



SAHLGRENKA ACADEMY

LONG-TERM FOLLOW-UP AFTER THIRD VENTRICLE COLLOID CYST SURGERY: A COMPARISON OF OPEN AND ENDOSCOPIC SURGICAL TECHNIQUES

Degree Project in Medicine

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Table of Contents

Abstract	2
Sammanfattning på svenska	3
Introduction	4
Background and histopathology	4
Clinical picture.....	4
Management options	6
Current evidence.....	7
Specific objectives.....	8
Patients and methods	8
Journal assessment.....	10
Clinical interview	11
Ethics	12
Data collection and statistical analysis	12
Results.....	13
Post-operative stay lengths	13
Neuropsychological testing and quality of life	13
Discussion with conclusions	15
Strengths and limitations.....	16
Conclusions.....	17
Acknowledgements	18
References.....	19
Appendices	21
Appendix 1: Consultation checklist (Swedish).....	21
Appendix 2: Case report form (Swedish).....	22
Appendix 3: Instructions for psychometric testing (Swedish)	29

Abstract

Background and objectives

Colloid cysts are rare benign intracranial tumours. Although not a true neoplasia, a growing cyst may lead to obstruction of cerebrospinal fluid circulation.

Treatment is surgical, with the two most common options being excision of the lesion either by an open microsurgical technique, or by endoscopy. Because of the typical location of cysts near neural pathways of the limbic system, intra-operative damage can lead to memory impairment.

This study aimed to 1) see if the endoscopic technique leads to reduced post-operative stay lengths as indicated by previous studies, and 2) investigate if there are any differences in long-term results with regards to memory function and quality of life.

Method

Fifty-one ($n = 51$) patients were treated surgically for colloid cysts between 1998 to 2017 (34 with open microsurgery, 17 with endoscopy). Journals were assessed to gather data about post-operative stay lengths. Twenty-two patients agreed to participate in clinical interviews with neuropsychological testing.

Results

Median follow up time was 7.6 years. The endoscopy cohort had a shorter median stay length of 3 days, compared to a median of 6 days in the open cohort ($p < 0.05$).

A lower quality of life in terms of depressive mood and subjective memory function was found in the endoscopy cohort compared to the open cohort ($p < 0.05$ for both variables), however in the neuropsychological tests, no differences in memory were found.

Conclusion

This study suggests that hospital stay lengths are shorter in patients treated using the endoscopic method, which is in line with findings from previous studies. Subjective memory function and depressive scores were worse in this cohort, however objective neuropsychological tests did not support this perceived difference. Further and more elaborate, larger studies are warranted in the future.

Sammanfattning på svenska

Kolloidcystor är sällsynta, godartade blåsor i hjärnan med en typisk lokalisering i tredje ventrikeln. De utgör under en procent av alla hjärntumörer, men är i egentlig mening inga äkta tumörer, utan snarare blåsor med geleartat innehåll av varierande konsistens. Tillståndet är i sig ofarligt, men kan snabbt bli livshotande om cystorna växer till en tillräcklig storlek och täpper till cirkulationen av vätska i hjärnans hålrum.

Behandlingen utgörs i första hand av kirurgi, som syftar till att avlägsna blåsmassan eller dränera hjärnvätska. De två vanligaste ingreppen är den så kallade öppna mikrokirurgiska tekniken där man gör en större öppning i skallen för att med mikroskop operera, eller den endoskopiska tekniken där man genom ett mindre borrhål för ner ett titthålsinstrument genom skallbenet och opererar bort blåsan. Den förstnämnda tekniken är ett större ingrepp och i teorin kan den endoskopiska tekniken vara mindre riskfylld på kort sikt på grund av att det blir mindre skada på skallben och omkringliggande hjärnmassa, något andra studier också pekat på. De har även hittat skillnader i vårdtider, vilket ofta visat sig vara lägre hos endoskopiskt opererade.

Till vår kännedom finns det i nuläget inga studier som tittar på långtidsresultat avseende livskvalitet och minnesförmåga. Denna studie syftade till att se om skillnader i dessa operativa tekniker finns med avseende på postoperativ vårdtid och långtidsresultat av minnesfunktion med hjälp av minnestester och livskvalitet via enkäter.

Femtioen patienter opererades för kolloidcystor på Sahlgrenska Universitetssjukhuset mellan 1998-2017. Alla journaler granskades för att hämta data om hjärnabbildningar med röntgen eller magnetkamera och siffror för postoperativa vårdtider. Av dessa hade fyra avlidit, och 25 deltog inte i kliniska intervjuer av olika skäl, vilket resulterade i 22 patienter som deltog i intervjuerna; 7 i den endoskopiska gruppen respektive 15 i den öppna mikrokirurgiska.

Vi fann att den endoskopiskt opererade gruppen hade lägre vårdtider jämfört med den öppet opererade, med 3 dagars skillnad i median. Ingen skillnad fanns mellan grupperna vid minnestestning, men den endoskopiska gruppen upplevde subjektivt mer minnesproblem och något högre depressivitet enligt enkätsvaren. Med tanke på studiens låga antal deltagare och den begränsade studiedesignen krävs det fler studier i framtiden för att dra en grundade slutsatser.

Introduction

Background and histopathology

Colloid cysts are rare, benign intracranial lesions (or, more accurately, developmental malformations) typically located in the anterior roof of the third ventricle of the brain¹, accounting for somewhere between ~0.3-2% of all brain tumours²⁻⁴. As the name indicates, they are truly cystic and not neoplasms.

Histologically the cysts consist of a thin wall, which encapsulates the inner contents referred to as the colloid. The wall consists of an outer, fibrous layer containing collagen and an inner layer of cuboidal or columnar epithelium, which is mucin-producing². The colloid varies in composition between subjects, which accounts for the differences in imaging appearance and actual texture and color (ranging from mucous-like liquid to cheese-like).

Though there seems to be no definitive consensus on the etiology, various theories exist. One such theory proposes that the cysts originate from the paraphysis, a third ventricle structure derived from neuroectoderm that is present transiently in human embryos^{2,5}. There are inconsistencies in this theory, however, as demonstrated by a study that found that carbohydrate epitopes exhibited by colloid cysts and their contents, have also been reported for the mucins of salivary glands, uterine cervix, gall bladder and colon⁶, which points to an endodermal origin.

Clinical picture

The cysts, not being cancerous in their nature, are in themselves not dangerous. In fact, some asymptomatic colloid cysts are discovered incidentally (in fact, most are discovered incidentally, according to local experience at Sahlgrenska University hospital) when imaging the brain with computer tomography (CT) or magnetic resonance imaging (MRI) for other reasons (see *Figure 1*). However, should a colloid cyst reach sufficient size, it may obstruct cerebrospinal fluid circulation partially or completely (see *Figure 2*), leading to obstructive hydrocephalus with progressive or intermittent headaches of varying intensity as the main symptom⁷⁻¹⁰. Other symptoms may be nausea, vomiting, cognitive changes, visual blurring secondary to papilledema, rapid loss of consciousness and even death in severe cases⁷. In one case report, the authors describe a sudden death in a 17-year old girl with a two-year history of intermittent headaches, with a colloid cyst being the cause of death as confirmed by autopsy (see *Figure 3*). This demonstrates well enough that colloid cysts are, if left untreated, a potentially very dangerous condition.

Though colloid cysts can be present at any age, most reported patients are between 30 to 60 years of age⁷.

