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Behavioral profile of unruptured intracranial aneurysms: a systematic review

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Abstract

Objectives: To systematically review the literature on the neuropsychological, psychosocial, and functional profiles of patients with unruptured intracranial aneurysms. **Methods**: This review was limited to peer-reviewed research articles that reported cognitive, psychosocial, and/or functional profiles of patients with unruptured intracranial aneurysms. Studies were identified through Medline and PsychINFO by searching "(unruptured [intracranial OR cerebral] aneurysm) AND (cogniti* OR neuropsycholog* OR anxiety OR depression OR [quality of life] OR work OR employment OR [activities of daily living] OR [instrumental activities of daily living])." Only articles that were published since January 1997 were considered. Reference lists of included articles were inspected for additional studies. Only articles in English were included. Case studies were excluded. Twenty-two articles were included in this review. **Results**: The literature demonstrates that although treatment for unruptured intracranial aneurysms allays anxiety, it also results in an observable, though transient decline in cognition and daily functioning. Even before treatment, preliminary evidence hints that these patients are not free of such impairments. **Conclusions**: The algorithm that underlies the decision to treat an unruptured intracranial aneurysm ought to add more weight to the neuropsychological, psychosocial, and functional profiles of these patients. The clinical relevance of these patients does not begin and end with their risk of rupture.

Introduction

A saccular intracranial aneurysm is a focal out-pouching of a cerebral artery that is at risk of rupture. The prevalence of unruptured intracranial aneurysms (UIAs) is about 3.2%.[1] Most are asymptomatic, being discovered incidentally or detected by familial screening. The 5-year cumulative rupture rate of UIAs ranges from 2.5% to 50%, depending on the size and location of the UIA.[2,3] Although the risk of rupture is small, the consequences thereof are dire. Rupture results in an anuerysmal subarachnoid hemorrhage (aSAH), a medical emergency whose resultant mortality and morbidity are substantial.[4] aSAH is responsible for 27.3% of all stroke-related years of potential life lost before the age of 65.[5]

As prophylaxis, patients with UIAs may undergo treatment, whether it be surgical clipping or endovascular coiling. Although mortality is a rare outcome of these procedures, neither of them is without risks of morbidity.[6] The risks of mortality and neurological disability have been estimated to be around 2.6% and 10.9%, respectively.[7] Therefore, the decision to undergo or to forego treatment is not an easy one to make.[8,9] It is especially difficult considering that UIAs are observed most frequently in middle-aged individuals who have many years of family, social, and work life ahead of them. It is in this context that a physician must establish which of these two risks, that of rupture or that of treatment, is greater. Only when equipped with this knowledge can a patient make a truly informed decision.

The algorithm that underlies the decision to treat an UIA ought to also include information about the cognitive, psychosocial, and functional outcomes of treatment. These outcomes have already been reviewed by Towgood et al.[6] Since this review, 18 studies have contributed to this literature. The objective of this article is twofold: first, it will discuss the cognitive, psychosocial, and functional profiles of UIA patients before treatment; second, it seeks to provide an updated review of the studies that have investigated the cognitive, psychosocial, and functional outcomes of UIA treatment.

Methods

This review was limited to peer-reviewed research articles that reported cognitive, psychosocial, and/or functional profiles of UIA patients. Studies were identified through Medline and PsychINFO by searching "(unruptured [intracranial OR cerebral] aneurysm) AND (cogniti* OR neuropsycholog* OR anxiety OR depression OR [quality of life] OR work OR employment OR [activities of daily living] OR [instrumental activities of daily living])." Only articles that were published since January 1997 were considered. Reference lists of included articles were inspected for additional studies. Only articles in English were included. Case studies were excluded. Twenty-two articles were included in this review.

Results

Neuropsychological, psychosocial, and functional profiles of UIA patients before treatment

Neuropsychological profile

Although the cognitive functioning of UIA patients has been tested before treatment, it has been done so only in the context of how it changes after treatment. What has not yet been investigated is whether these changes are from normal or already impaired cognitive functioning. Indeed, there is a dearth of discussion on the pretreatment cognitive status of UIA patients. Three studies have made it possible to retrospectively detect the presence of neuropsychological impairment in their patient samples[10–12]; all of them provide evidence that UIA patients are not free of impairment before treatment. Fukunaga et al.[10] observed that 7 of 30 patients scored less than 27 on the Mini-Mental State Examination (MMSE), with one patient scoring as low as 22. Haug et al.[11] observed impairments in executive function, intellectual functioning, and visual memory in 15 UIA patients. Less convincing evidence is provided by Towgood et al.,[12] who observed that 1 of 23 patients scored less than or equal to 27 on the Telephone Interview for Cognitive Status (TICS).

Notwithstanding the preliminary evidence of cognitive impairment in untreated UIA patients, one issue has not yet been addressed: why do UIA patients have this impairment before treatment? The answer to this question may be gleaned from studies of patients with vascular cognitive impairment (VCI).

