previous studies had initiated changes in the treatment routines for these patients. It was also regarded as unethical, considering our previous results, not to prevent severe hypoxemia and peroperative hypotension. The results of the intervention were therefore compared with the outcome of the patients in Paper I.
The Systat™ statistical package was used for calculations (Wilkinson 1987, Wilkinson 1990). The chi-square test, Yates’ corrected chi-square test, Student’s t-test, Mann Whitney U-test, Pearson correlation coefficients, the odds ratios and 95% confidence intervals for odds ratios were used when relevant as indicated in the text (Feinstein 1985, Sandercock 1989). The Bonferroni correction was used to adjust for probabilities. To find independent clinical ACS predictors, multiple linear regression analyses were used in Papers I, II and III (Draper 1966). In the multiple linear regression models the F-ratio and the P-value were used to demonstrate the statistical significance of the model. The squared multiple R was used to illustrate the explanatory degree of the model. The predictors of the geriatric stroke rehabilitation in Paper III were calculated by the use of orthogonal scores from a factor analysis representing clinical variables. In Paper IV a logistic regression model (Dobson 1982) was used in the SAS program package. Also in Paper VI logistic regression models were used to find independent ACS predictors in the two patient samples but the calculations were made in the SPSS program package. In this thesis logistic regression models are also presented for the prediction models presented in Paper I and III. A logistic regression model is preferable as a multiple linear regression model may have some unwanted properties such as the risk of the predictions of new observations ending up outside the range [0,1]. An iterative maximum likelihood procedure was used in the SAS and SPSS program packages where the results obtained are interpreted from the exact distribution (binomial) of the response variable (ACS). The choice of different program packages for the logistic regression analyses was made for technical and financial reasons. A P-value of less than 0.05 was regarded as statistically significant.
RESULTS

ACS FREQUENCY

A summary of the ACS frequency in different papers are presented in Tables 7 and 8.

<table>
<thead>
<tr>
<th>Paper</th>
<th>N</th>
<th>Mean Age (range)</th>
<th>Male/Female</th>
<th>Dementia (%)</th>
<th>ACS (%)</th>
<th>ACS&gt;7 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. All patients</td>
<td>111</td>
<td>79 (65-96)</td>
<td>28/83</td>
<td>15</td>
<td>61</td>
<td>40</td>
</tr>
<tr>
<td>II. Patients</td>
<td>57</td>
<td>78 (65-95)</td>
<td>11/46</td>
<td>0</td>
<td>44</td>
<td>28</td>
</tr>
<tr>
<td>Retrospect. of paper I</td>
<td>111</td>
<td>79 (65-96)</td>
<td>28/83</td>
<td>-</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>Retrospect. of paper II</td>
<td>57</td>
<td>78 (65-95)</td>
<td>11/46</td>
<td>-</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Retrospect. control 1</td>
<td>66</td>
<td>79 (65-96)</td>
<td>22/44</td>
<td>-</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>Retrospect. control 2</td>
<td>68</td>
<td>78 (66-95)</td>
<td>24/44</td>
<td>-</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>VI. Intervention</td>
<td>103</td>
<td>80 (65-102)</td>
<td>28/75</td>
<td>22</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospect. of paper II</td>
<td>57</td>
<td>78 (65-95)</td>
<td>11/46</td>
<td>-</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Retrospect. control 1</td>
<td>66</td>
<td>79 (65-96)</td>
<td>22/44</td>
<td>-</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>Retrospect. control 2</td>
<td>68</td>
<td>78 (66-95)</td>
<td>24/44</td>
<td>-</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>VI. Intervention</td>
<td>103</td>
<td>80 (65-102)</td>
<td>28/75</td>
<td>22</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lucid at admission</td>
<td>66</td>
<td>78 (65-94)</td>
<td>14/52</td>
<td>0</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

- = Not assessed
TABLE 8. ACS FREQUENCY IN THE STUDIED SAMPLES OF STROKE PATIENTS.

<table>
<thead>
<tr>
<th>Paper</th>
<th>N</th>
<th>Mean Age (range)</th>
<th>Male/ Female</th>
<th>Dementia (%)</th>
<th>ACS (%)</th>
<th>ACS&gt;7 days(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III. All stroke patients</td>
<td>145</td>
<td>73 (40-101)</td>
<td>90/55</td>
<td>6</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>IV. Selected stroke patients</td>
<td>83</td>
<td>75 (44-89)</td>
<td>52/31</td>
<td>2</td>
<td>42</td>
<td>-</td>
</tr>
</tbody>
</table>

ACS was common both in the representative prospective sample of patients with femoral neck fractures (61%) and in that of stroke patients (48%). The majority of patients developing ACS in these two samples were acutely confused for more than one week. The ACS frequency of the intervention study (VI) was lower than that of the control study (I) (61% vs 48%, p<0.05). When comparing patients lucid at admission in Paper VI with the corresponding patient sample in Paper II, there were fewer patients in the intervention study who were acutely confused for more than seven days (9% in the intervention study compared with 28% in the control study, p<0.01).
PREDISPOSING ACS FACTORS

ACS predictors in the non-intervention hip-fracture patient sample in Paper I are shown in Table 9.

TABLE 9. ACS PREDICTORS IN PATIENTS WITH FEMORAL NECK FRACTURES. Results of logistic regression model in Paper I. Dependent variable: postoperative acute confusional state (ACS) in logistic transformation (N=111).

<table>
<thead>
<tr>
<th>Independent variables:</th>
<th>Wald</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.13</td>
<td>0.004</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Drugs with anticholinergic effects*</td>
<td>2.09</td>
<td>0.15</td>
</tr>
<tr>
<td>Depression</td>
<td>2.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Cerebrovascular diseases**</td>
<td>1.92</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac diseases***</td>
<td>0.86</td>
<td>0.35</td>
</tr>
<tr>
<td>Sex</td>
<td>0.001</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Chi-Square for the model: P-value<0.0001. Connection between predicted probabilities and responses observed: Concordant: 74%
* Drugs with anticholinergic effects include neuroleptics, antidepressants and other drugs with anticholinergic effects.
** Cerebrovascular diseases include cerebral infarction, cerebral hemorrhage and TIA
*** Cardiac diseases include heart failure, previous myocardial infarction, atrial fibrillation and angina pectoris.