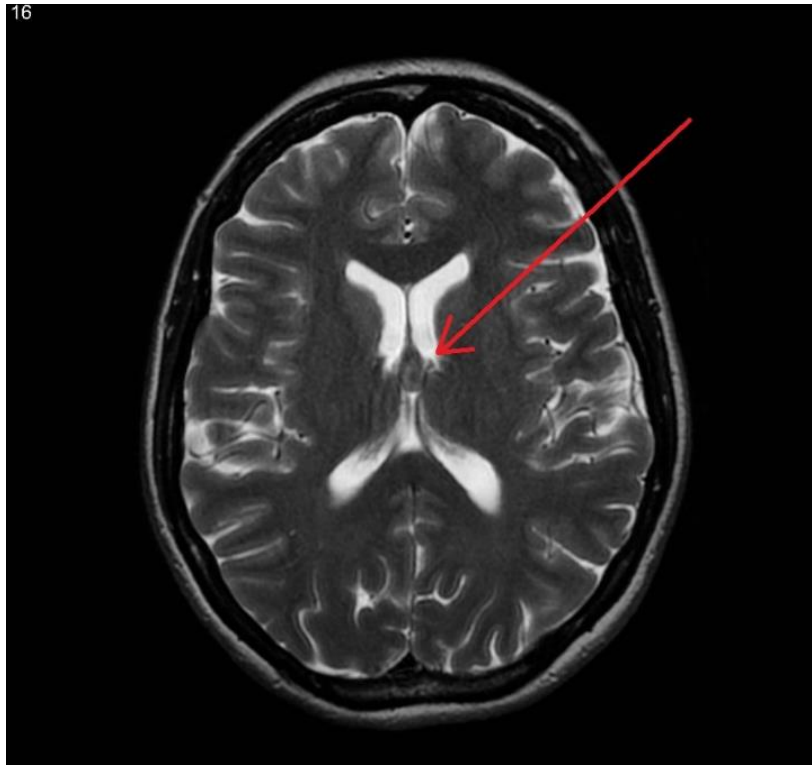


Figure 1. Axial magnetic resonance FLAIR image of an asymptomatic, colloid cyst discovered incidentally in patient seeking medical help for tinnitus. Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 4708.

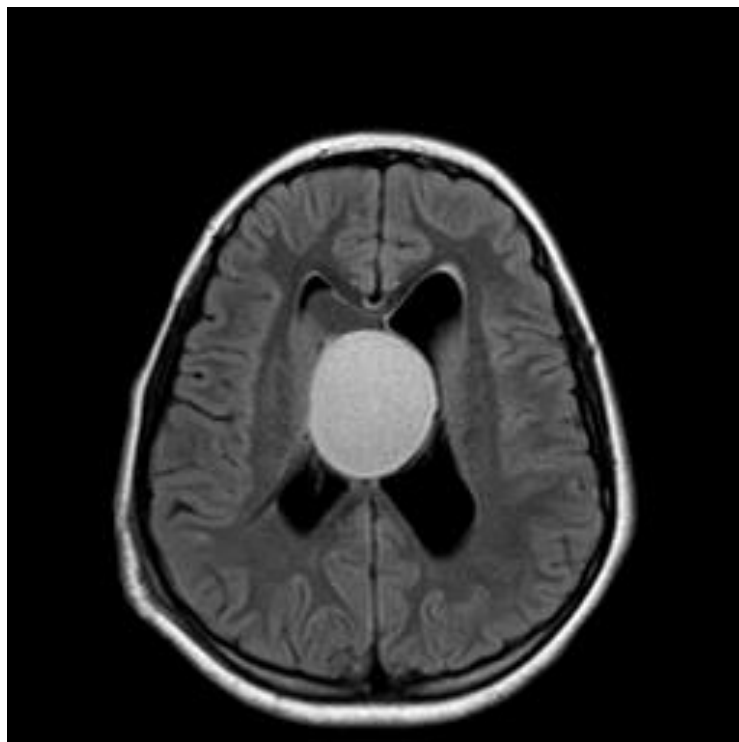


Figure 2. Axial magnetic resonance FLAIR image in patient presenting with severe headaches. Note the dilated ventricles. Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 26522

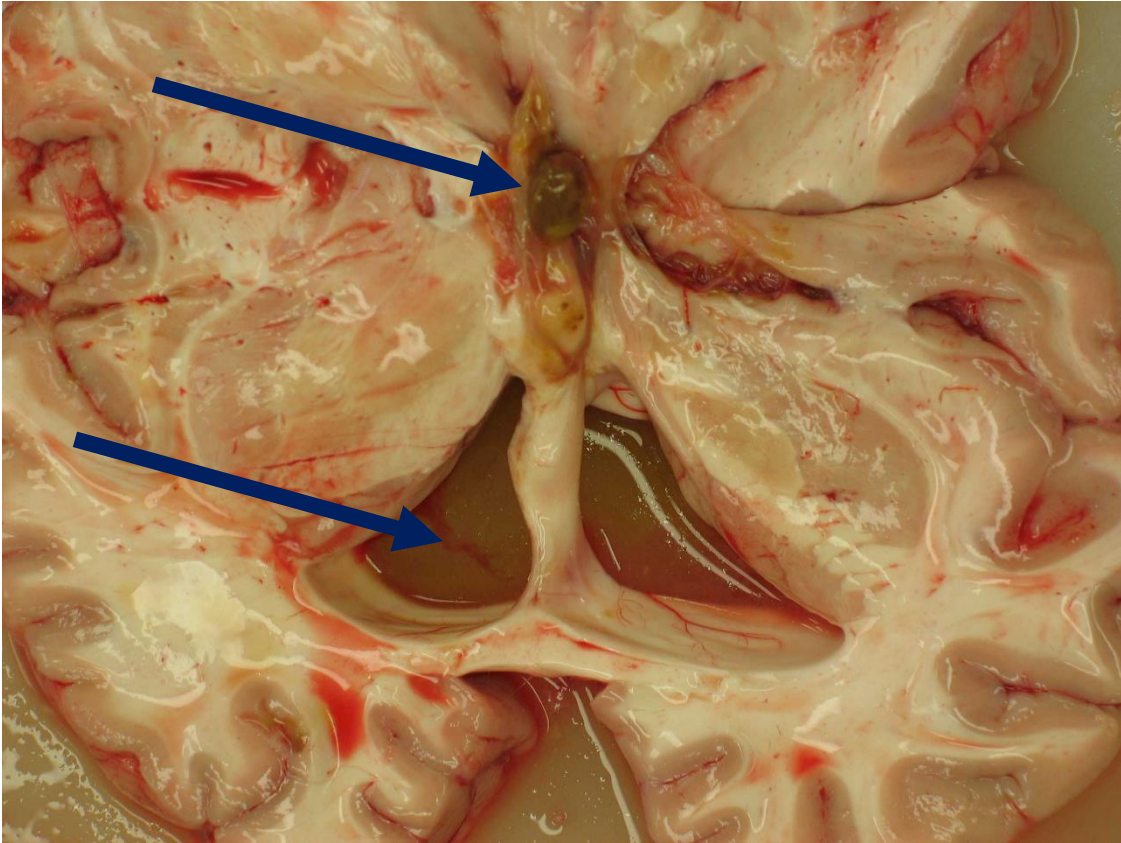


Figure 3. Autopsy of deceased 17-year old girl. Cause of death: obstructive hydrocephalus secondary to a colloid cyst. Adapted from Shaktawat, S. S., et al. (2006). "Unexpected death after headache due to a colloid cyst of the third ventricle." World Journal of Surgical Oncology 4(1): 47.

Management options

There are many options to choose from when treating these cysts, most of them based on one of two principles; 1) surgical cyst aspiration or complete removal by either open microsurgery through craniotomy with a transcortical or transcallosal approach, endoscopy or stereotactic aspiration⁷, or 2) bypassing the obstruction to restore cerebrospinal fluid communication through shunting.

Of the above mentioned, the two most common options being excision of the lesion either by an open microscopic technique or a more recent, less invasive (and therefore, less traumatic) endoscopic technique. As with any relatively complicated neurosurgical procedure, there are complications such as wound infection, abscesses, epileptic seizures and postoperative haemorrhaging. Indications for surgery are usually based on cyst size (>7-10 in diameter depending on local guidelines) as well as symptoms – asymptomatic patients with cysts <7 mm can be followed up passively over longer periods of time to observe cyst development, if any. Occasionally cysts are known to recur after surgery.