The pathophysiology that underlies cognitive impairment in VCI patients may be the same as that which underlies cognitive impairment in UIA patients. The risk factors for developing VCI are the same as those for developing an UIA; namely, smoking and hypertension have been demonstrated to increase one's risk of developing an intracranial aneurysm.[13,14] This is substantiated by the International Study of Unruptured Intracranial Aneurysms (ISUIA), in which 44.0% of 4060 patients were current smokers, 33.6% had a history of smoking, and 41.1% had hypertension.[3] Although VCI is largely a phenomenon of the aged, UIAs are most frequently observed in middle-aged individuals. This does not, however, preclude the possibility that vascular risk factors have already precipitated white matter abnormalities in UIA patients. It is established that the early and chronic presence of vascular risk factors is associated with white matter abnormalities later in life;[15] some studies have demonstrated that these abnormalities are noticeable as early as 30.[16] Bearing this in mind, it is not unreasonable to draw similarities between the underpinnings of cognitive impairment in VCI patients and those in UIA patients. That is, the cognitive impairment in UIA

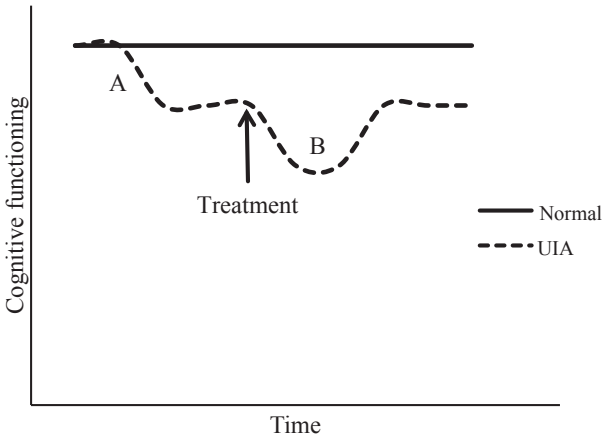

Figure 1. Comparison of cognitive functioning over time between UIA patients and the general population. (A) The long-term presence of vascular risk factors results in pathological changes in cerebral vasculature, which in turn results in damage to white matter and this results in a decline in cognitive functioning. (B) UIA treatment results in a transient decline in cognitive functioning. Although cognitive functioning returns to pretreatment levels, it remains below that of the general population.

patients may be underlain by focal white matter damage, the consequence of small, pathological changes to cerebral vasculature; in turn, these changes are a product of the long-term presence of vascular risk factors. Therefore, it is hypothesized that the cognitive functioning of UIA patients is subject to both the long-term presence of vascular risk factors and the treatment of their aneurysms (see "Neuropsychological, psychosocial, and functional profiles of UIA patients after treatment"). Although the effect of vascular risk factors on white matter is permanent, resulting in a persistent though subtle impairment in cognition, that of treatment is transient, resulting in a temporary though significant decline in cognition (Fig. 1).

Cognitive impairment in patients with untreated UIAs may find its roots in their anxiety (see Psychosocial profile). This hypothesis finds evidence from studies that have demonstrated poor cognitive functioning, especially in the domains of memory and executive function, in patients with anxiety disorders.[17] One explanation for this finding is that anxiety depletes cognitive resources.[18]

Evidence for this hypothesis can be gleaned from a study that demonstrates both elevated anxiety, as measured by the General Health Questionnaire-30, and impaired cognition, as measured by a neuropsychological battery, in patients with untreated UIAs.[11] To the extent that anxiety impairs cognition in patients with untreated UIAs, then the treatment of their aneurysms ought to allay anxiety and simultaneously improve cognition. The effect of relieving anxiety on cognition is difficult to discern considering that posttreatment cognition may also be informed by a myriad of factors, not the least of which is the treatment itself. Two studies have investigated both anxiety and cognition both before and after UIA treatment.[11,19] In the first study, investigators observed a significant decrease in state anxiety, as measured by the State-Trait Anxiety Scale, 1 month after surgical clipping. Although this was accompanied by a significant increase in performance IQ, as measured by the WASI-R, it was also accompanied by a significant decrease in delayed visual memory, as measured by the Rey Osterreith Complex Figure Test (ROCFT).[19] In the second study, anxiety, as measured by the General Health Questionnaire-30, was lower at both 3 and 12 months after surgical clipping. Although this corresponded to an improvement in performance on the Verbal and Design Fluency Tests, it also corresponded to a decline in performance on the Color-Word Interference test (CWIT).[11] Therefore, the effect of allaying anxiety on cognition remains an equivocal one.

Psychosocial profile

Harboring an intracranial aneurysm does not necessarily bear adverse health consequences. However, being made aware that one harbors an intracranial aneurysm could conceivably result in conditions of clinical relevance. It is not difficult to imagine how this awareness could make a patient feel as though he/she is a "ticking time bomb." This feeling is compounded by the patient's middle age; having many more years of life to live, work, and spend with family and friends, he/she has much to lose from the rupture of his/her aneurysm. The presence of psychiatric abnormalities has been substantiated by several studies. One study found that as a group, untreated UIA patients did not have higher levels of anxiety or depression than a reference population; however, there were several cases of patients with probable anxiety and depression.[20] These findings receive support from those of van der Schaaf et al.[21]; however, this study not only included nine patients with untreated UIAs but also 12 with arteriovenous malformations. The presence of anxiety before treatment is also evidenced by studies that observed a decrease in anxiety after treatment, after the risk of rupture was eliminated.[19,22,23]

Functional profile

The quality of life of these patients could be compromised by the knowledge that they harbor an intracranial aneurysm. This hypothesis has also received support from several studies: compared to reference populations, patients with untreated UIAs demonstrated a lower quality of life in the context of both physical and mental health.[11,20,23–25] Haug et al.[11] reported the employment statuses of UIA patients before treatment: though seven of 15 patients were working full-time, four were receiving disability benefits, and one had retired despite the sample's relatively young age range (42–63 years). The remaining patients were working part-time (2) or were undergoing training or rehabilitation (1). The reasons underlying each patient's work status were not reported. However, these results provide evidence that even before treatment, some UIA patients have functional impairment. In summary, though rupture is the greatest health risk to UIA patients, it is not the only risk to them; a considerable number of these patients have anxiety, depression, a poor quality of life, and perhaps cognitive and occupational impairment even before treatment.

Neuropsychological, psychosocial, and functional profiles of UIA patients after treatment

The findings of the studies of cognitive outcome are presented in Table 1 and those of the studies of psychosocial and functional outcomes are presented in Table 2.

Table 1. Neuropsychological outcome of UIA treatment.