In the logistic regression model (Table 9) of Paper I, old age was the only significant ACS predictor. It should however be observed that 16/17 (94%) patients with dementia, 15/17 (88%) with depression, 15/18 (83%) with previous stroke and 33/39 (85%) on regular treatment with drugs with anticholinergic effects developed ACS even though these variables did not reach statistical significance in the logistic regression model.
In Paper II, where postoperative ACS in a selected sample of patients was studied, regular treatment with drugs with anticholinergic effects and depression were found to be predictors of postoperative ACS.

ACS predictors in consecutive stroke patients were studied in Paper III and are shown in Table 10.

**TABLE 10. ACS PREDICTORS IN STROKE PATIENTS.**
Results of logistic regression model in Paper III. Dependent variable: Acute confusional state (ACS) in logistic transformation (N=145).

<table>
<thead>
<tr>
<th>Independent variables:</th>
<th>Wald Chi-square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of paresis</td>
<td>21.49</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>5.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Left-sided brain lesion</td>
<td>3.44</td>
<td>0.06</td>
</tr>
<tr>
<td>Previous ACS</td>
<td>3.19</td>
<td>0.07</td>
</tr>
<tr>
<td>Drugs with anticholinergic effects*</td>
<td>3.14</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac diseases**</td>
<td>2.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Sex</td>
<td>0.23</td>
<td>0.64</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.14</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Chi-Square for the model: P-value<0.0001. Connection between predicted probabilities and responses observed: Concordant: 85%  
* Drugs with anticholinergic effects include neuroleptics, antidepressants and other drugs with anticholinergic effects.  
** Cardiac diseases include heart failure, previous myocardial infarction, atrial fibrillation and angina pectoris.

In Paper III, extensive motor impairment and old age were independent ACS predictors in stroke patients. Left-sided brain lesions, previous episodes of ACS and regular treatment with drugs with anticholinergic effects were on the verge of being statistically significant ACS predictors.

ACS predictors for selected stroke patients with supratentorial ischemic stroke, in whom the hypothalamic-pituitary-adrenal axis...
was studied by the dexamethasone suppression test (Paper IV), are shown in Table 11.

**TABLE 11. ACS PREDICTORS IN PATIENTS WITH SUPRATENTORIAL CEREBRAL INFARCTION.** Results of a logistic regression model used to estimate the predicting value of included variables, after dexamethasone suppression test (Paper IV). Dependent variable: Acute confusional state (ACS) in logistic transformation (N=83).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald Chi-Square</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol*</td>
<td>6.45</td>
<td>0.01</td>
</tr>
<tr>
<td>Degree of paresis</td>
<td>6.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Left-sided brain lesion</td>
<td>4.02</td>
<td>0.05</td>
</tr>
<tr>
<td>Age</td>
<td>3.58</td>
<td>0.06</td>
</tr>
<tr>
<td>Anticholinergic medication</td>
<td>0.86</td>
<td>0.36</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.22</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Chi-square for the model: P-value=0.0002. Connection between predicted probabilities and responses observed: Concordant=80%.

*Plasma cortisol measured at 7 am after giving the patient 1 mg dexamethasone at 11 pm the day before.

Elevated plasma cortisol, which was common early after stroke, the degree of paresis on day four after admission and left-sided brain lesions turned out to be significant ACS predictors in the logistic regression model of Paper IV. Old age was on the verge of being a statistically significant ACS-predictor.

In Table 12 the logistic regression model used to analyze the ACS predictors in a consecutive sample of elderly patients treated for femoral neck fractures is shown (Paper VI). These patients were treated in accordance with the intervention program.
TABLE 12. ACS PREDICTORS IN PATIENTS WITH FEMORAL NECK FRACTURES. Results of logistic regression model of the intervention study (Paper VI). Dependent variable: Postoperative acute confusional state (ACS) in logistic transformation (N=103).

<table>
<thead>
<tr>
<th>Independent variables:</th>
<th>Wald</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>10.62</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex*</td>
<td>8.85</td>
<td>0.003</td>
</tr>
<tr>
<td>Depression</td>
<td>2.34</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac diseases</td>
<td>1.88</td>
<td>0.17</td>
</tr>
<tr>
<td>Age</td>
<td>1.17</td>
<td>0.28</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>0.25</td>
<td>0.62</td>
</tr>
<tr>
<td>Drugs with anticholinergic effects</td>
<td>0.02</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Chi-Square for the model: P-value<0.0001. Connection between predicted probabilities and responses observed: Concordant: 76%  
*Male sex was associated with an increased ACS risk in the intervention study.

Dementia and male sex were the independent ACS-predictors of the intervention study (VI).

ANAESTHETIC TECHNIQUE AND ACS

In paper II, 57 patients lucid on admission were randomized to receive either epidural or halothane anesthesia. One aim was to see if the anesthetic technique influenced the frequency of postoperative confusion. We found that 44% of the patients developed ACS correlating closely to a history of mental depression (P<0.01) and to the use of drugs with anticholinergic effects (P<0.005). There was no difference in the ACS frequency between the two anesthetic groups. In patients given halothane, however, early postoperative hypoxemia was associated with ACS (P<0.05). Patients who developed ACS had significantly more postoperative complications and almost four times longer total hospitalization time (Table 13). It was concluded that anticholinergic medication and a history of mental depression were
predominant risk factors for the development of postoperative ACS and more important than the anesthetic technique in this respect. In paper I there was a close connection between peroperative blood-pressure falls and postoperative ACS. Also in the intervention study (Paper VI) despite oxygen therapy, active prevention and treatment of blood-pressure falls, some patients exhibited hypoxia and/or peroperative hypotension, and almost all of them developed postoperative ACS.

ACS AND CLINICAL OUTCOME

Ward stay for patients with and without ACS in the different studies are shown in Table 13.

