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Neuropsychological outcome of patients operated upon for an intracranial aneurysm: analysis of general prognostic factors and of the effects of the location of the aneurysm

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SUMMARY One hundred and fourteen patients operated on for an intracranial aneurysm were followed up in order to investigate their neuropsychological outcome and to detect if there were any clinical features assessed around the time of operation that had prognostic significance. The neuropsychological examination evaluated language, apraxia, memory, intelligence and spatial ability. In the statistical analysis the overall severity of neuropsychological disorder was studied. "Late surgery timing" had a negative influence upon the neuropsychological outcome. There was not a difference between different aneurysm sites. Several patients with an apparently good clinical outcome showed neuropsychological deficits. Neuropsychological assessment is important in the evaluation of outcome after subarachnoid haemorrhage.

The factors that influence the prognosis of a patient with a ruptured intracranial aneurysm are being given increasing attention by neurologists and neurosurgeons. Reports of unselected samples that have studied neuropsychological or behavioural traits, have been less optimistic than investigations concerned exclusively with physical disabilities.[1-3]

A number of papers recently published by Swedish investigators,[4-5] were devoted to the neuropsychological outcome of patients operated on for an intracranial aneurysm, and analysed the effect of the timing of surgery. Their conclusion is that there are also indications of cognitive malfunctioning and psychological disturbances of varying severity in patients who had undergone late surgery, thus not confirming the earlier view that late operation was associated with a better prognosis. This is in line with the recent general conclusions drawn by Solomon and Fink.[6]

In this paper we analyse the neuropsychological outcome of a group of patients operated on for an intracranial aneurysm. Owing to the complexity of the problem and the large number of variables that can be analysed, the focus of this investigation was restricted to neuropsychological aspects of outcome. We aimed to determine if there are prognostic factors able to predict the general level of neuropsychological disability. The prognostic factors that we decided to analyse were the presence of vasospasm (pre- and post-operation), neurological severity, age, and operation timing. Separate papers[7 8] have addressed the details of the neuropsychological performance according to the different location of the aneurysms.

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Material and methods

Subjects

In this study we considered all the subjects who underwent operation for intracranial aneurysm in the Neurosurgical Department of the Milan University in the period from June 1974 to June 1984.

In that period, 251 patients were discharged after operation; table 1 shows the percentage of patients actually included in the study. In the group indicated as *Miscellanea* (table 1) two were affected by aneurysms of the internal carotid artery bifurcation, five of the vertebro-basilar system, and 10 by multiple aneurysms. Patients were sent a letter with

Table 1 *Patients participating in the study*

Aneurysm site	*Discharged*	*Not examined*	*Examined*
ACoA	83	40 (48%)	43 (52%)
MCA	64	37 (58%)	27 (42%)
PCoA	48	21 (44%)	27 (56%)
Misc.	56	39 (70%)	17 (30%)
Total	251	137 (55%)	114 (45%)

Key: ACoA = Anterior Comm. Art.
MCA = Middle Cerebr. Art.
PCoA = Poster Comm. Art.
Misc = *Miscellanea*

an invitation to attend for a clinical review. In 141 cases the patients (or their relatives) answered our letter: six were not willing to be examined, 10 did not complete the examination, nine subjects had died for reasons not related to the surgery, and two were excluded because they had suffered from a stroke after being discharged from the Hospital. The reasons that the remaining subjects (110 cases, =44% of discharged patients) did not accept this invitation were not investigated further. This possibly introduces a bias in the study, since some subjects may not have attended because of a poor clinical condition: this means, however, that the defective neuropsychological performances found in the present sample do not run the risk of overemphasising the deficits associated with ruptured aneurysms.

The sample examined in this investigation was composed of 114 subjects (52 male and 62 female). Mean age was 46·2 (SD = 11·1 with range 16–76) and mean education was 7·7 (SD = 3·9 with range 0–17). These patients underwent neuropsychological examination after a mean interval of 45·8 months after the operation (SD = 24·4 with range 7–115). These variables were included in the statistical analysis.

All patients underwent a standard microsurgical operation, with clipping of the neck of the aneurysm. Antifibrinolytic agents and, if necessary, corticosteroids and hypotensive drugs were given.