Study	Sample size	Tests	Follow-up period	Findings
The International Study of Unruptured Intracranial Aneurysms Investigators[26]	1172 996 clipped 176 coiled	General cognitive ability: MMSE, TICS	1 month, 1 year	1 month No aSAH history: 5.5% have CI, 6.1% have CI and neurological disability SAH history: 9.6% have CI, 1.0% have CI and neurological disability 1 year No aSAH history: 5.4% have CI, 3.3% have CI and neurological disability SAH history: 9.1% have CI, 1.5% have CI and neurological disability
Fukunaga et al.[10]	30 clipped	General cognitive ability: MMSE Executive function: kana-hiroi test, maze test	1 month, 3 months	1 month General cognitive ability: ↓ Executive function: ↓ 3 months General cognitive ability: = Executive function: =
Hillis et al.[29]	20 clipped	Working memory: digits forward (WAIS-R), digits backward (WAIS-R), symbol digit (WAIS-R) Visuospatial ability: block design Language: BNT Visual memory: Warrington recognition memory test, ROCFT Verbal memory: RAVLT Executive function: Stroop test Verbal fluency: COWAT Psychomotor ability: GPBT General memory: WMS-R	3 months	Working memory: = Visuospatial ability: = Language: = Visual memory: = Verbal memory: ↓ Executive function: ↓ Verbal fluency: ↓ Psychomotor ability: = General memory: =
Ohue et al.[27]	43 clipped	General cognitive ability: MMSE Executive function: kana-hiroi test Visuospatial ability: Kohs block design test Verbal memory: Miyake's memory test	1 month, 6 months	1 month General cognitive ability: 0% have impairment Executive function: 19% have impairment Visuospatial ability: 6% have impairment Verbal memory: 31% have impairment 6 months General cognitive ability: not tested Executive function: 100% returned to baseline Visuospatial ability: 100% returned to baseline Verbal memory: 60% returned to baseline
Tuffiash et al.[30]	25 clipped	General memory: WMS-R Visual memory: ROCFT Executive function: TMT Psychomotor ability: GPBT Verbal fluency: COWAT	1 week, 3–6 months	1 week: General memory: 12% have impairment Visual memory: 12% have impairment

(*Continued*)

Table 1. Continued.

Study	Sample size	Tests	Follow-up period	Findings
				Executive function: 0% have impairment Psychomotor ability: 8% have impairment Verbal fluency: 0% have impairment 3–6 months: all patients returned to baseline, except one, whose impairments were not specified
Wiebers et al.[3]	2368 patients 1917 clipped 451 coiled	General cognitive ability: MMSE, TICS	1 month, 1 year	1 month Clipping: 4.64% have CI, 4.23% have CI and neurological disability Coiling: 3.33% have CI, 1.77% have CI and neurological disability 1 year Clipping: 5.74% have CI, 2.76% have CI and neurological disability Coiling: 3.55% have CI, 2.00% have CI and neurological disability
Otawara et al.[35]	44 patients All clipped	General intelligence: WAIS-R General memory: WMS-R Visual memory: ROCFT	1 month	General intelligence: ↑ General memory: = Visual memory: ↑
Towgood et al.[31]	26 19 clipped 7 coiled	Language: BNT General intelligence: WAIS-III General memory: WMS-III Visual memory: ROCFT Executive function: TMT Verbal fluency: COWAT	6 months	Language: ↑ General intelligence: ↑ General memory: ↑ Visual memory: = Executive function: = Verbal fluency: =
Towgood et al.[12]	49 23 untreated 19 clipped 7 coiled	General cognitive ability: TICS	6 months	General cognitive ability: ↑
Haug et al.[11]	15 All clipped	Verbal memory: CVLT-II Visual memory: ROCFT Psychomotor ability: GPBT Working memory: digit span (WAIS-III), digit symbol (WAIS-III) Executive function: color-word interference test (DKEFS), TMT (DKEFS) General intelligence: WASI-R Verbal fluency: verbal fluency test (DKEFS) Visuospatial ability: design fluency test (DKEFS)	3 months, 12 months	3 months: Verbal memory: impairment Visual memory: impairment Psychomotor ability: impairment Working memory: no impairment Executive function: no impairment General intelligence: impairment Verbal fluency: no impairment Visuospatial ability: no impairment 12 months: Verbal memory: no impairment Visual memory: no impairment Psychomotor ability: impairment Working memory: no impairment Executive function: no impairment General intelligence: impairment Verbal fluency: no impairment Visuospatial ability: no impairment
Otawara et al.[38]	39 All clipped	General intelligence: WAIS-R General memory: WMS-R Visual memory: ROCFT	1 month	

(*Continued*)

Table 1. Continued.

Study	Sample size	Tests	Follow-up period	Findings
Kubo et al.[19]	28 All clipped	General intelligence: WAIS-R General memory: WMS-R Visual memory: ROCFT	1 month	General intelligence: ↑ General memory: = Visual memory: ↑
Pereira-Filho et al.[39]	40 All clipped	General cognitive ability: MMSE	1 month	General cognitive ability: =
Preiss et al.[32]	65 33 clipped 32 coiled	Verbal memory: auditory verbal learning test Executive function: TMT	1 year	Verbal memory: = Executive function: =
Seule et al.[28]	42 All clipped	Memory: RAVLT, RVDLT, non-verbal learning test, logical memory (WMS), digit span (WAIS), block-tapping test Attention: test of attentional performance, test of deux barrages Executive function: word fluency (COWAT), word design (five-point test), Stroop test, tower of London test Visual perception and construction: ROCFT, poppelreuter-ghent's overlapping figures test, spatial test	Mean 55 days	Memory: two have mild impairment, three have moderate impairment, none have severe impairment Attention: two have mild impairment, two have moderate impairment, none have severe impairment Executive function: four have mild impairment, one has moderate impairment, none have severe impairment Visual perception and construction: two have mild impairment, none have moderate impairment, none have severe impairment