It is known that one of the more debilitating complications that might result from colloid cyst surgery is transient or permanent memory impairment¹¹. This is likely a consequence of

the typical location of colloid cysts in proximity to neural pathways of the limbic system, which is known to be important in learning and memory formation. Unintentional intra-operative damage of adjacent structures – namely the fornices - related to memory function may lead to impairment. The fornices (see *Figure 4*), which join anteriorly to form the body of the fornix, is a bundle of fibers projecting from the hippocampal formation to the medial and lateral mammillary nuclei of the hypothalamus, the septal nuclei as well as the anterior thalamic nuclei¹. Two interesting separate studies with a total of 18 cases that examined the relation between fornix damage (as seen on post-operative MRI) and memory loss as measured by neuropsychological tests, both concluded that bilateral interruption of the fornix resulted in anterograde amnesia in all cases studied^{12,13}. The main type of memory affected seems to be recall memory.

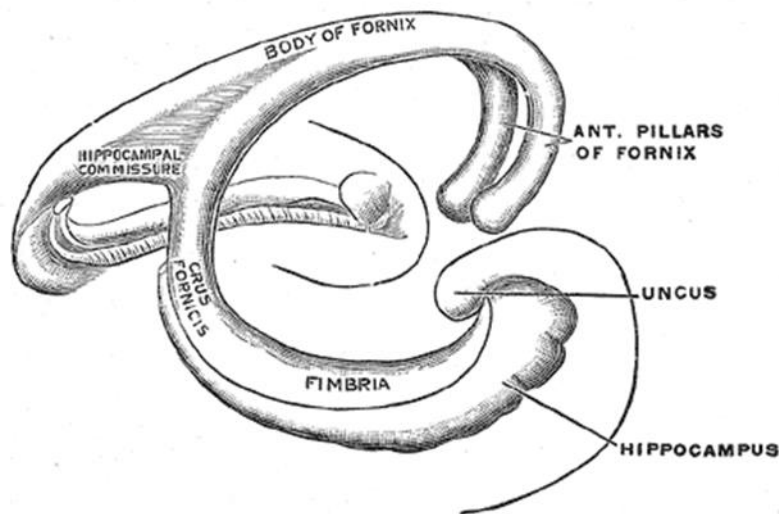


Figure 4. Picture by Henry Gray (1825–1861). Fig 747, Anatomy of the Human Body (1918)

Current evidence

One of the largest systematic reviews and meta-analysis of 1,278 patients by Sheikh et al. concluded that microsurgical resection of colloid cysts is associated with a higher rate of complete resection, lower rate of recurrence, and fewer reoperations than with endoscopic removal, but that the rate of morbidity is higher with microsurgery than with endoscopy¹⁴. Other studies and reviews have reached similar results and conclusions, and that the endoscopic technique generally leads to shorter post-operative stay lengths^{10,15,16}.

The respective strengths of both surgical techniques (as summarized by *Figure 5*) are taken into account (along with factors such as surgeon comfortability with each technique, age and history of the patient as well as the size of the colloid cyst) by neurosurgeons to decide which technique is deemed to be the most appropriate for each individual patient.

As earlier mentioned, cysts are known to recur, and as of yet there are no guidelines regarding long-term follow-up.

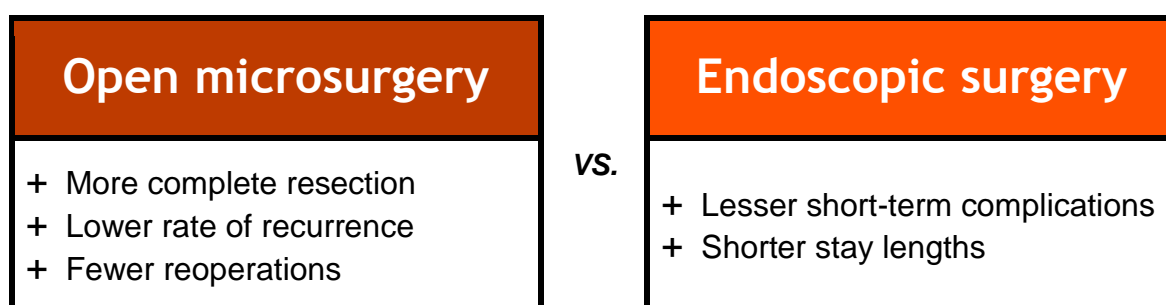


Figure 5. An illustrated comparison of the strengths of the two techniques with regards to colloid cyst removal.

Specific objectives

While there are studies comparing short-term complications, recurrence rates and hospital stay lengths between the two above mentioned techniques, to our knowledge, none to date have investigated differences, if any, between the groups regarding post-operative long-term quality of life and memory function.

This study aimed to primarily examine whether the endoscopic technique is superior in terms of reduced post-operative stay lengths as previous studies have indicated. The primary hypothesis is that the endoscopic technique leads to shorter stay lengths.

The secondary hypotheses are that there are no differences between the two techniques, neither when it comes to memory function nor life quality. The secondary aims of this study, therefore, are to investigate if possible, if there are any differences in long-term results with regards to memory function and quality of life.

Patients and methods

This study was designed as a register-based retrospective cohort study with prospective clinical follow-ups, as all subjects were already treated. To accomplish the primary objective of the study, journal assessment was performed to find data retroactively on stay lengths. For the secondary objectives, we set up a protocol (see *Appendix 1: Consultation checklist*) for prospective clinical interviews which included a follow-up interview according to a case report form (see *Appendix 2: Case report form*) neuropsychological testing, life quality questionnaires as well as MR imaging.

Of the 51 patients, only 22 participated in the clinical interviews, of which 7 were in the endoscopic cohort and 15 in the open microsurgical cohort (see *Figure 6: dropout flow-chart*). One patient in the open surgical cohort participated in the first part of the clinical interview,

but could not perform the tests or fill out the questionnaires because of brain fatigue, and was therefore excluded. Epidemiological information is presented in detail in *Table 1*.

Table 1. Epidemiological information on the subjects, divided by groups, subgroups and mode of participation.

OMC = open microsurgical cohort,

EC = endoscopic cohort

(Sub)group	Sex distribution (%)	Median age at date of surgery (years)	Median age at follow-up (years)	Median stay length (days)
Both cohorts, all subjects (n = 51)	61% male, 39% female	43	45 (n = 22)	5 (n = 47)
OMC, all subjects (n = 34)	56% male, 44% female	41	-	6 (n = 32)
OMC, dropouts/deceased (n = 19)	58% male, 42% female	49	-	6 (n = 18)
OMC, participants (n = 15)	53% male, 47% female	29	37	3 (n = 14)
EC, all subjects (n = 17)	71% male, 29% female	50	-	3 (n = 15)
EC, dropouts/deceased (n = 10)	60% male, 40% female	54	-	4 (n = 8)
EC, participants (n = 7)	86% male, 14% female	44	47	3