TABLE 13. WARD STAY IN THE ACUTE CARE WARDS FOR PATIENTS WITH AND WITHOUT ACS.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Type of ward stay</th>
<th>Ward stay (days)</th>
<th>Lucid patients</th>
<th>Patients with ACS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Orthopaedic dept</td>
<td>13</td>
<td>20</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Orthopaedic dept</td>
<td>13</td>
<td>25</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total ward stay of 1 year for previously non-hospitalized patients</td>
<td>22</td>
<td>77</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Stroke unit</td>
<td>13</td>
<td>19</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Stroke unit</td>
<td>16</td>
<td>23</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Orthopaedic dept</td>
<td>11</td>
<td>13</td>
<td>=0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Intervention)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS in Papers I-IV was associated with prolonged ward stay. In the intervention study, where ACS frequency was lower and ACS duration shorter, the difference in ward stay between patients with and without ACS was not significant.

Mortality for patients with and without ACS in the different papers are shown in Table 14.
TABLE 14. MORTALITY IN PATIENTS WITH AND WITHOUT ACS.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Total mortality in the acute care ward.</th>
<th>Total 6 month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lucid</td>
<td>ACS</td>
</tr>
<tr>
<td>I</td>
<td>(111 pat.)</td>
<td>1/43</td>
</tr>
<tr>
<td>II</td>
<td>(57 pat.)</td>
<td>0/32</td>
</tr>
<tr>
<td>III</td>
<td>(145 pat.)</td>
<td>2/76</td>
</tr>
<tr>
<td>IV</td>
<td>(83 pat.)</td>
<td>0/48</td>
</tr>
<tr>
<td>VI</td>
<td>(103 pat.)</td>
<td>4/54</td>
</tr>
</tbody>
</table>

* p<0.05 (Yates' corrected chi-square test)
** p<0.05 (chi-square test)

The other comparisons showed no statistical significant differences.

ACS in stroke patients (Paper III), was associated with a significantly higher mortality rate both during the acute care ward stay and at six months. In the studies on patients with femoral neck fractures the mortality rate was low. The differences in mortality between patients with and without ACS in Paper I, did not reach statistical significance. In the intervention study there was the same low mortality rate both in patients with and in patients without ACS.

ACS DIAGNOSIS AND DOCUMENTATION

In Paper V the assessment and treatment of ACS documented by the physicians and nurses who treated the patients in Papers I and II were studied. The ACS documentation in the records is summarized in Table 15.
TABLE 15. THE PHYSICIANS’ AND NURSES’ ACS DIAGNOSES AND INDICATIVE NOTES OF ACS IN PAPERS I AND II AND IN THE RETROSPECTIVE CONTROLS.

Comparison II includes only preoperatively lucid non-demented patients. The other three samples are comparable and include all patients irrespective of preoperative mental state.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ACS FREQUENCY</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLINICAL STUDY</td>
<td>CASE NOTE STUDY</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Comparison I</td>
<td>68</td>
<td>61</td>
<td>48</td>
<td>43*</td>
</tr>
<tr>
<td>(N=111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison II</td>
<td>25</td>
<td>44</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>(N=57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umeå retrospective control (N=66)</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>44*</td>
</tr>
<tr>
<td>Piteå retrospective control (N=68)</td>
<td>-</td>
<td>-</td>
<td>32</td>
<td>47*</td>
</tr>
</tbody>
</table>

* There was no statistically significant difference between the three comparable samples.

The study compared the results of two clinical studies with the results of case note studies of the same populations of patients and on the same care occasions. All patients were 65 or older and operated on for femoral neck fractures. All comparisons showed that both physicians and nurses diagnosed ACS unsatisfactorily and documented the patients' mental states poorly. This was especially true of patients who had prefracture dementia or were acutely confused even on admission. This was the probable explanation of the difference between comparisons I and II. The analysis of two retrospective case note control samples gave the same results as the retrospective analysis of the two clinical studies. Neither the physicians nor the nurses used any kind of diagnostic instrument to detect cognitive disorder in the patients.

Nurses documented ACS better in the records than the physicians but the documented nursing actions associated with ACS were
insufficient with a few exceptions. The most common nursing action associated with ACS was the administering of extra medication, often drugs with anticholinergic effects, on request.

**INTERVENTION**

The main results of the intervention can be seen in Tables 7, 13, 14, 16 and 17. The ACS frequency was lower, 48%, in the intervention study compared with 61% (p<0.05) in the control study (Table 16). Furthermore, the ACS occurring in the intervention study was less severe and of shorter duration than the ACS of the control study. The frequency of postoperative decubital ulcers, severe falls and urinary retention was also lower (Table 17). The mean duration of orthopaedic ward stay was 17 days in the control study and 12 days in the intervention study (p<0.001) (Table 13). The intervention program reduced the frequency, severity and duration of ACS which resulted in shorter orthopaedic ward stay (Tables 7 and 16).

The ACS predictors of the intervention study were different from those of the control study (Compare Tables 9 and 12). Old age was the independent ACS-predictor in Paper I and old age and male sex in Paper VI.

**TABLE 16. ACS FREQUENCY IN THE CONTROL STUDY AND IN THE INTERVENTION STUDY.**

<table>
<thead>
<tr>
<th></th>
<th>Control (N=111)</th>
<th>Intervention (N=103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>32</td>
<td>30</td>
<td>N.S.</td>
</tr>
<tr>
<td>%</td>
<td>28.8</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>Preoperative ACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>37</td>
<td>30</td>
<td>N.S.</td>
</tr>
<tr>
<td>%</td>
<td>33.3</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>Postoperative ACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>68</td>
<td>49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%</td>
<td>61.3</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>ACS ≥7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>44</td>
<td>30</td>
<td>N.S.</td>
</tr>
<tr>
<td>%</td>
<td>39.6</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>Severe ACS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%</td>
<td>29.7</td>
<td>6.8</td>
<td></td>
</tr>
</tbody>
</table>

*ACS was defined as severe if it caused documented severe caring problems.*
The ACS frequency was lower in the intervention study. The number of patients with severe ACS was also lower in the intervention study. Among patients who were lucid on admission, fewer patients in the intervention study were acutely confused for more than one week (Table 7) (16/57, 28% in Paper II compared with 6/66, 9% in the intervention study p<0.01, chi-square analysis).