Neuropsychological outcome

The International Study of Unruptured Intracranial Aneurysms[3,26] was the first to define morbidity after UIA treatment not only as neurological disability (Rankin score ≥3), but also as neuropsychological impairment (MMSE score <24 or TICS score <27). The total rates of morbidity were 12.5% 1 month posttreatment and 11.7% 1 year posttreatment. Notably, regardless of the time of assessment, type of treatment, and history of aSAH, the rate of neuropsychological impairment was higher than that of neurological disability. This suggests that a considerable proportion of morbidity after UIA treatment is accounted for by neuropsychological impairment. Therefore, a strictly neurological definition of morbidity could substantially underestimate morbidity after UIA treatment. Since the ISUIA, several studies have investigated whether or not UIA treatment impairs neuropsychological functioning.

Executive function

Eight studies have examined executive function and its subdomains: inhibitory control, verbal fluency, and cognitive flexibility.[10,11,27–32] The studies by Fukunaga et al.,[10] Ohue et al.,[27] and Seule et al.[28] are difficult to compare to the others, since they failed to explicitly define impairment in executive function, to assess executive function both before and after treatment, and/or to do so using validated tests. Consequently, the following discussion focuses only on the remaining five studies.

Inhibitory control

Inhibitory control was tested by means of the Stroop test or the CWIT of the Delis-Kaplan Executive Function System (DKEFS). Hillis et al.[29] observed a significant increase in the time to complete the Stroop interference trial 3 months after surgery, a finding that is suggestive of poor outcome. Similarly, Haug et al.[11] observed an increase in the time to complete the CWIT inhibition trial 3 months after surgery; however, 12 months after surgery, the time to complete the inhibition trial decreased below that before surgery. Time to complete the inhibition/switching trial, designed to be more difficult than the inhibition trial, increased both 3 and 12 months after surgery. In a comparison with normative data, Hillis et al. still observed impaired performance; despite the less conservative definition of Haug et al., impaired performance was not detected. This makes it difficult to arrive at a conclusion about the status of inhibitory control after UIA treatment.

Table 2. Psychosocial and functional outcomes of UIA treatment.

Study	Sample size	Tests	Follow-up period	Findings
Raaymakers et al.[37]	18 All clipped	Quality of life: SIP, SF-36	3 months, 12 months	3 months Quality of life: ↓ (SIP: household management, mobility, social interaction, ambulation, alertness/behavior, work, recreation pastimes, eating, physical subset, psychosocial subset, total; SF-36: physical functioning, social functioning, physical role limit, vitality, pain) 12 months Quality of life: = (exception: SF-36: physical role limit, vitality, pain)
Brilstra et al.[25]	49 32 clipped 17 coiled	Quality of life: SF-36, EuroQol Mood: HADS	3 months, 12 months	Clipped: 3 months Quality of life: SF-36: ↓ (social functioning, general mental health, vitality, bodily pain); EuroQol: = Mood: ↑ depression 12 months Quality of life: SF-36: ↑ (exception: role limitations because of emotional problems, bodily pain); EuroQol: = Mood: = Coiled: 3 months Quality of life: SF-36: ↑ (role limitations because of physical health problems); EuroQol: = Mood: = 12 months Quality of life: = Mood: =
Otawara et al.[22]	37 All clipped	Anxiety: STAI	1 month	Anxiety: trait anxiety: =; state anxiety = ↓
Towgood et al.[12]	49 23 untreated 26 treated 19 clipped 7 coiled	Quality of life: SF-36, SRRS Depression: BDI Anxiety: STAI	6 months	Quality of life: SF-36: ↓ (health perception); SRRS: = Depression: = Anxiety: =
Solheim et al.[36]	63 37 clipped 26 coiled	Quality of life: SF-36 Mood: HADS Employment status	5.5 years	Clipped: Quality of life: ↓ (role physical, role emotional) Mood: 11 probable anxiety, 11 probable depression Employment status: working = 12; sick leave = 6; disability insurance = 12; retired = 7 Coiled: Quality of life: ↓ (role physical, role emotional) Mood: 8 probable anxiety, 4 probable depression Employment status: working = 11; sick leave = 1; disability insurance = 8; retired = 6
Yamashiro et al.[23]	67 All clipped	Quality of life: SF-36 Mood: HADS	3 months, 1 year, 3 years	3 months: Quality of life: ↑ mental health; ↓ bodily pain Mood: ↓ anxiety, depression 1 year: Quality of life: ↑ physical functioning, social functioning, physical limitations, emotional limitations, mental health, vitality Mood: ↓ anxiety, depression 3 years: Quality of life: similar to reference population Mood: ↓ anxiety, depression

(*Continued*)

Table 2. Continued.

Study	Sample size	Tests	Follow-up period	Findings
Yamashiro et al.[24]	149 All clipped	Quality of life: SF-36 Mood: HADS	2.8 years	Quality of life: low physical functioning, general health perception, physical role limits, emotional role limits Mood: low anxiety, depression
Haug et al.[11]	15 All clipped	Quality of life: GHQ-30, SF-36 Employment status	3 months, 12 months	3 months Quality of life: GHQ-30: ↓ (coping); SF-36: ↓ (social functioning, role physical) Employment status: full-time = 3, part-time = 1, disability benefits = 4, retired = 1, temporary sick leave = 5, rehabilitation = 1 12 months Quality of life: GHQ-30: ↓ (well-being); SF-36: ↓ (role physical, general health, bodily pain) Employment status: full-time = 8, part-time = 1, disability benefits = 4, retired = 1, work training/rehabilitation = 1
Kubo et al.[19]	28 All clipped	Anxiety: STAI	1 month	Anxiety: trait anxiety: =; state anxiety = ↓
Buijs et al.[20]	173 81 untreated 92 treated 73 clipped 57 coiled	Quality of life: SF-36, EuroQol Mood: HADS	4.7 years	Quality of life: = Mood: =