All patients underwent CT both before and after operation. The presence of pre-operative arterial spasm was ascertained by means of angiography and post-operative "vasospasm" was diagnosed if the patient developed neurological deficit, if CT showed signs of ischaemia and lack of evidence of rebleeding.[6] The clinical state of the time of the surgical intervention was scored with the scale devised by Hunt and Hess[9] with reference to the worst clinical condition observed during the period; in the statistical analysis the five categories of this scale were collapsed into three points (I = 1 and 2; II = 3; III = 4 and 5). At follow up the disability was scored with (1) Glasgow Outcome Scale (GOS),[10] and (2) with a Disability Scale in use by the Neurosurgical Unit of the Milan University, which takes into account clinical, emotional and social outcome (CES outcome, see table 2). Data on Glasgow Outcome Scale are reported as this Scale is widely employed in the clinical practice; however, it did not seem fully satisfactory for the fine-grained classification of patients with good recovery, because no distinction is made between entirely normal subjects and subjects with minimal disorder, especially when the latter concerns emotional life and social adjustment; moreover, with a greater emphasis on the social and emotional aspects, the outcome severity may worsen.

The clinical variables of the sample are shown in table 3.

Neuropsychological assessment

Patients were given the following neuropsychological battery:

(A) Language

(1) Object naming of some objects of common use (n = 3) and of their features (n = 13).
(2) Verbal fluency with semantic cue: the patient is requested to produce as many names of animals as possible within a time limit of one minute.
(3) Verbal fluency with phonological cue;[11] the patient is given three letters within a time limit of one minute for each of them.
(4) Verbal auditory comprehension (Token Test)[12]

(B) Apraxia

1. Ideomotor Apraxia.[13]

(C) Memory

(1) Bisyllabic word immediate memory span.[12]
(2) Cube tapping immediate memory span.[12]
(3) Bisyllabic word learning[12]
(4) Cube tapping learning[14] having a supra-span cube string

(D) Intelligence

(1) Raven's Progressive Matrices.[15]
(2)Weigl's Sorting test[12]: the patient has to sort some objects according to different features (form, colour, size, etc.)

Table 2 *Categories of Glasgow outcome scale (GOS)*

Good recovery:	Patient can lead a full and independent life with or without minimal neurological deficit.
Moderately disabled:	Patient having neurological or intellectual impairment but is independent.
Severely disabled:	Conscious patient but totally dependent on others to get through the activities of the day.
Persistent vegetative state	
Death	
(For a full description, see ref 1.)	

Categories of clinical, emotional and social outcome (CES)

Excellent:	The patient resumes the previous life, without apparent defects; all facets of social and emotional life are unimpaired.
Good:	Moderate anxiety or depression; and/or minimal deficits in social integration; and/or minimal neurological deficits. Epilepsy (if present) is perfectly controlled.
Moderately impaired:	The patient is autonomous, but is affected by psychic disturbances which call for a specific treatment, and/or by definite neurological deficit; considerable difficulties in social integration. Control of epilepsy may be not fully satisfactory.
Severely impaired:	The patient suffers from incapacitating neuropsychic disturbances and is dependent on daily support.

Table 3 *Clinical characteristics of the sample*

Timing of operation						
Days	1–3	4–9	10–14	15–60		
No of patients	5	43	25	41		
Vasospasm	*Without spasm*		*With spasm*			
Pre-operation	92		22			
Post-operation	99		15			
Worst Clinical Status Observed in Different Periods (Hunt and Hess)	*1*	*2*	*3*	*4*	*5*	*tot*
Pre-operation	8	52	25	25	4	114
Operation	46	45	17	5	1	114
Post-operation	19	34	36	23	2	114
Whole clinical course	3	33	34	38	6	114

Interval (months) between surgery and control = 45·7, SD = 24·5 (range: 7–115)

Glasgow Outcome Scale (at control)	
Good recovery	= 103 (90%)
Moderately disabled	= 11 (10%)
Severely disabled	= 0 (0%)
CES evaluation (at control)	
Excellent	= 45 (39%)
Good	= 47 (41%)
Moderately impaired	= 18 (16%)
Severely impaired	= 4 (4%)