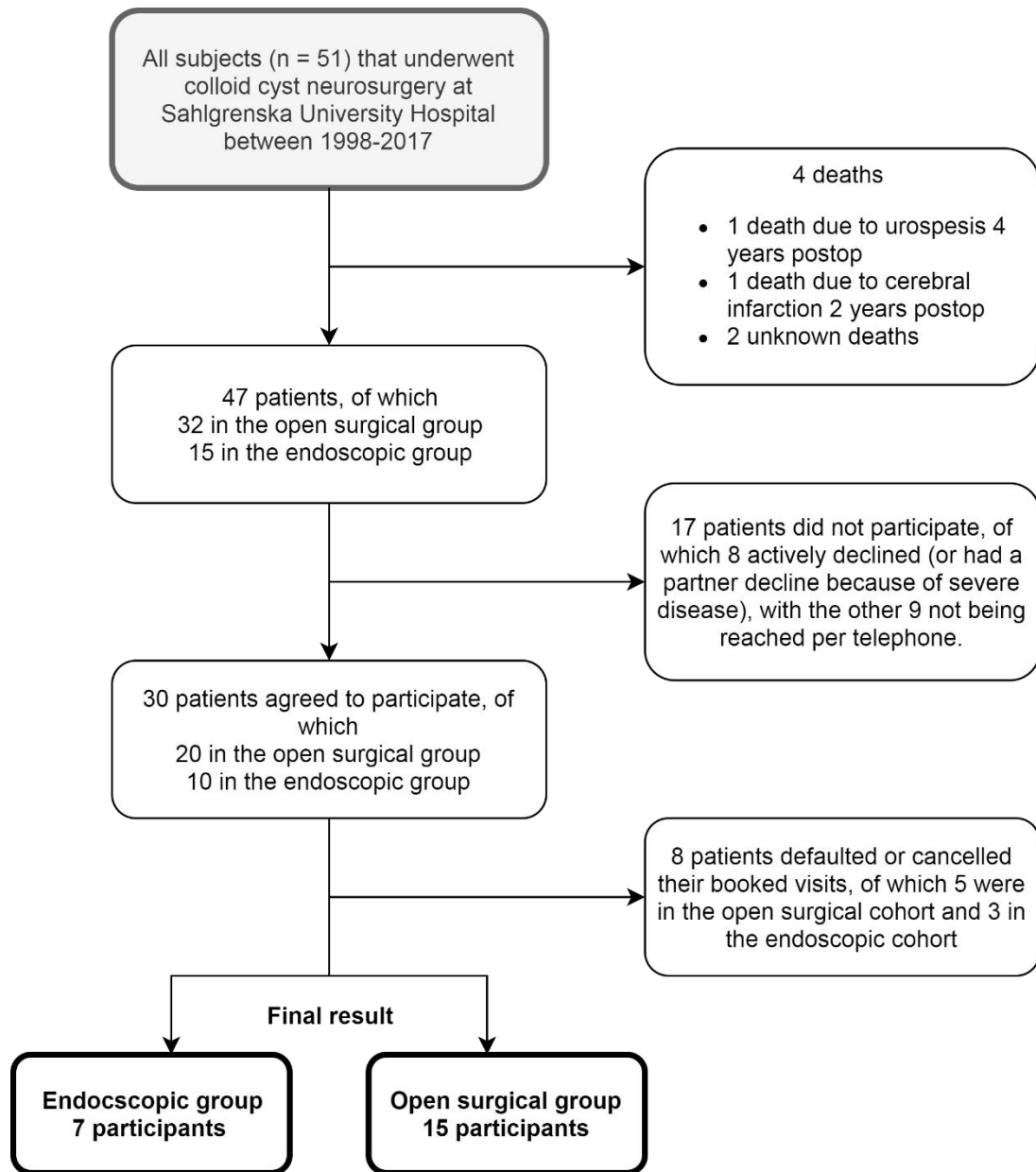


Figure 6. Dropout flow-chart.

Journal assessment

All 51 patient journals and archives of journals were assessed to gather data on post-operative stay lengths. Of these, four patient journals did not exist or did not contain relevant information, therefore post-operative stay length data for a total number of 47 patients was gathered.

Stay lengths were calculated as the number of days between the date of surgery and the date of discharge as given by journal epicrisis.

Clinical interview

The interviews were held in the Sahlgrenska university hospital in Gothenburg, Sweden. All the components of the interviews, including the psychometric testing, was administered by the main author of this paper.

After a brief welcoming, the patient was instructed in the agenda for the interview. After this, the patient was asked to sign a consent form (see the section *Ethics*). If granted, the interview would proceed according to a specified agenda (please refer to *Appendix 1: Consultation checklist* for the exact order of tasks).

A short description for each of the quality of life questionnaires and neuropsychological tests administered follows in *Table 2* and *Table 3* respectively. All the questionnaires and tests administered were in Swedish, or if not available in Swedish, translated from English by a certified neuropsychologist.

Table 2. Quality of life and memory questionnaires.

Questionnaire	Aims	Description
EQ-5D-5L ¹⁷	Quality of life	EQ-5D consists of 5 items /dimensions of life quality as well as a visual-analogue scale for self-rating the subjective health level. The English value set for calculating an index was used as a Swedish is not yet available.
Hospital Anxiety and Depression Scale (HADS) ¹⁸	Mental health	A well-known scale with 7 items for depression and 7 items for anxiety
Everyday Memory Questionnaire-Revised (EMQ-R) ¹⁹	Subjective memory	13 items examining subjective memory related to daily activities and living
Self-Administered Comorbidity Questionnaire (SCQ) ²⁰	Health screening	Questionnaire with 13 items on common medical conditions and their impact on functional status
Life Satisfaction Questionnaire (LiSat-11) ²¹	Quality of life	11 items targeting various domains related to life satisfaction.
Saltin-Grimby Physical Activity Level Scale (SGPALS) ²²	Physical activity	A one item, four-level scale for weekly physical activity level

Table 3. Neuropsychological (psychometric) tests and their descriptions. The following battery of tests were assembled by a certified neuropsychologist experienced with neurosurgical diseases, for the patients to undergo. The tests were administered according to a written set of instructions, as provided by aforementioned neuropsychologist.

Psychometric test	Intended to measure	Comments
Rey Auditory Verbal Learning Test™ (RAVLT) ²³	Verbal learning and retention	See reference.
Brief Visuospatial Memory Test–Revised™ (BVMT-R) ²⁴	Visual learning and retention	See reference.
Information: a test of general knowledge, with 20 questions in ascending order of difficulty.	Recollection of general knowledge	A test of 20 items, testing common knowledge in an ascending order of difficulty.
Word pairs	Verbal paired learning and retention	See <i>Appendix 3</i> .
Image pairs	Visual paired recollection	See <i>Appendix 3</i> .

Ethics

Prior to subject recruiting, the study was approved by the regional ethics board of Gothenburg (diary no. 309-18), and all subjects were informed of the study by letter and telephone. Those who participated gave informed, written consent after reading a study information sheet. The study was performed in alignment with the principles of the Declaration of Helsinki.

Data collection and statistical analysis

Data was collected in printed forms and questionnaires, then transferred to and stored in password-protected spreadsheets in Microsoft Excel, until the stage of data-gathering through clinical interviews and journal assessment was finished. From then, data was deidentified and exported to SPSS for subsequent analysis.

As for the method of statistical analysis, a non-parametric statistical analysis was chosen for all variables, namely the Mann-Whitney U test, because the distribution of collected data for the various variables was not known, and because we had a small number of participating subjects. Because of the limited number of participants (both due to the rare nature of the disease, as well as the high dropout rate), power analysis was omitted.

Results

Post-operative stay lengths

In total, 47 journals were assessed. The endoscopy cohort (15 patients) had a shorter stay length than the open cohort (32 patients), with a median of 3 days as compared to 6 days in the open cohort ($p < 0.05$). *Figure 7* shows the distribution of these groups with a box-plot.

Two patients suffered from immediate post-operative complications; one in the open microsurgical cohort with seizures, and one in the endoscopic cohort with wound infection. Two other patients in the endoscopic group (who did not participate in interviews) both had to undergo reoperation with open microsurgery due to insufficient colloid cyst removal with endoscopy.

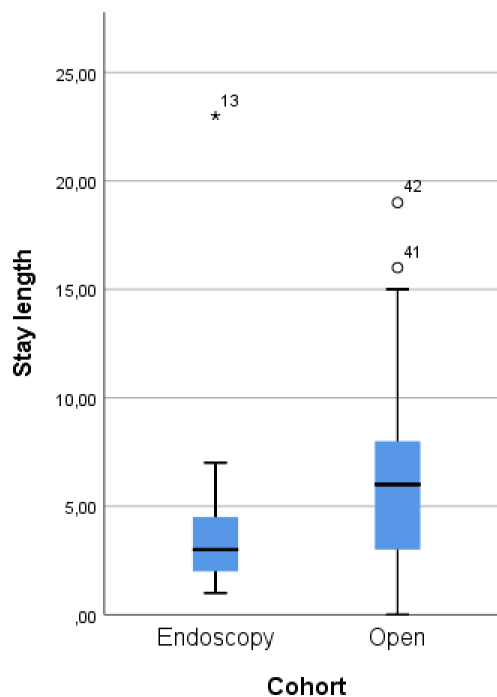


Figure 7. Box-plot of stay lengths in the two cohorts ($p < 0.05$).