**TABLE 17. POSTOPERATIVE COMPLICATIONS IN THE CONTROL STUDY AND IN THE INTERVENTION STUDY.**

<table>
<thead>
<tr>
<th></th>
<th>Control (N=111)</th>
<th>Intervention (N=103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>26</td>
<td>23.4</td>
<td>15</td>
</tr>
<tr>
<td>Urinary infections</td>
<td>26</td>
<td>23.4</td>
<td>33</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>21</td>
<td>18.9</td>
<td>9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8</td>
<td>7.2</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>3.6</td>
<td>8</td>
</tr>
<tr>
<td>Decubital ulcers</td>
<td>14</td>
<td>12.6</td>
<td>4</td>
</tr>
<tr>
<td>Feeding problems</td>
<td>8</td>
<td>7.2</td>
<td>5</td>
</tr>
<tr>
<td>Severe falls</td>
<td>6</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Yates' corrected chi-square test.

No differences remained significant after the Bonferroni adjustment for probabilities.

Fewer patients had urinary retention, decubital ulcers and severe falls in the intervention study. Five of the severe falls with new fractures and other complications in the control study occurred among patients with postoperative ACS who also had the longest orthopaedic ward stays.
DISCUSSION

ACS FREQUENCY

The ACS frequency in the paper including a prospective representative sample of elderly patients with femoral neck fractures was 61% (Paper I). In the corresponding sample of stroke patients of all ages the ACS frequency was 48% (Paper III). The patients were observed during a period, long enough to detect changes in their mental state. Their prefracture and prestroke mental state was also assessed by means of interviews with relatives or caregivers. The interrater reliability was controlled as described under methods. These procedures support the reliability of the ACS diagnosis, and may also explain the high percentage of ACS found in this study.

The criteria for entry to the stroke unit (Paper III and IV) exclude patients with stroke causing only cognitive disturbances without focal neurological deficits. Therefore, our ACS frequency data early after the incident of stroke probably indicate the minimum frequency rate. The DSM-III-R ACS (delirium) criteria may occasionally be difficult to apply to patients with acute stroke because of a fluctuating ACS course and various neuropsychological symptoms from the stroke. In the present studies, careful monitoring with repeated cognitive testing and frequent patient observations have probably reduced the ACS underdiagnoses to a minimum. The risk for overdiagnoses were probably reduced by following the time-course of the patient’s cognitive function but diagnostic problems remained in a few patients with aphasia, dementia and psychosis.

Despite the selection of patients without signs of mental confusion or dementia on admission and the use of short operative procedures in Paper II, 35% (20/57) developed confusion during the first postoperative week. In another five patients (9%), confusion appeared before and persisted after surgery.

In the retrospective studies of Paper V, a lower ACS frequency was found than in the prospective studies on the corresponding groups of patients. The results of Paper V showed that ACS was unsatisfactorily diagnosed and poorly documented in the case note material when compared with the results of the clinical studies. A retrospective approach leads to an underestimation of the ACS frequency as shown.
in the comparisons between the clinical studies and the case note studies. However, when comparing the retrospective case note ACS frequency with the case note analysis of the clinical study samples, a similar ACS frequency can be found. This supports the fact that the high ACS frequency is a general problem in the care of elderly hip-fracture patients. The ACS frequency in the various papers is not essentially different from that reported in the literature, summarized in Tables 3, 4 and on page 16 regarding stroke patients.

The most important results of the intervention, Paper VI, were the lower ACS frequency (47.6% compared with 61.3%, p<0.05), the shorter duration and the decreased severity of postoperative ACS. The intervention aimed mainly at protecting the cerebral oxidative metabolism, which is one of the main hypotheses about the pathophysiology of ACS. The second hypothesis, that ACS is a reaction to stress mediated by hypercortisolism, was not included in the prevention of postoperative ACS, but the treatment of complications associated with postoperative ACS has probably reduced the stress for the patients and thereby reduced the duration and severity of postoperative ACS.

**PREDISPOSING ACS FACTORS**

The independent significant ACS predictor in Paper I was old age. Dementia, regular use of drugs with anticholinergic effects, depression and previous stroke were on the verge of being significant. In Paper II, the conclusion was that anticholinergic medication and a history of depression were predominant risk factors for the development of postoperative confusion and more important than the anesthetic technique in this respect.

In the stroke patients of Paper III the degree of extremity paresis and old age were independent ACS predictors. Left-sided brain lesions, previous ACS and treatment with drugs with anticholinergic effects came close to being significant ACS predictors. In Paper IV, ACS in patients with supratentorial stroke was independently associated with high cortisol levels after a dexamethasone suppression test, extensive motor impairment and left-sided brain lesion. Old age was on the verge of being a significant independent ACS predictor.

In Paper VI dementia and male sex were significant ACS predictors.
A high proportion of the patients with femoral neck fractures in Paper I (35.1%) were regularly treated with drugs having anticholinergic effects, which have also been shown to be an ACS risk factor in Papers II and III and in the literature (Itil 1966, Tune 1981, Mondimore 1983, Miller 1988, Thienhaus 1990). Also in the retrospective studies of Paper IV treatment with drugs having anticholinergic effects was closely associated with ACS (data not shown). This is perhaps the most important ACS predictor that could be prevented by a more restrictive use of drugs with anticholinergic effects in the elderly. Unfortunately many old vulnerable patients are treated with this type of drugs; 35% of the patients with femoral neck fractures in Paper I and according to the literature up to 60% of nursing home residents (Blazer 1983).

However, the prediction models of the different Papers explain only a minor part of the ACS frequency. All patients with femoral neck fractures are exposed to trauma, pain, sudden relocation, anesthesia and surgery. Stroke patients are exposed to sudden disablement, sudden relocation and several medical complications. All these events, often unavoidable, bring about stress, especially for the old and vulnerable patient and are probably the main reasons for the high ACS frequency (Coccaro 1984, Arnetz 1985). The most vulnerable patients will probably develop ACS irrespective of treatment. In these cases it is important to treat and prevent the consequences of ACS. In many cases ACS in itself seems to place the patient in a vicious circle that may prolong his ACS. This may partly be due to the disturbed sleep-wake cycle and the increased psychomotor activity which often results in total exhaustion.