Verbal fluency

The Controlled Oral Word Association Test (COWAT) or the Verbal Fluency test of the DKEFS was used to test verbal fluency. It is thought that the letter fluency trial, wherein a participant must list as many words as possible that start with a specific letter (e.g., F) in 1 min, is a more suitable assessment of executive function than the category fluency trial, wherein a participant must list as many words as possible that belong to a specific category (e.g., animals) in 1 min. Although Hillis et al.[29] and Haug et al.[11] reported performances on the letter fluency trial, it is not certain whether those reported by Tuffiash et al.[30] and Towgood et al.[31] are on the letter fluency trial, category fluency trial, or a combination of both trials. Although Hillis et al. observed impaired verbal fluency 3 months after surgery, Haug et al., Tuffiash et al., and Towgood et al. did not do so in a range of 1 week to 1 year after treatment. What differentiates the former study from the latter study is the distribution of aneurysm location in each sample of patients: whereas 39% of aneurysms in the former study stem from the anterior cerebral, anterior communicating, or pericallosal artery, only 0%, 6%, and 15% of aneurysms in the latter studies stem from these arteries, respectively. Studies suggest that the integrity of the areas supplied by these arteries is critical for intact verbal fluency.[33,34] The aneurysm locations reported by Hillis et al. are pooled from 20 unruptured and 27 ruptured patients; since aneurysms in the posterior circulation are more likely to rupture than those in the anterior circulation, it is likely that the ruptured patients did not contribute much to the number of anterior circulation aneurysms. The impaired verbal fluency was observed by Hillis et al. regardless of whether performance before treatment was compared to that after treatment, the approach used by Tuffiash et al. and Towgood et al., or postoperative means were compared to published means of healthy controls, the approach used by Haug et al. Therefore, it appears as though verbal fluency remains intact after UIA treatment, though this may depend on the location of the UIA.

Cognitive flexibility

A patient's capacity for cognitive flexibility was gauged by the Trail Making test. It is thought that performance on the B version, wherein a participant must draw lines between both letters and numbers in sequence (i.e., from 1 to A, from A to 2, from 2 to B, etc.) is a better proxy of executive function than the A version, wherein a participant must draw lines between only letters or numbers in sequence (i.e., from A to B, from B to C, etc.). Although Haug et al.,[11] Towgood et al.,[31] and Preiss et al.[32] reported performances on the B version of this test, it is not certain whether that reported by Tuffiash et al.[30] is on the A version, B version, or a combination of both versions. None of these studies observed impaired cognitive flexibility in a range of 1 week to 1 year after treatment, whether performance before treatment was compared to that after treatment,[30–32] or postoperative means were compared to published means of

healthy controls.[11] This provides evidence that cognitive flexibility remains intact after UIA treatment.

Memory

Nine studies have evaluated memory, whether it be verbal, visual, or working memory.[11,19,27–32,35] The findings of Seule et al.[28] have been excluded from the following discussion because they are not domain-specific.

Verbal memory

Comparisons of the studies that assessed verbal memory are difficult to make in light of the variability in the tests that were used to assess this domain. Despite this variability, these studies seem to adhere to a common temporal pattern: if verbal memory was assessed within 3 months, then impairment therein was observed; if it was assessed beyond 6 months, then it was observed to be intact. Twenty UIA patients demonstrated impairment in both the immediate and delayed recall trials of the Rey Auditory Verbal Learning Test 3 months after surgery;[29] impairment in the delayed, but not the immediate recall trial was still demonstrated in a comparison of the UIA patients with healthy controls. Likewise, Ohue et al.[27] and Haug et al.[11] observed impairment in Miyake's Memory Test and the California Verbal Learning Test-II (learning and short- and long-term memory trials) 1 month and 3 months after surgery, respectively. However, these impairments were not observed at a long-term follow-up, 6 and 12 months after surgery, respectively. Similarly, Towgood et al.[31] and Preiss et al.[32] failed to detect impairment in subtests of the Wechsler Memory Scale-III (WMS-III; Logical Memory I and II, Word Lists I and II) and the Auditory Verbal Learning Test 6 and 12 months after treatment, respectively. Therefore, it appears as though UIA treatment results in impairment in verbal memory; however, this impairment is transient, resolving itself over several months after treatment.

Visual memory

The studies that have evaluated visual memory did so using the ROCFT. Two of the studies[19,35] reported an improvement in the recall trial and no change in the copy trial of this test 1 month after surgery. Both groups conceded that this finding could be a consequence of practice effects. Having controlled for practice effects by using variants of the ROCFT, Tuffiash et al.[30] reported no change in the recall trial, but did report a decline in the copy trial 1 week after surgery. This decline was attributed to 3 of 25 patients. Three to 6 months after surgery, however, these patients performed at preoperative levels. In agreement with this finding, Hillis et al.[29] and Towgood et al.[31] failed to detect a decline in performance on the ROCFT 3 and 6 months after treatment, respectively. Other tests of visual memory, the Warrington Recognition Memory test and the Face Recognition I and II subtests of the WMS-III, respectively, did not yield different results. Finally, Haug et al.[11] reported that the mean ROCFT score 3 months after surgery was more than 0.5 standard deviations below the published mean of healthy controls, their definition of cognitive impairment. However, such impairment was also observed before treatment, making it difficult to attribute the postoperative deficits to the treatment; in fact, the mean ROCFT score increased both 3 and 12 months after surgery. These studies do not suggest that UIA treatment results in long-term impairment in visual memory.