Neuropsychological testing and quality of life

Median follow up time was 7.6 years (range 2.3 to 20.3 years).

Analysis of the Information test was omitted, as recollection of decade old, consolidated information was not relevant to examining memory formation and short-term recall.

In the neuropsychological tests, our data did not find any significant difference in objective memory function ($p > 0.05$ for all variables) between the two cohorts in any of the administered tests, see *Figure 8* below.

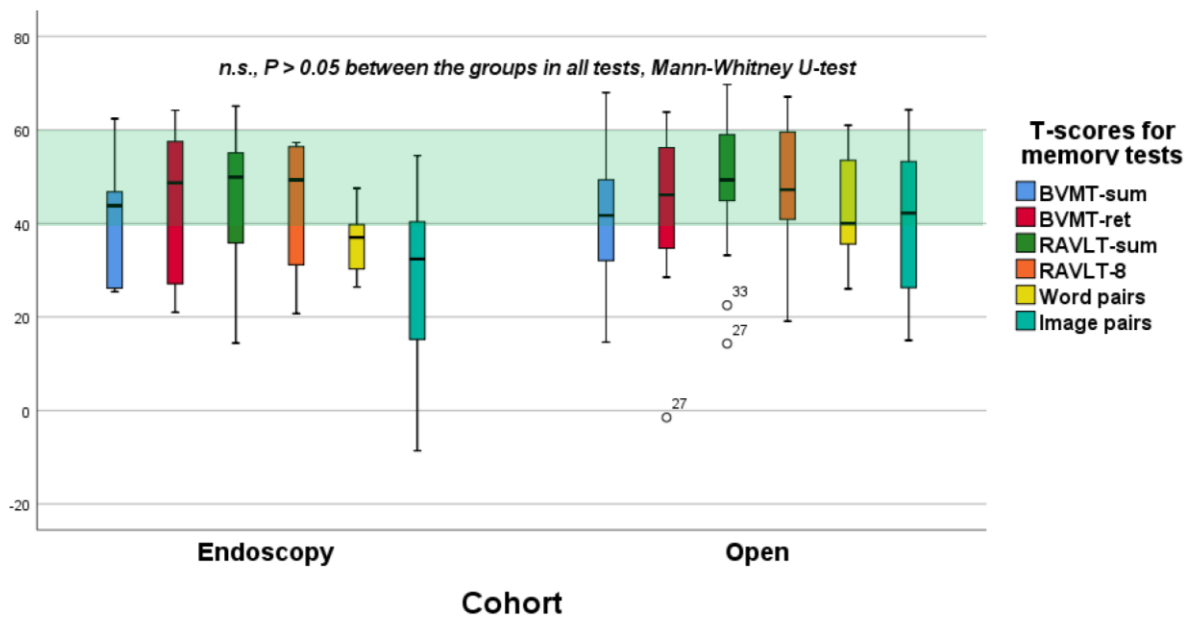


Figure 8. Clustered box-plots showing the two groups and their resulting distributions of T-scores from the psychometric tests. T-scores are standardized (to a standard population of the same age), with 50 points considered to be average, although average results generally fall in the range 40 - 60 points. Note that the medians of the paired tests fall out slightly below average for the endoscopic group. Please see Table 3 for details regarding the specific psychometric tests and their acronyms. The suffixes -sum and -ret correspond to the sum of scores during the first few test rounds and time-delayed retention score respectively.

Regarding quality of life, only EQ-5D-5L, HADS, EMQ-R results were analysed. SCQ as well as SGPALS were omitted because after the clinical interviews, they were considered to be irrelevant due to the fact that cognitive impairment or brain fatigue was the chief post-operative persisting symptom of the patients. LiSat-11 was omitted in favor of the more well-known EQ-5D-5L.

No significant differences in quality of life as measured by EQ-5D-5L was found between the groups. However, the endoscopic cohort scored collectively higher on the depression (but not the anxiety) component of HADS, with a median of 6 points as compared to 1 point in the open microsurgical cohort. The endoscopic cohort also scored a significantly lower subjective memory function with EMQ-R, with the medians 27 points and 6 points for the endoscopic and open cohort respectively (in this scale, a higher score means worse perceived memory). To summarize, the endoscopic cohort had significantly higher depressive moods and lower perceived memory function, compared to the open cohort ($p < 0.05$ for both variables). The difference in subjective memory was not in line with the non-significant results of objective memory testing between the groups.

Discussion with conclusions

Our study confirms the notion that endoscopic resection of colloid cysts leads to lower hospital stay lengths, as earlier evidenced by other studies¹⁴⁻¹⁶.

The most dreaded complication is memory dysfunction. There was a difference in subjective memory with a worse memory reported in the endoscopic group, however this finding was not supported objectively by the battery of psychometric tests. With the exception of the paired tests in the endoscopic group, all median test scores were within the standard range, comparable to healthy age-matched individuals.

There are several possible explanation for the non-difference between the groups, aside from the obvious possibility of low statistical power. One would be that the battery of tests in this study has a low validity for the type of memory impaired by colloid cyst surgery, that is, that they are not good at measuring the kind of memory impairment that is affecting some of the patients. Of course, ideally, one would have to compare pre and post-operative tests for each individual subject, rather than between groups, and then draw any conclusions regarding validity.

Because the lower subjective memory function in the endoscopic cohort was accompanied by higher rates of depression, another theory arises: the higher rates of depressiveness, if they truly correlate with clinical, long-lasting depression, would be at least an important factor in subjectively perceived memory. Depression is known to affect memory function in a negative way²⁵. Depression, then, could theoretically be caused by long-lasting brain fatigue or other neurological symptoms that could also in theory be specific to the endoscopic approach. Of course, it could also be the other way around: depression induced by memory impairment affecting the daily life. This said, the median HADS depression score for the endoscopic group was only 6. A large review by Bjelland et al. found that a cut-off of 8 points for both depression and anxiety in HADS correlated best with the respective diagnoses²⁶. Therefore, the 6 point score is hard to correlate with actual depression, especially considering the fact that all questionnaire answers are cross sectional data, and that depression is a clinical diagnosis based on longitudinal information on mood states, among other things.

Another consideration regarding the depressiveness is that both depression and subjective memory could be more prevalent in a population of higher age. As seen in *Table 2*, the median age during follow up was 47 for participants in the endoscopic group, compared to a median age of 37 for participants in the open group.

In theory, perhaps some differences could be explained due to the fact that endoscopic procedures are performed transcortically, whereas colloid cysts treated with open microsurgery can be approached transcallosally as well as other ways. Depending on the approach and angle of approach used, different areas of the brain can be injured during surgery to create a trajectory to the colloid cysts in the third ventricle (i.e. a cortical injury, or a callosotomy). Depending on the individual, specific functions of those areas and inherent differences in white and grey-matter tissue sensitivity, perhaps this could explain the

differences in mental health and quality of life. Yet another explanation could be inherent to the limitations of the endoscopic technique. While it is superficially less traumatic to the cranium, dura mater and cortex on the way down to the target colloid cyst, the two-handed control and inferior precision of the instrument compared to the open surgical technique might in fact be more traumatic down at the level of the colloid cyst and the fornix which lies in close proximity. This could mean an increased risk of fornix damage, which has been shown to impair recall memory.

Strengths and limitations

The largest strength of this study was the prospective standardized interviews (even though the study in itself is retrospective) with clinical psychometric testing and quality of life examination. To our knowledge, no other studies to date have examined such outcomes, especially not so many years after treatment. Considering the fact that the disease examined is a low prevalence, rare disease, generating and gathering data takes many years. The number of patients in the present study are relatively high compared to other studies, which is also a strength.

There are, however, limitations with this study that must be discussed before drawing any conclusions. The by far most important bottleneck would be the limited number of participants due to the high dropout rate. Of the 51 patients alive at the commencement of this study, 9 were neither available by telephone, nor did they respond to our letters. Another 8 actively declined either by themselves or by proxy through a related, in which case the most common reason for declining participation was a reported limiting medical conditions such as dementia, stroke, aphasia, terminal cancer. The second most common reason was that the subject was living too far away and thought it to be inconvenient to participate for logistical reasons.