(E) Spatial ability
(1) Constructional Apraxia[12] (copy of seven simple geometric drawings).
(2) Judgment of Line Orientation (Benton)[16]
In addition, the patients were given (1) a task of visual exploration to detect the presence of unilateral neglect (crossing a number of small circles scattered on a sheet of paper), and (2) a tactile object naming task (stimulus objects were presented to the left hand) in order to discover possible naming disturbances originating from callosal disconnection. The results of these "qualitative" tests will not be considered here, and will be reported in the papers concerned with the detailed neuropsychological pattern specific for each aneurysm location.

Statistical methods
The original scores of 10 of the 13 neuropsychological tests considered in this paper have been adjusted for age, education and when indicated, for the influence of the sex of the subject according to the parameters estimated through a multiple regression model in a previous investigation[12] which included 321 normal subjects. The adjusted scores of the control sample have been ranked in order to obtain non-parametric tolerance limits for the lower 5% of the population with 95% confidence.[17]

For the three remaining tests (Block-tapping spatial learning, Ideomotor apraxia and Line Orientation Test) cut-off scores for normality were available, based on smaller control groups but on analogous criteria.

The statistical analysis considered the number of scores corresponding to a "pathological" performance for each subject. The incidence of "pathological" scores (n out of 13) was assumed to approach a binomial distribution and was studied by means of a logit-linear regression model assuming a binomial distribution of the statistical error; the outcome of this method yields points that are chi-square distributed. In the logistic regression we checked whether data were overdispersed, and the dispersion parameter was estimated and introduced in the statistical workout.[18] For the analysis we resorted to the GLIM System.[19]

The statistical design included the effects of age, sex, timing of the operation, pre-operative arterial spasm and post-operative "vasospasm", neurological status (the worst neurological condition observed in the clinical course) and the interval elapsed between operation and neuropsychological assessment.

Factors were studied (1) one at the time, and (2) within the complete statistical model, in order to evaluate each factor adjusted for its overlapping with the other variables included in the statistical design. Interactions were evaluated between the variables which were still significant in the latter analysis.

For the five factors corresponding to the hypotheses on which the experiment focused (that is, spasm (pre- and post-operation), neurological status, age and operation timing) significance thresholds were set on a Bonferroni basis. Except for timing, hypotheses were one-tailed, thus the threshold was set at 0·10/5 = 0·020; for timing threshold was 0·010.

In order to compare the neuropsychological outcome of subjects affected by aneurysms of different arteries, a further analysis restricted to the samples of ACoA, MCA and PCoA (n = 97) was carried out. The differences between aneurysm sites were studied within a model that also included the factors found to be significant in the analysis of the whole sample.

In this investigation we did not take into account a number of variables, namely the CT findings and the EEG evaluation. The reason was that CT pictures do not lend themselves to a classification based on a definite but small number of cells, and that a dichotomous normal/not-normal classification is not very informative; the same applies to EEG. Needless to say, if one wants to evaluate statistically an experiment with reasonable power and protection, too many variables (and comparisons) are not allowed unless the number of subjects is exceedingly high. In this case, we decided to limit ourselves to "bedside" clinical data. CT, EEG and clinical data are further discussed by Laiacona *et al*[7] and Barbarotto *et al.*[8]

Results

At follow-up, 103 patients (90%) had Good Recovery on the Glasgow Outcome Scale (GOS), and only 11 were Moderately Disabled (table 3). The distribution of the patients according to the CES evaluation is also shown in table 3: only 39% of the patients did not show any deterioration with respect to previous life in working activity, social habits and emotional life; 41% showed minimal deficits, 16% a moderate and 4% a severe impairment. On the whole, these figures are similar to those found by other Authors.