**ANESTHESIA AND ACS**

There was no difference in the frequency of postoperative mental confusion or mortality between patients given epidural analgesia and patients given general anesthesia. Our results are in agreement with most of the studies summarized in Table 5. Only few authors have studied postoperative ACS though. However, in a study by Chung (Chung 1987), the retention of the mental function after spinal anesthesia in patients operated on for transurethral resection of the prostate or undergoing pelvic floor repair was better than that of patients given general anesthesia. In Paper II, confusion following
general anesthesia correlated with a significant reduction in arterial oxygen tension values from the preoperative to the early postoperative period. In contrast to Hole (Hole 1980), we found a high frequency of postoperative confusion in patients who had been operated on under epidural analgesia. Patients with confusion in the epidural group had no postoperative reduction in arterial oxygen tension. Thus, hypoxemia was not the only cause of postoperative ACS.

Spinal anesthesia was associated with a significantly higher intraoperative decrease in arterial blood pressure than halothane or narcotic anesthesia. This is consistent with previous studies comparing regional and general anesthesia, in comparable patient groups (McKenzie 1980, Davis 1981). In Paper II we found no correlation between the degree or duration of hypotension and the frequency of postoperative confusion. However in Paper I and in Paper VI there was a close connection between peroperative hypotension and postoperative ACS. In Paper I 18/21 (86%) and in Paper VI 9/10 (90%) of the patients with peroperative hypotension to 80 mmHg or lower developed postoperative ACS.

ACS AND CLINICAL OUTCOME

In Paper I the consequences of ACS were prolonged ward-stay at the orthopedic department, a greater need for long-term care on discharge, and poor walking ability on discharge and six months after surgery. In addition the confused patients had more complications, such as urinary problems, feeding problems and decubital ulcers, as compared with the nonconfused patients.

In Paper II patients developing postoperative confusion had significantly more postoperative complications and the total hospitalization time during the first year after the fracture was four times longer for patients who developed postoperative ACS.

In Paper III few stroke patients with prolonged ACS could be discharged to their homes. Furthermore, as in other groups of elderly patients, ACS in stroke patients has a profound influence on the length of hospital stay and mortality (Table 13 and 14). In Paper IV, as shown in these tables, the ward-stay for patients with ACS was also prolonged.
In the intervention study (Paper VI), the shorter ward stay was considered to be the result of the lower frequency, shorter duration and decreased severity of postoperative ACS and its complications. In the intervention study, patients with and without ACS had almost the same length of orthopaedic ward stay and the same mortality rate both during the orthopaedic ward stay and at 6 months.


**ACS DIAGNOSIS AND DOCUMENTATION**


ACS has been reported to be a common, important symptom, and sometimes the only symptom of an organic disease in the elderly (Hodkinson 1976, Dixon 1984, Cobden 1984, Bayer 1986, Wroblevski 1986, Black 1987, Fox 1988). The cost and burden of undiagnosed and untreated organically induced mental disturbances is probably very high (Horvath 1986). Therefore, assessment of cognitive ability in elderly patients is necessary; if the patient is cognitively disturbed, the cause of the disturbance must be established. It is essential to distinguish between ACS and dementia, and, when in doubt, the patient should be regarded as acutely confused and assessed for the etiology (Lipowski 1989). If ACS is neglected or misdiagnosed as dementia, the following assessment and treatment may be inadequate. The differences between the case
notes and the clinical studies of the two comparisons (Paper V; Tables II and III) indicated that the risk for poor assessment and documentation is much greater for patients who are cognitively disturbed already on admission. The big difference between the clinical and case note frequency of ACS in comparison I, including demented patients, is considered to be due to the fact that neither the physicians nor the nurses, in many cases, made any clear distinction between ACS and dementia. Furthermore, non-demented patients, who were acutely confused on admission, were often considered to be demented, and there were no documented attempts to assess or treat these patients’ cognitive disturbances. This indicates that the physicians and nurses were less aware of mental changes in patients who they regarded as demented. The retrospective Umeå case note study supports the contention that the on-going clinical studies on ACS did not influence the assessment and documentary routines. Less than half of the preoperatively acutely confused patients were demented and for many of them, both demented and non-demented, the causes of their ACS could be prevented or treated (Paper I). Medical assessment and care are often limited in patients with cognitive impairment and diagnosed dementia (Palmer 1983, Volicer 1986a, Volicer 1986b, Fleishman 1987). It is therefore extremely important that patients are not diagnosed as demented without proper assessment. It is also important to diagnose ACS in demented patients, as it is often a symptom of a complicating condition. The Piteå retrospective control indicated that the poor assessment and documentation is probably a widespread problem in the care of elderly hip-fracture patients. It has also been reported that other groups of physicians are unaware of the patients' mental function and its implication for the assessment and treatment (Rubin 1987). These results stress the fact that assessment and documentation of ACS has to be improved in the care of elderly patients (Brady 1987). The poor assessment and documentation of ACS is a threat to the patients, as a correct ACS diagnosis is a prerequisite for further assessment of its underlying causes and the consequent necessary medical and nursing care.
INTERVENTION

As early as in 1955, Bedford suggested that cerebral circulatory failure, including anoxia, anaemia, deficiency in nutrients and stroke were important etiological mechanisms for postoperative confusion (Bedford 1955). In Paper VI, despite oxygen treatment, severe hypoxemia occurred in some patients and contributed to their ACS. In Paper I there was a close relationship between peroperative hypotension and postoperative confusion. The number of patients with severe peroperative hypotension was lower in the intervention study, but hypotension remained an important risk factor for postoperative confusion in the intervention study. These results are thought to support the hypothesis that a reduction in the cerebral oxidative metabolism is an important ACS cause (Blass 1979, Gibson 1981, Blass 1983, Hirsh 1984, Lipowski 1987).