Another methodological weakness was the retrospective nature of the study. neuropsychological tests administered were compared group-wise post-operatively, but there was no pre-operative data for each subject. There are inherent, difficult reasons for this: some of the patients present with acute, life-threatening symptoms and are therefore not suited for pre-operative evaluation. Neuropsychological evaluation takes time and requires a patient to be of sufficient cognitive awareness. However, even if these tests were to be administered before surgery, test scores could be distorted by symptoms of the untreated colloid cyst. For example, if an untreated patient suffers from headache and nausea, they would highly likely not perform as well as they would in the absence of those symptoms. This would mean that any difference detected between pre and post-operative psychometric tests in those select cases would not be strictly related to the surgical procedure.

A further major limitation is the highly varying time between surgery and neuropsychological testing and quality of life follow-up. This makes way for error, especially regarding quality of life and mental health, as the incidence of new unrelated life events or medical conditions that can affect the patients increases with time, which may not only impacts test results, but also increase the likelihood that patients decline participation due to irrelevance (e.g., for a patient who underwent surgery 10-20 years ago without long-term complications) or severe

functional disability due to age-related disease. In roughly 45% of interviewed subjects (10 subjects), the follow up time was >9 years. However, in theory the same could be said of the opposite: newly treated patients with no complications might not feel inclined to participate and be tested for memory problems and life quality, in contrast with patients who have suffered complications for years since their procedure. The highly variable follow-up time, aside from affecting quality of life results, could impact observed stay lengths, as it introduces a risk of possible changes in medical routines and post-operative care that could affect both clinical outcomes and stay lengths.

With that said, even if all follow-ups would be enacted after a fixed amount of time, it would still not account for the fact that mental health and life quality questionnaires are very non-specific. Though memory impairment and other neurological deficits induced by surgery are of course very real and potentially very large factors in how treated individuals perceive their lives, many other unrelated factors can affect mental health and life quality. The only way this limitation can be adjusted for is to compare pre-operative baseline memory function with post-operative test results. Regarding the rare occurrence of the disease it also seems reasonable that one should collect information on colloid cyst surgical procedures and their complications in national registers.

We also have to mention the possibility of a Type 1 error. Multiple tests (n = 10 including stay length, memory and quality of life tests) were analysed for statistical significance with an alpha error level set to 5% as per usual standard. In theory an alpha error of 5% would mean roughly 1 in 20 tests would show significance due to chance and not because of an actual difference. Therefore, there is a possibility, however likely or unlikely, that at least one of our positive findings may be due to chance.

The study was not controlled for neither colloid cyst size at the time of resection nor surgeon skill. It did not strictly define what specific neurosurgical approaches should be included into the open microsurgical cohort.

In short, we recommend future multicenter, prospective register-based studies. Besides radiological data, surgical information and complication registration, they could include pre and post-operative tests of memory functions as well as quality of life assessments.

Conclusions

We found shorter post-operative stay lengths after endoscopic surgery compared to open technique, in accordance with previous studies.

The patients who underwent endoscopic surgery experienced a more impaired memory, but we found no difference in objective memory tests. Furthermore, there was a tendency to increased self-reported depressivity according in the group who underwent endoscopic surgery.

Further and more elaborate research is needed, preferably in a fully prospective manner with larger sample sizes, to draw grounded conclusions regarding long-term memory function and quality of life outcomes in surgically treated colloid cyst patients.

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References

1. Blumenfeld, H. Neuroanatomy through clinical cases. p. 204, 837 (Sinauer Associates, Sunderland, MA, 2010).
2. Macdonald, R.L. Colloid cysts in children. in *Textbook of Neuro-Oncology* (eds. Berger, M.S. & Prados, M.D.) p. 735-737 (Elsevier Saunders, Philadelphia, 2005).
3. Ahmed, S.I., *et al.* Third Ventricular Tumors: A Comprehensive Literature Review. *Cureus* 10, e3417-e3417 (2018).
4. Jeffree, R.L. & Besser, M. Colloid cyst of the third ventricle: a clinical review of 39 cases. *J Clin Neurosci* 8, 328-331 (2001).
5. Nagaraju, S., O'Donovan, D.G., Cross, J. & Fernandes, H. Colloid cyst of the third cerebral ventricle with an embryological remnant consistent with paraphysis cerebri in an adult human. *Clin Neuropathol* 29, 121-126 (2010).
6. Veerman, E.C., Go, K.G., Molenaar, W.M., Amerongen, A.V. & Vissink, A. On the chemical characterization of colloid cyst contents. *Acta Neurochir (Wien)* 140, 303-306; discussion 306-307 (1998).
7. Yadav, Y.R., Yadav, N., Parihar, V., Kher, Y. & Ratre, S. Management of colloid cyst of third ventricle. *Turk Neurosurg* 25, 362-371 (2015).
8. Spears, R.C. Colloid cyst headache. *Curr Pain Headache Rep* 8, 297-300 (2004).
9. Young, W.B. & Silberstein, S.D. Paroxysmal headache caused by colloid cyst of the third ventricle: case report and review of the literature. *Headache* 37, 15-20 (1997).
10. Sabanci, P.A., *et al.* Transcortical Removal of Third Ventricular Colloid Cysts: Comparison of Conventional, Guided Microsurgical and Endoscopic Approaches and Review of the Literature. *Turk Neurosurg* 27, 546-557 (2017).
11. Nitta, M. & Symon, L. Colloid cysts of the third ventricle a review of 36 cases. *Acta Neurochirurgica* 76, 99-104 (1985).
12. Aggleton, J.P., *et al.* Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. *Brain* 123, 800-815 (2000).
13. McMackin, D., Cockburn, J., Anslow, P. & Gaffan, D. Correlation of fornix damage with memory impairment in six cases of colloid cyst removal. *Acta Neurochir (Wien)* 135, 12-18 (1995).
14. Sheikh, A.B., Mendelson, Z.S. & Liu, J.K. Endoscopic versus microsurgical resection of colloid cysts: a systematic review and meta-analysis of 1,278 patients. *World Neurosurg* 82, 1187-1197 (2014).
15. Horn, E.M., *et al.* Treatment options for third ventricular colloid cysts: comparison of open microsurgical versus endoscopic resection. *Neurosurgery* 60, 613-618; discussion 618-620 (2007).
16. Grondin, R.T., Hader, W., MacRae, M.E. & Hamilton, M.G. Endoscopic Versus Microsurgical Resection of Third Ventricle Colloid Cysts. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques* 34, 197-207 (2007).
17. Herdman, M., *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 20, 1727-1736 (2011).

18. Zigmond, A.S. & Snaith, R.P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67, 361-370 (1983).
19. Royle, J. & Lincoln, N.B. The Everyday Memory Questionnaire – revised: Development of a 13-item scale. *Disability and Rehabilitation* 30, 114-121 (2008).
20. Sangha, O., Stucki, G., Liang, M.H., Fossel, A.H. & Katz, J.N. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 49, 156-163 (2003).
21. Melin, R., Fugl-Meyer, K.S. & Fugl-Meyer, A.R. Life satisfaction in 18- to 64-year-old Swedes: in relation to education, employment situation, health and physical activity. *J Rehabil Med* 35, 84-90 (2003).
22. Rödger, L., *et al.* Self-reported leisure time physical activity: a useful assessment tool in everyday health care. *BMC Public Health* 12, 693 (2012).
23. Schmidt, M. *Rey auditory verbal learning test: A handbook*, (Western Psychological Services Los Angeles, CA, 1996).
24. Benedict, R.H. *Brief visuospatial memory test--revised: professional manual*, (PAR, 1997).
25. Burt, D.B., Zembar, M.J. & Niederehe, G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 117, 285-305 (1995).
26. Bjelland, I., Dahl, A.A., Haug, T.T. & Neckelmann, D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 52, 69-77 (2002).