(A) Prognostic factors on the whole sample
Table 4 shows the mean number of pathological scores presented by patients in the 13 neuropsychological

Table 4 *Neuropsychological result according to the clinical variables. Figures refer to the mean number (SD) of pathological scores (out of 13 tests) for the subjects belonging to each cell. Chance number of pathological scores per subject is expected to be 0·65, (0·79)*

Timing				
Days	1–3	4–9	10–14	15–60
	1·20 (1·3)	1·02 (1·3)	1·24 (1·8)	1·80 (1·9)
Vasospasm	*No*	*Yes*		
Pre-operation	1·34 (1·7)	1·59 (1·5)		
Pre-operation	1·34 (1·5)	1·77 (2·6)		
Clinical status (Hunt and Hess)	*1–2*	*3*	*4–5*	
Pre-operation	1·14 (1·87)	1·40 (2·28)	1·83 (2·97)	
Operation	1·21 (2·02)	1·94 (2·94)	2·17 (2·17)	
Post-operation	1·19 (2·02)	1·17 (2·03)	2·04 (3·0)	
Whole-course	1·03 (1·42)	1·24 (1·35)	1·75 (2·04)	

tests administered according to the level of the experimental variables. A detailed report of the single neuropsychological scores can be found in the papers devoted to the analysis of the neuropsychological pattern of the different aneurysm sites.[7-8] On the basis of our definition of "pathological score" (lower 5% of the normal population), the number of chance pathological scores for a normal subject over the 13 tests is expected to be 0·65 (0·79). The mean number of pathological scores is reported here for its informative value, but was not used as such in the statistical analysis (see statistical methods). Consequently a normal subject should not have more than one pathological score out of 13 tests.

Table 5 shows the results of the statistical analysis. In the logistic regression analysis of the prognostic factors, the dispersion parameter was found to be 1·75, and this value was introduced in the statistical processing. The result shows that delayed timing was associated with a worse neuropsychological prognosis; the effect of neurological severity did not reach statistical significance, but showed a considerable trend toward significance.

Table 6 shows the percentage of patients falling in the different cells of the Hunt and Hess scale before the operation according to the surgery timing. It turns out that the late surgery group was not different from the other groups with respect to the clinical evaluation. Moreover, the overall neurological severity had been introduced in the statistical design, and for this reason the evaluation of timing effect is not biased (see statistical methods). The significance of the timing of surgery still held true even when the neurological states which were evaluated before operation, at operation and after operation were all introduced in the statistical design (chi-square = 9·428, df = 1, p = 0·002), replacing the overall neurological evaluation reported in Table 5.

(B) Effect of the aneurysm location

To evaluate whether different sites had a distinct neuropsychological prognosis, we carried out an analysis on the restricted sample (n = 97) of subjects with aneurysm of ACoA, PCoA and MCA. The analysis included, besides aneurysm site, the timing of surgery and the neurological status. Again, the dependent variable was the number of pathological scores found in each patient and the significance was evaluated by means of a logit-linear model assuming a binomial distribution. The aneurysm site was never significant, either when considered alone (chi-square = 1·290, df = 2, p = NS) or after adjustment for the above mentioned factors (chi-square < 1, df = 2, p = NS).

(C) Relationship between neurological and neuropsychological outcome

In order to compare neuropsychological and neurological status of the patients, we cross-classified each patient according to the number of pathological scores he obtained on the neuropsychological examination (0 and 1 *versus* 2 or more) and (1) the GOS, or (2) the CES evaluation.

Table 5 *Statistical analysis of the factors influencing the neuropsychological outcome*

	Factors (one at the time)			*Factors (adjusted)*		
Source of variability	*chi-sq.*	*df*	*p*	*chi-sq.*	*df*	*p*
Age	1·054	1	NS	< 1	1	NS
Sex	< 1	1	NS	< 1	1	NS
Timing	7·307	1	0·007	10·009	1	0·002
Vasospasm (pre-operation)	< 1	1	NS	< 1	1	NS
Vasospasm (post-operation)	< 1	1	NS	< 1	1	NS
Neurological status	5·332	2	NS (0·069)	6·310	2	NS (0·042)
Interval between operation and exam	< 1	1	NS	< 1	1	NS

Table 6 *Neurological status pre-operation (Hunt and Hess Scale) according to the surgery timing*

	Hunt and Hess Scale Points		
Timing (days)	*1 and 2*	*3*	*4 and 5*
1–3	2 (40%)	1 (20%)	1 (40%)
4–9	22 (51%)	10 (23%)	11 (26%)
10–14	15 (60%)	6 (24%)	4 (16%)
15–60	21 (51%)	8 (19%)	12 (29%)
total	60 (53%)	25 (22%)	29 (25%)

Chi-Square = 2·17, df = 6, p = NS.