In the control study (Paper I), the only significant ACS predicting variable was old age. It should however be observed that 16/17 (94%) patients with dementia, 15/17 (88%) with depression, 15/18 (83%) with previous stroke and 33/39 (85%) on regular treatment with drugs with anticholinergic effects developed ACS even though these variables did not reach statistical significance in the logistic regression model. What these variables have in common is a reduced metabolic capacity with decreased transmitter levels in the brain (Blazer 1982, Gottfries 1983, Hardy 1985, Gottfries 1987).

In the intervention study (Paper VI), the ACS predicting variables were dementia and male sex. Patients with dementia have a low ACS threshold, so postoperative ACS is probably difficult to prevent. It was also impossible to administer oxygen therapy to some of the demented patients. Nevertheless, it is important to treat these patients carefully and to realise that ACS in demented patients might be a symptom of a complication or condition which can be treated. There is a certain number of clinically relevant differences between men and women that might explain the higher ACS frequency among the men of the intervention study.

Despite that depression did not reach significance in the logistic regression models; the great majority of patients with depression in both studies developed ACS (15/17 (88%) in the control study and 8/11 (73%) in the intervention study). The serotoninergic and the noradrenergic transmitter systems are the most affected in the case...
of depression (Blazer 1982). These systems are reported to be less sensitive to hypoxia than the cholinergic system (Gibson 1981, Hirsch 1984). The intervention program does not seem to protect patients with depression from ACS which might indicate an alternative ACS mechanism. Several studies (Kraal 1962, Kraal 1975, Murphy 1981, Carpenter 1982, Kosics 1985, Wolkowitz 1990) have shown that depressed patients have elevated cortisol levels and might thus explain why they are more likely to develop ACS. This ACS mechanism is supported in Paper IV. Hypercortisolism in depression is also reported to be connected with agitation, delusions, disturbed sleep, psychomotor alterations, cognitive impairment and left-sided brain lesions (Lipsey 1985, Kocsis 1985, Miller 1987, Brown 1988, Bolla-Wilson 1989).

The changes in the ACS prediction model (Paper VI) are considered to be a result of the efforts made to improve the brain oxygenation. Old age, stroke, and treatment with drugs with anticholinergic effects have in common a decreased cholinergic activity in the brain. It has been suggested that decreased cholinergic activity might be the most important transmitter disturbance in ACS (Itil 1966, Blass 1979, Tune 1981, Mondimore 1983, Miller 1988, Thienhaus 1990). The cholinergic system has also been reported to be particularly sensitive to hypoxia (Blass 1979, Gibson 1981, Hirsch 1984). The intervention program might have protected some patients with such risk factors from ACS.

The assessment of patients with postoperative ACS, and the treatment of associated complications have also reduced the duration and severity of their ACS, thereby preventing or inhibiting cerebral metabolic disturbances mediated at least partly by stress-hypercortisolism.

From a methodological point of view, a randomized experimental study would have been preferable to the use of a historic control. However, this was not possible due to changes in the anesthesiologic treatment routines initiated by the earlier studies. Ethical aspects supported the decision not to deny certain patients oxygen treatment and a more active prevention and treatment of severe hypotension. Because of the method used, the results of the intervention should be interpreted with some caution. However, during both studies the routines from admission to discharge were carefully observed and we
have found no other differences between the study periods than those described in the intervention program. It should also be observed that the patients of the two studies are comparable as for most of the relevant background variables. The only prefracture variable, with an ACS predicting value, that differed between the two study samples was cerebrovascular disorders, which were in fact more common in the intervention sample. With the Bonferroni correction of probabilities there were no differences in background variables between the two studies. There were no differences in the psycho-pharmacological treatment of patients with ACS or in the organization of the nursing care between the groups. During both studies, the patients were observed and tested by the same methods and by the same physicians at the same intervals. The caregivers were also interviewed about the patients at the same intervals and to the same extent in both studies.

The lower frequency and severity and the shorter duration of ACS in the intervention study are considered to be the results of the geriatric-anesthesiologic program. However, the frequency of postoperative ACS is still very high. All patients with femoral neck fractures are exposed to trauma, pain, sudden relocation, anesthesia and surgery. All these unavoidable incidents bring about stress, especially for the old and vulnerable hip-fracture patients (Arnetz 1985) and are probably the main reasons for the high ACS frequency. As in Paper IV, where hypercortisolism was an independent ACS-predictor in stroke patients, several studies have reported prolonged hypercortisolism in hip-fracture patients (Frayn 1983, Barton 1987, Roberts 1990). Unfortunately no attention has been paid to the patients' cognitive function in relation to the hypercortisolism in these studies. However, it is probably not a daring assumption that also in hip-fracture patients ACS is associated with hypercortisolism but it remains to be established.

ETIOLOGY AND PATHOGENESIS

There are two major hypotheses about the pathogenesis and pathophysiology of ACS (Lipowski 1987). The first hypothesis suggests that a reduction in cerebral oxidative metabolism and the consequent reduction in neurotransmitters cause ACS (Blass 1979, Blass 1983). This hypothesis is supported by studies showing that
the cerebral acetylcholine synthesis is especially sensitive to hypoxia (Gibson 1981, Hirsch 1984). A close link between ACS and impaired cholinergic activity has been reported by several authors (Itil 1966, Tune 1981, Mondimore 1983, Miller 1988, Thienhaus 1990). The second hypothesis suggests that ACS is a reaction to various types of stress mediated by elevated plasma cortisol levels influencing the neuron function (Kraal 1962, Kraal 1975, Carpenter 1982, McEwen 1987, McEwen 1988). High cortisol levels are closely related to postoperative ACS (McIntosh 1985). Hypercortisolism probably disturbs cerebral metabolism, especially for the cholinergic neurons in hippocampus (Paper IV). Both of these mechanisms may be involved in the ACS pathogenesis in stroke patients and in patients with femoral neck fractures.

A simplified model of the pathophysiology of ACS is presented in Figure 1.