Working memory

Working memory was evaluated by means of the Digit Span and Digit Symbol subtests of the Wechsler Adult Intelligence Scale (WAIS). None of these studies[11,29,31] detected a decline in performance on either of these tests in a range of 3–12 months after treatment. However, in the study by Hillis et al.,[29] UIA patients demonstrated poorer performance on the Digit Symbol compared to healthy controls. In determining the effect of UIA treatment on cognition, however, a comparison between patients and controls is not as appropriate as one between patients' performances before and after treatment. Towgood et al.[31] observed an improvement in performance on the Digit Symbol 6 months after treatment, a finding that they attributed to practice effects. These investigators also assessed working memory using the Letter-Number Sequencing subtest of the WMS-III, again failing to detect a decline in performance. These studies do not suggest that working memory is impaired after UIA treatment.

Other cognitive domains

Language

The studies that have evaluated language suggest its preservation after UIA treatment. Two studies assessed naming[29,31] using the Boston Naming Test, failing to detect impairment therein in a range of 3–6 months after UIA treatment. Vocabulary was assessed by Haug et al.[11] by means of the vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence-Revised (WASI-R): though mean scores were more than 0.5 standard deviations below the normal mean both 3 and 12 months after UIA treatment, the preoperative mean score was correspondingly low, suggesting that surgery did not exacerbate preoperative deficits in vocabulary. This is substantiated by a study

that failed to detect impairment in vocabulary 6 months after treatment.[31]

Visuospatial ability

Using the block design subtest of the WAIS or the WASI-R, studies have observed the sparing of visual memory in a range of 3–12 months after treatment.[11,29,31] Haug et al.[11] also failed to detect impairment in this domain using the design fluency subtest of the DKEFS. In contrast, Ohue et al.[27] observed visuospatial impairment using the Kohs Block Design test, 1 month after treatment; however, such impairment was limited to only 2 of 36 patients, both of whom returned to preoperative levels 6 months after treatment.

Psychomotor ability

Studies suggest the preservation of psychomotor ability as measured by the Grooved Pegboard test in a range of 1 week to 1 year after UIA treatment.[11,29,30] Although Tuffiash et al.[30] observed poor performance on this test 1 week after treatment, this was limited to only 2 of 25 patients, both of whom returned to preoperative levels 3–6 months after treatment. Likewise, Haug et al.[11] observed poor performance on this test 3 and 12 months after surgery; however, performance was comparably poor before surgery. This finding suggests that although psychomotor ability may be impaired before treatment, this impairment is not aggravated by the treatment.

Clipping versus coiling

The studies that have made comparisons between UIA patients treated by surgical clipping and those treated by endovascular coiling failed to detect differences in cognitive outcomes. In the ISUIA, a comparison of the rate of neuropsychological impairment between clipped and coiled patients was not performed. However, rates of cognitive impairment, as elicited by the MMSE or the TICS, were generally and slightly higher in clipped than in coiled patients regardless of aSAH history and time of assessment.[3] Using a comprehensive battery of neuropsychological tests, Towgood et al.[31] did not observe differences between 19 clipped and seven coiled patients. Likewise, no differences were observed between 33 clipped and 32 coiled patients in performance on the Auditory Verbal Learning test or the Trail Making test.[32] The small sample sizes and inescapably nonrandomized design of these studies make it difficult to definitively conclude that clipping and coiling have comparable effects on cognition. An investigation that is based on both a comprehensive battery of tests and a high sample size is called for to determine the difference, if any, between the effects of clipping and coiling on cognition.

Psychosocial outcome

The effect of UIA treatment on anxiety and depression has been the subject of several studies. Using the State-Trait Anxiety Inventory (STAI), Otawara et al.[22] observed no change in trait anxiety, but did observe a decrease in state anxiety 1 month after surgery in 37 UIA patients. These findings were replicated in a sample of 28 UIA patients older than 70.[19] Using the Hospital Anxiety and Depression Scale (HADS), Yamashiro et al.[23] yielded similar results: both anxiety and depression decreased significantly as soon as 3 months after surgery in 67 UIA patients; these lower levels of anxiety and depression were stable for 3 years. Two studies[12,20] failed to detect a treatment effect; however, in these studies, psychosocial outcome, as measured by the STAI and the Beck Depression Inventory or the HADS, was compared between a group of untreated and treated patients, rather than between the same group of patients before and after treatment.

Regardless of a treatment effect, some studies have sought to determine whether UIA patients have anxiety or depression after treatment. In comparisons with reference populations, UIA patients did not have psychosocial impairment from about 2.8–4.7 years after treatment.[20,24] Although Brilstra et al.[25] found higher levels of depression in UIA patients treated by surgical clipping, these patients did not have higher levels of anxiety 3 months after surgery; furthermore, UIA patients treated by endovascular coiling did not have higher levels of either depression or anxiety than the reference population in the same period of time. In a comparison between clipped and coiled patients, these investigators failed to detect differences in anxiety or depression. This finding finds support from that of Solheim et al.:[36] no differences in anxiety or depression were observed between clipped and coiled patients about 5.5 years after treatment. In summary, it appears as though UIA treatment alleviates the anxiety that stems from harboring an intracranial aneurysm that is at risk of rupturing. Posttreatment anxiety does not differ between clipped and coiled patients and is comparable to that of healthy individuals.