Appendices

Appendix 1: Consultation checklist (Swedish)

Revision 2018-07-02

Checklista patientkonsultation – projekt kolloidcystor

Del 1 – förfrågande, CRF + allmänhälstotillstånd

- Hälsa, låt patienten slappna av 1-2 min. Fråga hur det står till och om patienten har några frågor om vad som kommer att hända.
 - "Du får först fylla i några korta formulär, sen ska vi gå genom ditt allmänna tillstånd och dina nuvarande bekymmer."
 - "Därefter kommer vi att minnestesta dig"
 - "Slutligen några formulär till för att skatta din livskvalitet och välmående"
- Informera om testet och att det kan ta upp till tre timmar att utföra hela konsultationen, men att det antagligen kommer att ta mindre tid.
- Be patienten skriva på "**Förfrågan om deltagande**" (**OBS! VIKTIGT**), efter att ha frågat om de är införstådda på allt som kommer att hända.
- Be patienten fylla i SCQ.
- Utför intervju enligt CRF-frågor. Hoppa över det som ska kollas upp i journal eller svaras av MR-undersökning.
- Kort bensträckare kan vara lämpligt, då minnestestningen kan ta en lång stund.

Del 2 – subjektiv resp. objektiv minnestestning

- Subjektiv minnestestning – patienten fyller i EMQ-R.
- Objektiv minnestestning – läs instruktioner
 - RAVLT
 - BVMT-R
 - Information
 - (Repetition BVMT-R)*
 - Ordpar
 - Bildpar
 - (Repetition RAVLT)*

Del 3 – livskvalitet

- Självfyllda formulär som patienten ska fixa
 - EQ-5D-5L
 - LiSat-11
 - HAD
 - Grimby

Ifyllda formulär	
Förfrågan om deltagande	
SCQ	
EMQ-R	
CRF	
EQ-5D-5L	
LiSat-11	
HAD	
Grimby	

Avklarade minnestest	
RAVLT	
BVMT-R	
Information	
<i>(BVMT-R repetition)</i>	
Ordpar	
Bildpar	
<i>(RAVLT repetition)</i>	

Appendix 2: Case report form (Swedish)

CRF kolloidcystor

Avsnitt eller frågor markerade med * (asterisk) ska fyllas i under konsultation.

Basdata

1. * Personnummer (AAAAMMDD-XXXX)

2. * Levande eller död
Markera alla som gäller.

Levande

Död

3. Dödsorsak från dödsorsaksregistret
(om död)

4. **Kön**
Markera alla som gäller.

Man

Kvinna

5. * Alder vid uppföljningsbesök

6. Alder vid ingreppstid

7. * Längd (cm)

8. * Vikt (kg)

2018-07-07

9.

*** Tidigare historia (före operation)**

Markera alla som gäller.

- Hypertoni
- Diabetes mellitus
- Kognitiv sjukdom
- Övriga neurologiska diagnoser?

Psykiatrisk anamnes/diagnoser?

Rökning? Omfattning

Interventionsdata

10.

Operationsmetod

Markera alla som gäller.

- Endoskopisk
- Öppen
- Annan (shunt)

11.

Operationsdatum

12.

*** Tid för symtomdebut ELLER
radiologiskt slumphynd (datum)**

2018-07-07

13.

*** Insjuknandesymtom**

Markera alla som gäller.

- Svår huvudvärk
- Återkommande huvudvärk
- Om återkommande hv, värst på morgonen?
- Epilepsianfall
- Kräkningar och illamående
- Synsymtom
- Irritabilitet
- Nedsatt fokus/uppmärksamhet
- Radiologiskt slumpfynd
- Vet ej

14.

*** Övriga symtom, ej på ovanstående lista?**

15.

*** Peroperativa komplikationer (enligt patient)**

16.

Peroperativa komplikationer (enligt journal)

17.

Operationstid

2018-07-07

18. **Vårdtid (totalt inkl SU + andra sjukhus)**

19. *** Reoperationer**

Markera alla som gäller.

1

2

3

4

Övrigt: _____

MRI data, preoperativ

20. **Sidoventrikelvidd (mm)**

21. **Maximal vidd på tredje ventrikeln**

22. **Masslesion nära tredje ventrikeln**

Markera alla som gäller.

Ja, diameter (mm) i alla tre plan

Nej

23. **Signalintensitet på T2-bild**

24. **Förekomst av cavum septum pellucidum**

Markera alla som gäller.

Ja

Nej

2018-07-07

25. **Förekomst av cavum vergae**

Markera alla som gäller.

- Ja
 Nej

26. **Övriga patologier synbara?**

Markera alla som gäller.

Ja,

Nej

MRI data, vid uppföljningstillfälle

27. **Sidoventrikelvidd (mm)**

28. **Maximal vidd på tredje ventrikeln**

29. **Masslesion nära tredje ventrikeln**

Markera alla som gäller.

Ja, diameter (mm) i alla tre plan

Nej

30. **Signalintensitet på T2-bild**

31. **Förekomst av cavum septum pellucidum**

Markera alla som gäller.

- Ja
 Nej

2018-07-07

32. **Förekomst av cavum vergae**

Markera alla som gäller.

- Ja
 Nej

33. **Synbara postoperativa patologier?**

Markera alla som gäller.

Ja,

Nej

34. **Recidiv av kolloidcysta?**

Markera alla som gäller.

- Ja
 Nej

* Livskvalitet postoperativt

35. **Förekomst av insjuknandesymtom, postoperativt?**

Markera alla som gäller.

- Svår huvudvärk
 Återkommande huvudvärk
 Om återkommande hv, värst på morgonen?
 Epilepsianfall
 Kräkningar och illamående
 Synsymtom
 Irritabilitet
 Nedsatt fokus/uppmärksamhet
 Vet ej

36. **Övriga symtom, ej på ovanstående lista?**

2018-07-07

37. **Minnesfunktionen, jämfört med innan operationen?**

Markera alla som gäller.

- 1. Mycket sämre
- 2. Lite sämre
- 3. Ungefär samma nivå
- 4. Lite bättre
- 5. Mycket bättre
- Vet ej

38. **Funktionsnivå**

Markera alla som gäller.

- Pensionär
- Sjukskriven
- Arbetande
- Arbetslös
- Student
- Övrigt: _____

39. **Familj (singel, sambo, gift)**

Markera alla som gäller.

- Singel
- Gift
- Sambo
- Har barn
- Särbo

40. **Utbildningsnivå**

Markera alla som gäller.

- Avklarad grundskola
- Avklarade gymnasiala studier
- Examinerat på högskolenivå

Appendix 3: Instructions for psychometric testing (Swedish)

"Du kommer att få göra fem uppgifter som används för att mäta hur minne och inlärning fungerar. Två av uppgifterna går ut på att försöka minnas ord, två går ut på att försöka komma ihåg bilder och en uppgift handlar om att du ska försöka dra dig till minnes sådant som du kanske känner till sedan tidigare, alltså att minnas gamla kunskaper."

"Det första minnestestet handlar om ord:"

Instruktion till testet RAVLT (Rey Auditory Verbal Learning test)

"Jag kommer att läsa en lista med ord för dig. När jag har läst färdigt vill jag att upprepar de ord som du kommer ihåg. Du får upprepa dem i vilken ordning du vill, eller så som det faller sig. Lyssna noga medan jag läser. Det här är orden..."

Testledaren (tl) noterar den ordning i vilken orden upprepas i protokollet. Om en testperson (tp) frågar ifall han redan sagt ett ord skall tl besvara frågan. Däremot skall tl inte göra påpekanden om att ett ord redan sagts då detta kan distrahera patienten. När tp antyder att han inte kan minnas fler ord läser tl upp listan igen efter att ha givit följande instruktion:

"Nu kommer jag att läsa orden igen. När jag läst dem vill jag att du upprepar alla ord som du kan minnas, även de ord som du sade den här gången. "Jag läser ..."
Säg hellre "även de ord som du sagt tidigare" vid försök 3-5. Om nödvändigt upprepas "Det spelar ingen roll i vilken ordning du säger orden. Säg bara alla de ord som du kan minnas" inför "Jag läser ...".