ACS has been associated with cerebrovascular lesions affecting a large variety of specific locations, such as thalamus, midbrain, diencephalic and posterior-inferior brain areas, the right frontostriatal region, the temporoo-occipital cortex, the left posterior cerebral artery territory and the hippocampus (Horenstein 1967, Medina 1974, Medina 1977, Mesulam 1976, Mullally 1982, de Reuck 1982, Levine 1982, Schmidley 1984, Graff-Radford 1984, Santamaria 1984, Price 1985, Balter 1986, Dunne 1986, Mori 1987, Bogousslavsky 1988, Devinsky 1988, Garcia-Albea 1989). A common denominator for many of these lesion sites is that the neocortex hemisphere is disconnected from the limbic structures. It seems likely that acute confusion after stroke is not the result of one or several specific brain lesions but rather a consequence of a disruption of an integrative system. This disruption may be structural or functional in its nature and may involve neuroendocrine systems. The fact that confusion often clears after the first few days after stroke onset (Paper III) points to functional rather than structural damage as the major cause of confusion.

Stroke causes ischemia and disturbed oxygenation in the brain. Hypoxia is an important mechanism for brain damage (Siesjö 1981, Gibson 1988a). Hippocampus has been reported to be especially sensitive to hypoxia (Gibson 1988b). Hypoxia is found in a great proportion of patients with hip fractures (Bedford 1955, Katz 1972,
Martin 1977, Phillips 1977, Paper II and VI). A disturbance in cerebral oxidative metabolism is an important ACS mechanism as suggested as early as in 1955 by Bedford and by Engel in 1959. In animal models hippocampal ischemia produced necrosis in the CA1 pyramid cells and resulted in memory deficits suggested to be relevant to human memory deficits caused by mild ischemic brain damage in clinical situations (Auer 1989).

Hypercortisolism is common early after stroke (Feibel 1977, Olsson 1989, Olsson 1990, Korsic 1990, Paper IV) and prolonged and persistent hypercortisolism has been reported for femoral neck fracture patients by several authors (Frayn 1983, Barton 1987, Roberts 1990). It is clear from animal models that hypercortisolism disturbs neuron function, causes neuronal death and disturbs cognitive function (Micco 1980, Sapolsky 1986b, de Kloet 1987, Armanini 1990, Woolley 1990). It has also been shown in animal models that the toxic effect of cortisol on hippocampal neurons increases with aging (Kerr 1989). Sapolsky suggested that cortisol endangers hippocampal neurons by impairing their energy metabolism (Sapolsky 1986a, Horner 1988) and thereby also potentiating ischemic injury to neurons (Sapolsky 1985). He also showed that the ischemic brain damage was worsened when cortisol levels were manipulated after the ischemic insult (Sapolsky 1985).

Glucocorticoids has been reported to cause hippocampal damage in monkeys and Sapolsky therefore suggests that "sustained hypercortisolism (whether due to stress, Cushing's syndrome or exogenous administration) might damage the human hippocampus" (Sapolsky 1990b). A close connection between hypercortisolism and disturbances in cognitive function has also been described in man; both in patients with Cushing's syndrome (Whelan 1980, Starkman 1981, Starkman 1986), in healthy volunteers (Wolkowitz 1990) and in medical treatment with corticosteroids (Reckart 1990). In patients with chronic cognitive disturbances, such as Alzheimer's disease, a decreased suppressability of the HPA-axis by dexamethasone has been demonstrated (Balldin 1983, Charles 1986, Abou-Saleh 1987, Shrimankar 1989, Martignoni 1990). The non-suppression in Alzheimer's disease has been reported to be linked to hippocampal atrophy (de Leon 1988).
The ACS can probably place the patient in a vicious circle, with prolonged ACS. The ACS is in itself stressing for the patient (MacKenzie 1980) which might maintain the hypercortisolism (Gaillard 1987, Caggiula 1989). Animals exposed to repeated stress has been reported to develop sustained hypercortisolism (Vernikos 1982). ACS is often associated with complications, e.g. urinary retention and myocardial infarction which may prolong hypercortisolism. Other complications, e.g. pulmonary embolism and pneumonia may also cause or aggravate hypoxia and thereby prolong ACS. ACS causes caring problems (Brännström 1989) which often results in treatment with drugs with anticholinergic effects (Paper V). Anticholinergic medication is an important risk factor for ACS according to the literature (Itil 1966, Tune 1981, Preskorn 1982, Mondimore 1983, Miller 1988, Thienhaus 1990). In experimental studies, on healthy volunteers, anticholinergic medication caused cognitive impairment and changes in the EEG's of the same type as in the case of ACS (Roth 1959, Ostfeld 1960, Itil 1966, Pro 1977, Zisook 1986, Koponen 1989).

In Papers I, II and III, treatment with drugs with anticholinergic effects was an independent ACS risk factor. According to the records, in Paper V, the patients' medication was never suggested to be the cause of ACS. In many cases the nurses' ACS documentation was followed by notes on extra medication, in many cases drugs with anticholinergic effects. No diagnostic reasoning or indications for the drug treatment were documented.

Patients with ACS often exhibited postoperative nutritional problems (Brännström 1990, Paper I) which might also place the patient in a vicious circle (Goodwin 1983). Nutrition deficiency of various kinds has been reported to cause and prolong ACS (Leeder 1981, Day 1988). Malnutrition is common in hip-fracture patients and also associated with prolonged ward-stay and higher mortality (Older 1980, Bastow 1983, Cooper 1987).

The risk of developing decubital ulcers among patients with cognitive dysfunction, e.g. ACS, has been reported to increase (Paper I, Ek 1982, Nicholson 1988). During ACS the patient does probably not experience the development of ulcer and/or can not protect himself. During the intervention, the lower frequency of decubital ulcers was probably the result of the lower frequency and duration of ACS.
There has been some discussion as to when confusional state should be regarded as dementia. Many of the ACS causes might of course lead to permanent brain damage if they are not diagnosed and rapidly treated (Byrne 1987). The prolonged ACS could also, through disturbed cerebral oxidative metabolism and hypercortisolism, cause progressive irreversible brain damage and dementia. In animal models it has been shown that glucocorticoid hypersecretion, hippocampal neuron death, and cognitive impairments form a complex degenerative cascade of aging (Meaney 88). The mechanisms of the development of dementia after stroke have to be elucidated in research in the future (Blank 1984, Lipsey 1985, Agarwaal 1987, Tatemichi 1990).