Functional outcome

Quality of life

Generally, studies have failed to detect a long-term effect of treatment on the quality of life of UIA patients. Although Raaymakers et al.,[37] using both the Sickness Impact Profile and the Medical Outcome Study Short Form 36 (SF-36), observed a decreased quality of life 3 months after surgery, it returned to preoperative levels

12 months after surgery, with physical role limit, pain, and vitality remaining suboptimal. Similar results were yielded by Haug et al.[11] In keeping with these findings, according to the SF-36, UIA patients who underwent surgical clipping demonstrated a decreased quality of life 3 months after treatment, but approached preoperative levels 12 months after treatment.[25] In the same study, there was no decrease in the quality of life of UIA patients who underwent endovascular coiling 3 and 12 months after treatment. These results were mirrored using the EuroQoL-5D. Not only did Yamashiro et al.[23] fail to detect a decline in quality of life, they found an improvement in it 3 years after surgery. Two studies assessed the effect of treatment on the quality of life of UIA patients by comparing a group of patients with untreated UIAs to one with treated UIAs.[12,20] Both studies failed to detect differences between these groups, except that untreated patients had a poorer perception of their health than patients who had been treated 6 months before testing.[12]

Studies have investigated whether or not treated UIA patients have a poor quality of life notwithstanding the effect of treatment. Buijs et al.[20] compared quality of life, as measured by the SF-36, between UIA patients treated within 4.7 years and a reference population, observing that the patients scored lower on physical function, role physical, general health, and vitality. No such differences were detected by the EuroQoL-5D. This is in contrast to the finding by Yamashiro et al.[24] that no SF-36 domains were impaired in UIA patients 3 years after treatment. This discrepancy may be attributable to the 6% of 92 patients with permanent complication-related symptoms in the former study and the only one of 67 patients with considerable disability, according to the modified Rankin Scale, in the latter study. Solheim et al.[36] compared the quality of life, as measured by the SF-36, between UIA patients who underwent surgical clipping and those who underwent endovascular coiling within 5.5 years. Although coiled patients tended to score higher than clipped patients, no significant differences were found between them. In summary, it appears as though UIA treatment does not result in a permanent decline in quality of life. Whether or not treated UIA patients have a quality of life on par with that of healthy individuals may depend on the degree to which they have disability. Preliminary evidence indicates no difference in the quality of life of UIA patients treated by surgical clipping and endovascular coiling.

Employment status

Solheim et al.[36] categorized 63 UIA patients treated within 5.5 years into one of four employment categories: working, sick leave, disability insurance, and retired. Of 37 UIA patients treated by surgical clipping, 32.4% were working and 18.9% had retired. Notably, 32.4% were receiving disability insurance and 16.2% were on sick leave. Similar though slightly more favorable percentages were found for the 26 patients who underwent endovascular coiling: 42.3% were working, 23.1% had retired, 30.8% were receiving disability insurance, and 3.8% were on sick leave. Employment status was not recorded before treatment, making it difficult to attribute the absence from work to the treatment itself. This limitation cannot be ascribed to a study by Haug et al.,[11] wherein employment was assessed before treatment, in addition to 3 and 12 months thereafter. Of 15 UIA patients, nine were working full- or part-time, one had retired, four were receiving disability benefits, and one was undergoing work training before treatment. Although this distribution became considerably less favorable 3 months after treatment (four working full- or part-time, one retired, four receiving disability benefits, five sick leave, one rehabilitation), it returned to preoperative levels by 12 months after treatment (nine working full- or part-time, one retired, four receiving disability benefits, one undergoing work training). Both of these studies suggest that a considerable proportion of UIA patients do not have optimal employment statuses after treatment; however, the latter study indicates that such statuses exist even before treatment, suggesting that they are not a result of the treatment itself.

Conclusion

The decision to treat an UIA remains complex, controversial, and contingent on a myriad of variables. The optimization of outcomes of this decision can be achieved only by knowledge of not only the risks of aneurysm rupture and of neurological disability consequent to UIA treatment but also of the neuropsychological, psychosocial, and functional outcomes thereof. This review finds that UIA treatment allays the anxiety that accompanies harboring an UIA and that it does not result in long-term decline in the quality of life of the patients who harbor them. Despite the depth of research on the effect of UIA treatment on neuropsychological outcomes, a consensus has not yet been achieved. This review finds that the effect of UIA treatment on cognition is domain-specific: there is a sparing of some domains (verbal fluency, cognitive flexibility, working memory, language, visuospatial ability, psychomotor ability) and a transient decline in others (verbal and visual memory); a conclusion about inhibitory control was not arrived at.

This review brings attention to the behavioral statuses UIA patients before treatment. Already established is the

anxiety, depression, and poor quality of life that burden untreated UIA patients. What have not yet been comprehensively investigated are the cognitive and occupational statuses of untreated UIA patients; this review finds that it is likely that impairment in these domains exists. That UIA patients have psychosocial, quality of life, and perhaps cognitive, and occupational impairments even before treatment suggests that their clinical relevance does not begin and end with their risk of rupture; therefore, their interaction with the health care system ought not be limited only to moderating this risk.

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Authors' Contributions

Michael J. Bonares performed the literature search, composed the manuscript, and created its tables and figure. A. Leonardo de Oliveira Manoel edited the manuscript. R. Loch Macdonald came up with the subject of the manuscript. Tom A. Schweizer came up with the subject of the manuscript and edited the manuscript.

Conflict of Interest

None declared.