Regarding the GOS, we found that 31% of the subjects with Good Recovery on GOS were neuropsychologically impaired (2 or more pathological scores), and that 27% of those Moderately Disabled on GOS performed normally on neuropsychological tests (0 or 1 failure). As to CES evaluation, 13% of patients with CES = Excellent were impaired neuropsychologically (2 or more failures), whereas 51% of those with CES worse than Excellent were within the norm on neuropsychology.

Regarding the prognostic value of the time of intervention on the neurological and general social-emotional defects, a logisitic regression of GOS and CES (the best category versus the other ones) on timing did not discover any significant effect (chi-square < 1).

Discussion

Our results indicate that neuropsychological outcome after surgery for a ruptured aneurysm is related to the time of operation, late surgery patients faring worse, and possibly to the neurological condition at the operation. The detrimental effect of late surgery is surprising; it cannot be attributed to a sample bias, because (1) the initial neurological severity did not differ according to the timing of surgery, and (2) neurological severity, vasospasm and the other relevant variables were included in the statistical design, separating their possible influences on operation time and on outcome. Moreover, none of the foregoing clinical factors influenced significantly the neuropsychological outcome. Inspection of table 4 shows that the detrimental effect of late surgery is probably related to operations carried out two weeks after bleeding, because patients operated on in the first two weeks do not differ remarkably in terms of the number of pathological scores. In the study by Sonnesson *et al*,[5] timing of operation was not a significant factor, early operation was carried out within three days, and late operation after at least nine days, and these authors did not include subjects operated on between four and nine days, nor did they distinguish within the group operated on after nine days; these latter, in our case, are rather heterogeneous. In the Swedish study, moreover, only two timing groups were made, whereas in our case the surgery delay was included in the statistical evaluation, effected by means of a logistic regression. Also the neuropsychological scoring was graded differently in our study. Inspection of Table 4 suggests that it is more appropriate to speak of a late surgery disadvantage, rather than of an early surgery advantage, because only 4% of the patients were operated on within three days, (versus 41% of Sonesson *et al*[5]); owing to this fact, our data do not bear a direct contribution to the choice of operation time in the terms discussed by Sonesson *et al.*[5]

It is interesting to note that timing of intervention does not influence the prognosis of the Glasgow Outcome Scale and of the Clinical, Emotional and Social outcome scale (CES). The latter result may be related to the greater sensitivity of neuropsychological tests to score residual abilities of patients. Alternatively, the disadvantage of late surgery may be attributed to "toxic" factors that act diffusely on the cerebral cortex, without producing focal injuries of the brain (see, for example, the hypothesis put forward by Ropper and Zervas[2]). The relative independence on the neuropsychological from the neurological variables can be also found in the fact that 31% of the subjects with Good Recovery on GOS had two or more pathological scores on neuropsychology, whereas 27% of the subjects Moderately Disabled on GOS were within the norm on neuropsychology.

No difference in the general neuropsychological severity was found between different aneurysm sites, in agreement with the observations made by Ljunggren *et al.*[4] Obviously, this finding does not imply that the pattern of neuropsychological defect is similar in the different groups.

In conclusion, the main results of this investigation indicate a prognostic disadvantage for patients who underwent delayed surgery. This confirms the observation of Sonesson *et al*[5] that early intervention is not followed by a worse neuropsychological outcome. Neuropsychological assessment provides a useful dimension in evaluation and specifically increases its diagnostic power. In this study, only an index of general neuropsychological severity was taken into account, and this limits the information that this instrument can provide. In the other papers which describe our study[7,8] we analyse in detail the neuropsychological defects associated with the different aneurysm sites, distinguishing between the several neuropsychological functions examined, and for each function use a more detailed analysis of the degree of impairment.

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