The results of this study support the two main hypotheses of the ACS pathophysiology. There is substantial evidence, especially in animal models, that the two ACS-mechanisms interact closely but that their importance probably varies in different individuals and situations. These possible pathways are of course not the whole scenario of the ACS pathophysiology. Other mechanisms and their interaction with the cortisol-axis, the acetylcholine synthesis and neuron function must be further elucidated.

The Reticular Activating System (RAS) and its noradrenergic system are probably involved to some extent. In Korsakoff’s psychosis a close connection between depletion of the noradrenergic system and cognitive activation has been demonstrated (Mair 1983). The disturbed sleep-wake-cycle might indicate involvement of the serotoninergic system. In animal models the serotoninergic system seems to activate the HPA-axis (Calogero 1990).

ACS in patients treated for Parkinson’s disease indicates that the dopaminergic system interacts with the cognitive function. Several neurotransmitters have been shown to be involved in the regulation of the HPA-axis (Tuomisto 1985).

Interleukin (IL-1) is an important mediator of generalized host responses to tissue injury or infection (Sipe 1990). Interleukin IL-1 has been reported to have a stimulatory effect on cortisol secretion (Whinter 1990, Sundar 1990). Cortisol stimulates PAI-1 which inhibits the fibrinolysis thereby increasing the risk of thromboembolic complications for the patients (Durum 1990). Several patients, both with femoral neck fractures and with stroke,
had thromboembolic complications associated with prolonged ACS. If these thromboembolic complications are mediated by interleukin-cortisol-PAI and if ACS can be mediated direct by interleukin or by interleukin-hypercortisolism remains to be confirmed. There is evidence that interleukin has a direct central nervous effect, shown for instance by the ability to induce slow-wave sleep in animals (Chedid 1984).

Excitatory amino-acids, especially glutamate perhaps (Sapolsky 1990a), which, like acetylcholine, is reported to be particularly sensitive to hypoxia are probably also involved in the ACS pathophysiology.

The molecular mechanisms, altering neuron function, such as electrolytes and free radicals are also likely to be involved either primarily or secondarily. Even if we know very little of the complicated neuronal ACS mechanisms the present model appears to be a good basis for further basic research and intervention studies.
FIGURE 1. A SIMPLIFIED MODEL FOR THE PATHOPHYSIOLOGY OF ACS IN ELDERLY PATIENTS DISCUSSED IN THE PRESENT STUDY.

HIP-FRACTURE STROKE
Somatic and psychosocial stress

DISTURBED OXYGENATION

HYPERCORTISOLISM

ENERGY/NUTRIENT DEPRIVATION

CEREBRAL METABOLISM
(neurotransmitter metabolism e.g. acetylcholine)

ANTICHOLINERGIC MEDICATION

CARING PROBLEMS
(e.g. Disturbing behaviour, Nutrition problem, Decubital ulcers, Sleep disturbances)

COMPLICATIONS
(e.g. Urinary retention, Pulmonary embolism, Pneumonia, Myocardial infarction)

PROLONGED HYPERCORTISOLISM AND/OR REPEATED OR PROLONGED HYPOXIA CAUSES PERMANENT BRAIN DAMAGES AND DEMENTIA?
The value of the two main hypotheses is that they can be applied to most of the suggested ACS causes (Table 7). The two performed interventions in ACS, Paper VI mainly with the protection of the cerebral oxidative metabolism, and the study by Williams (Williams 1985b) which could be said to lessen the psychosocial stress of the patient, reduced ACS.

A prevention of factors compromising cerebral metabolism or prevention of the neuronal toxic effect of high plasma cortisol induced by stress might be two approaches that could prove effective in the prevention and treatment of ACS. High cortisol levels could prolong ACS by the direct or indirect neurotoxic effect of cortisol with the consequent disturbance of cognitive function. Also ACS in itself is a stress factor for the patient which might cause hypercortisolism, placing the patient in a vicious circle. The most common mistake in the management of patients with ACS is to neglect environmental and psychological intervention (Beresin 1988). The prevention, treatment and care must also be individualized (Wolanin 1981, Blank 1984, Foreman 1984, Bergman 1986, Foreman 1989b). Calm and careful nursing of the patient often reduces the stress and in some cases improves the patient’s cognitive function. Etiologic ACS factors of organic and psychological origins may act through either of these mechanisms or through both.
GENERAL SUMMARY AND CONCLUSIONS

ACS was common in stroke patients and in hip fracture patients and was often associated with risk factors and complications that could be prevented or treated.

The main ACS risk factors in the patients with femoral neck fractures were old age, dementia, previous stroke, depression and regular treatment with drugs with anticholinergic effects.

In patients with femoral neck fractures, ACS was not associated with the type of anesthesia but with peroperative blood pressure falls and early postoperative hypoxia and the conclusion is that it is the performance rather than the type of anesthesia that is important to the development of postoperative ACS.

In stroke patients hypercortisolism, extensive paresis, old age, left-sided brain lesion, previous ACS and regular treatment with drugs with anticholinergic effects were the most important ACS risk factors.

Most of the risk factors found in this study are consistent with the following two major ACS hypotheses:
1. Reduced capacity or disturbance of the cholinergic system in the brain due to factors compromising the cerebral oxidative metabolism or caused direct by anticholinergically acting drugs.
2. Elevated plasma cortisol level as a reaction to stress or as a direct result of factors disturbing the hypothalamic-pituitary-adrenal axis. Hypercortisolism might endanger the neuron metabolism thereby causing ACS.

ACS in elderly patients relates to various complications, high mortality, prolonged ward stay and a great need for geriatric care.

As a correct ACS diagnosis is a prerequisite for the assessment of its causes and consequent treatment, underdiagnoses and poor documentation of ACS is a threat to the patients.
The intervention in postoperative ACS confirmed the conclusions drawn in Papers I-V, since the result of the intervention was reduced frequency, duration and severity of postoperative ACS. Intervention reduced the orthopaedic ward stay for the patients, and thus, a great deal of suffering for elderly patients and high costs for society could be prevented if intervention was applied.
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