References

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 2011;10:626–636.
2. Morita A, Kirino T, Hashi K, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med 2012;366:2474–2482.
3. Wiebers DO, Whisnant JP, Huston J, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003;362:103–110.
4. Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke 2010;41:e519–e536.
5. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology 1998;50:1413–1418.
6. Towgood K, Ogden JA, Mee E. Neurological, neuropsychological, and psychosocial outcome following treatment of unruptured intracranial aneurysms: a review and commentary. J Int Neuropsychol Soc 2004;10:114–134.
7. Raaymakers TWM, Rinkel GJE, Limburg M, Algra A. Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. Stroke 1998;29:1531–1538.
8. Piepgras DG. Controversy: clipping of asymptomatic intracranial aneurysm that is < 7 mm: no. Stroke 2013;44: S100–S102.
9. Steinberg GK. Controversy: clipping of asymptomatic intracranial aneurysm that is < 7 mm: yes. Stroke 2013;44: S97–S99.
10. Fukunaga A, Uchida K, Hashimoto J, Kawase T. Neuropsychological evaluation and cerebral blood flow study of 30 patients with unruptured cerebral aneurysms before and after surgery. Surg Neurol 1999;51:132–138.
11. Haug T, Sorteberg A, Sorteberg W, et al. Surgical repair of unruptured and ruptured middle cerebral artery aneurysms: impact on cognitive functioning and health-related quality of life. Neurosurgery 2009;64:412–420.
12. Towgood K, Ogden JA, Mee E. Psychosocial effects of harboring an untreated unruptured intracranial aneurysm. Neurosurgery 2005;57:858–864.
13. Taylor CL, Yuan Z, Selman WR, et al. Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: hypertension and other risk factors. J Neurosurg 1995;83:812–819.
14. Deka R, Koller DL, Lai D, et al. The relationship between smoking and replicated sequence variants on chromosomes 8 and 9 with familial intracranial aneurysm. Stroke 2010;41:1132–1137.
15. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–48.
16. DeCarli C, Fletcher E, Ramey V, et al. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. Stroke 2005;36:50–55.
17. Airaksinen E, Larsson M, Forsell Y. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. J Psychiatr Res 2005;39:207–214.
18. Wetherell JL, Reynolds CA, Gatz M, Pedersen NL. Anxiety, cognitive performance, and cognitive decline in normal aging. J Gerontol B Psychol Sci Soc Sci 2002;57:246–255.
19. Kubo Y, Ogasawara K, Kashimura H, et al. Cognitive function and anxiety before and after surgery for asymptomatic unruptured intracranial aneurysms in elderly patients. World Neurosurg 2010;73:350–353.
20. Buijs JE, Greebe P, Rinkel GJE. Quality of life, anxiety, and depression in patients with an unruptured intracranial aneurysm with or without aneurysm occlusion. Neurosurgery 2012;70:868–872.
21. Van der Schaaf IC. Quality of life, anxiety, and depression in patients with an untreated intracranial aneurysm or arteriovenous malformation. Stroke 2002;33:440–443.

22. Otawara Y, Ogasawara K, Kubo Y, et al. Anxiety before and after surgical repair in patients with asymptomatic unruptured intracranial aneurysm. Surg Neurol 2004;62:28–31.
23. Yamashiro S, Nishi T, Koga K, et al. Improvement of quality of life in patients surgically treated for asymptomatic unruptured intracranial aneurysms. J Neurol Neurosurg Psychiatry 2007;78:497–500.
24. Yamashiro S, Nishi T, Koga K, et al. Postoperative quality of life of patients treated for asymptomatic unruptured intracranial aneurysms. J Neurosurg 2007;107: 1086–1091.
25. Brilstra EH, Rinkel GJE, Van der Graaf Y, et al. Quality of life after treatment of unruptured intracranial aneurysms by neurosurgical clipping or by embolisation with coils. A prospective, observational study. Cerebrovasc Dis 2004;17:44–52.
26. The International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. N Engl J Med 1998;339:1725–1733.
27. Ohue S, Oka Y, Kumon Y, et al. Importance of neuropsychological evaluation after surgery in patients with unruptured cerebral aneurysms. Surg Neurol 2003;59:271–277.
28. Seule MA, Stienen MN, Gautschi OP, et al. Surgical treatment of unruptured intracranial aneurysms in a low-volume hospital–outcome and review of literature. Clin Neurol Neurosurg 2012;114:668–672.
29. Hillis AE, Anderson N, Sampath P, Rigamonti D. Cognitive impairments after surgical repair of ruptured and unruptured aneurysms. J Neurol Neurosurg Psychiatry 2000;69:608–615.
30. Tuffiash E, Tamargo RJ, Hillis AE. Craniotomy for treatment of unruptured aneurysms is not associated with long-term cognitive dysfunction. Stroke 2003;34:2195–2199.
31. Towgood K, Ogden JA, Mee E. Neurological, neuropsychological, and functional outcome following treatment for unruptured intracranial aneurysms. J Int Neuropsychol Soc 2005;11:522–534.
32. Preiss M, Netuka D, Koblihová J, et al. Cognitive functions before and 1 year after surgical and endovascular treatment in patients with unruptured intracranial aneurysms. Br J Neurosurg 2012;26:514–516.
33. Stuss DT, Alexander MP, Hamer L, et al. The effects of focal anterior and posterior brain lesions on verbal fluency. J Int Neuropsychol Soc 1998;4:265–278.
34. Vieira ACC, Azevedo-Filho HRC, Quinino S, et al. Language, memory, and verbal fluency changes in patients with aneurysmal subarachnoid hemorrhage: results of a preoperative investigation. World Neurosurg 2011;75:653–659.
35. Otawara Y, Ogasawara K, Ogawa A, Yamadate K. Cognitive function before and after surgery in patients with unruptured intracranial aneurysm. Stroke 2005;36:142–143.
36. Solheim O, Eloqayli H, Muller TB, Unsgaard G. Quality of life after treatment for incidental, unruptured intracranial aneurysms. Acta Neurochir 2006;148:821–830.
37. Raaymakers TWM. Functional outcome and quality of life after angiography and operation for unruptured intracranial aneurysms. J Neurol Neurosurg Psychiatry 2000;68:571–576.
38. Otawara Y, Ogasawara K, Kubo Y, et al. Comparison of postoperative cognitive function in patients undergoing surgery for ruptured and unruptured intracranial aneurysm. Surg Neurol 2009;72:592–595.
39. Pereira-Filho A, Pereira A, Faria M, et al. Microsurgical clipping in forty patients with unruptured anterior cerebral circulation aneurysms. Arq Neuropsiquiatr 2010;68:770–774.