Det måste framgå tydligt att tp skall ta med även de ord han återgett vid första försöket. Instruktionen rörande den ordning i vilken orden sägs behöver sällan upprepas.

Listan läses på nytt under försök 3, 4 och 5 med samma instruktion som till försök 2.

Tl får uppmuntra tp. Tl får tala om hur många ord patienten lyckats upprepa om patienten undrar.

När försök 5 avslutats läser testledaren Lista B med instruktioner som gör det tydligt att tp nu kommer att ställas inför en ny lista.

"Nu kommer jag att läsa en annan lista för dig. När jag har läst den vill jag att du upprepar de ord du kan minnas från den nya listan. Du får upprepa dem i vilken ordning du vill.

Efter försöket med Lista B ges följande instruktion

"Nu vill jag att du försöker minnas orden från den första listan igen. Försök att komma ihåg så många som möjligt."

Instruktion till BVMT-R

Se till att tp har tillgång till papper och penna. Lägg pappersark till övriga försök så att de är lättåtkomliga.

"Den här uppgiften handlar om att du ska försöka komma ihåg vad du ser.

Jag kommer att visa dig en bild med sex figurer på. Jag vill att du ska titta noga på figurerna så att du kommer ihåg så många av dem som möjligt. Jag kommer att hålla upp bilden framför dig i 10 sekunder, sedan tar jag bort. När jag tagit bort den vill jag att du försöker rita var och en av figurerna så som den såg ut och på rätt plats på papperet."

Håll upp bilden framför ansiktet på tp i tio sekunder (stoppur) och ta sedan bort den, säg: Ok, då kan du rita.

När tp är klar, ta teckningen och lägg den utom synhåll, säg:

"Bra, då får du se bilden igen. När jag tar bort den gör du ett nytt försök. Du ska ta med också de som du ritade den här gången."

Håll upp bilden i 10 sekunder som tidigare, ta bort den och be tp rita igen. Upprepa sedan för ett tredje försök.

Instruktion till testet Information

**"Det här testet handlar om saker som du kanske känner till sedan tidigare
"Besvara bara frågorna som jag ställer så gott du kan."**

Tp läser frågornas ordagrant med start från fråga nr 3.

Retention BVMT-R

Förse tp med nytt tomt ark och penna, säg:

"Nu vill jag att du försöker rita de där figurerna igen, så som du minns dem."

Instruktion till testet Ordpar

Med **TRYCK** avses ett tryck på mellanslagstangenten, pg dn, nedåtpil eller högerpil eller vadhelst annat som bläddrar framåt i Power Point.

Inled med tom skärm.

”Det här testet heter Ordpar (TRYCK).

Du kommer att få se en rad olika par bestående av två ord på skärmen. Det första ordet kommer att vara skrivet med vit text (TRYCK) och det andra kommer att vara grönt (TRYCK).

Din uppgift är att komma ihåg det andra ordet, det som är grönt.

De båda hänger samman på så sätt att de tillhör samma övergripande kategori.

(TRYCK) Nu får du se två övningsexempel. Försök att komma ihåg vilket grönt ord som hänger ihop med det vita ordet i varje par.

(TRYCK) Hud

(TRYCK) Pupill. Den gemensamma kategorin här är alltså kroppsdelar, men som du ser har vi valt två ord som det ändå inte är självklart att man kopplar ihop.

(TRYCK) Palm

(TRYCK) Morot. Här är den gemensamma kategorin växter, men liksom tidigare är det två ord som inte har någon självklar koppling.

(TRYCK) Ok, vilket ord stod tillsammans med hud?

(TRYCK) Och vilket ord stod tillsammans med palm?”

Test 1

”Nu kommer du att få se 10 ordpar i rad. När du har sett alla ordpar kommer du att få se de vita orden igen, men i en annan ordningsföljd, och då vill jag att du försöker minnas vilket det gröna ordet i varje par var.” (TRYCK)

När bilden med frågetecknet kommer, säg:

”Nu får du se de vita orden igen, ett i taget, och för varje ord skall du försöka komma ihåg det gröna ordet som hörde ihop med det vita. Kom ihåg att orden tillhör samma övergripande kategori även om kopplingen kan verka långsökt.”

Test 2

Nu kommer 10 nya ordpar. Du skall göra på precis samma sätt som tidigare. Försök alltså att komma ihåg det gröna ordet i varje par.

?

När bilden med frågetecknet kommer, säg:

”Nu får du se de vita orden igen, ett i taget, och för varje ord skall du försöka komma ihåg det gröna ordet som hörde ihop med det vita. Kom ihåg att orden tillhör samma övergripande kategori även om kopplingen kan verka långsökt.”

Test 3

Nu kommer de sista 10 ordparen. Gör precis som tidigare. Försök komma ihåg det gröna ordet i varje par.

?

När bilden med frågetecknet kommer, säg: "Nu får du se de vita orden igen, ett i taget, och för varje ord skall du försöka komma ihåg det gröna ordet som hörde ihop med det vita. Kom ihåg att orden tillhör samma övergripande kategori även om kopplingen kan verka långsökt."

Instruktion till testet Bildpar

Med **TRYCK** avses ett tryck på mellanslagstangenten, pg dn, nedåtpil eller högerpil eller vadhelst annat som bläddrar framåt i Power Point.

Inled med tom skärm.

”Det här testet heter Bildpar (**TRYCK**).

Du kommer att få se en rad olika bildpar på skärmen. Varje par består av två identiska bilder. En av bilderna kommer att vara placerad i mitten av skärmen, så här (**TRYCK**).

Den andra bilden, tvillingbilden, kommer att vara placerad på någon av följande åtta platser i skärmens utkant:

I ett av hörnen (**TRYCK 4 GÅNGER**),

rakt till vänster (**TRYCK**)

eller rakt till höger (**TRYCK**) om bilden i mitten,

rakt ovanför (**TRYCK**)

eller rakt under (**TRYCK**) bilden i mitten (**TRYCK**).

Det är bara på någon av de här åtta platserna (**räkna fram positionerna och TRYCK 8 gånger**)

i utkanten av skärmen som tvillingbilden kommer att vara placerad,

aldrig emellan dem som här (**TRYCK**),

och aldrig närmre bilden i mitten som här (**TRYCK**).

Din uppgift är att komma ihåg var tvillingbilden var placerad.

Nu får du göra två övnings exempel. Försök att komma ihåg var tvillingbilderna är placerade.

(TRYCK) (anden)

(TRYCK) (kyrkan)

(TRYCK) Ok, var var den andra anden placerad?

(TRYCK) Och var var den andra kyrkan placerad?

Test 1

”Nu kommer du att få se 15 bildpar i följd. När du har sett de bildparen kommer du att få se mittenbilderna igen, men i en annan ordningsföljd, och då vill jag att du försöker minnas var tvillingbilderna var placerade.”

Test 2

”Nu kommer ytterligare 15 bildpar. Försök lägga på minnet var tvillingbilderna är placerade, precis som tidigare.”

RAVLT, fördröjd återgivning

Efter ca 30 minuter med annan testning ges instruktionen

”Nu vill jag att du försöker komma ihåg så många som möjligt av orden från den första listan som jag läste upp för dig tidigare.”

Tp med mer påtagliga minnessvårigheter kan behöva mer tydliga påminnelser om uppgiften så som ”i början läste jag upp en lista med 15 ord för dig, jag läste den fem gånger och du försökte komma ihåg så många som möjligt av orden”. Då syftet är att få reda på hur många av orden som tp kan behålla över tid är sådana påminnelser helt adekvata.

Omedelbart efter försöket ges följande instruktion:

”Nu kommer jag att läsa upp tre ord i taget för dig. I varje sådan grupp om tre ord finns det ett ord som var med på listan. De andra två har inte varit med. Jag vill att du skall säga vilket av de tre orden som du känner igen eller som du tror har varit med.”