# INTRACRANIAL ARACHNOID CYSTS

## EPIDEMIOLOGY, MORPHOLOGY AND SURGICAL OUTCOME

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*Out of the night that covers me,*
*Black as the Pit from pole to pole,*
*I thank whatever gods may be*
*For my unconquerable soul.*

*In the fell clutch of circumstance*
*I have not winced nor cried aloud.*
*Under the bludgeoning of chance*
*My head is bloody, but unbowed.*

*Beyond this place of wrath and tears*
*Looms but the Horror of the shade,*
*And yet the menace of the years*
*Finds, and shall find me, unafraid.*

*It matters not how strait the gate,*
*How charged with punishments the scroll*
*I am the master of my fate,*
*I am the captain of my soul.*


*William Ernest Henley*

*To the kind of love that lights our way, drives away our fears and fills our hearts with warmth*

*To my family Shahnaz, Khashayar and Parmis for filling my life with this love*

*In loving memory of my most beloved uncle Ardeshir Mansouri Bakhsh. You're always in our hearts and mind and your fun memories live on with us for the rest of our time*

# ABSTRACT

## BACKGROUND

Intracranial arachnoid cysts (AC) are malformations of the arachnoid membrane. They may cause symptoms, either by obstruction of the CSF flow or by compression of adjacent neural tissues. The aim of this thesis was to study the prevalence of AC and its relationship with the most common symptoms and signs, the morphology of AC, and the outcome after surgical treatment in children and adults.

## PATIENTS AND METHODS

The prevalence of AC and its relationship with the most common symptoms ascribed to it were examined in a population of 1235 individuals. For each case, ten age-matched controls were chosen from the same cohort for comparison of symptoms.

The clinical studies comprised two prospective studies: one in adults and one in children. Twenty-seven children and 125 adults were consecutively included. Of these, 22 children and 53 adults underwent surgery. Adults were investigated with a neuropsychological, clinical and physiotherapeutic test battery. Surgically treated adults underwent neuropsychological and balance tests five months postoperatively. Children were followed up both three months and 8.6 years (7-10.5 years) postoperatively. Volumetric measurements were performed for all included patients. AC morphology was investigated in tissue samples by light and electron microscopy in 24 consecutive patients included in/operated on in Study II and III.

## RESULTS

The prevalence of AC in the general population was 2.3 % with no difference between men and women. No relationship with the most common symptoms ascribed to AC was detected.

In surgically treated children, 59 % reported improvement after three months and 77 % after the long-term follow-up. Fifty-nine per cent still experienced remaining symptoms. In adults, 77 % reported improvement after the short-term follow-up; however, no improvement in the test results was seen postoperatively. No correlation was found between the reduction in AC volume and improvement, neither in adults, nor in children.

ACs could be divided into three groups, based on their diverse morphology.

## CONCLUSION

ACs are a common finding in the general population. The diverse morphology in AC suggests more than one pathophysiological origin of these cysts. The results after surgical treatment, together with the difficulties to link what has been considered characteristic symptoms in the presence of AC, suggest that a restrictive approach should be taken with regard to surgical treatment of AC in the absence of hydrocephalus.

## KEYWORDS

Arachnoid cysts, Cyst morphology, Epidemiology, Headache, Surgical outcome

# SAMMANFATTNING PÅ SVENSKA

Arachnoidala cystor (AC) är godartade cystor som finns i hela nervsystemet. AC upptäcks ofta som bifynd vid radiologiska undersökningar och kan vara helt asymtomatiska. Symptom i samband med intrakraniella AC uppkommer antingen p.g.a. hydrocephalus eller kompression av omgivande hjärnvävnad. Målet med denna avhandling var kartläggning av prevalens, morfologi och kirurgiska utfall hos barn och vuxna.

Prevalensen av AC och relationen till dess vanligaste symptom undersöktes hos 1235 individer som undersöktes mellan 1986-2000.

Kirurgiskt utfall utvärderades i två prospektiva studier. Tjugosju barn och 109 vuxna har inkluderades utav vilka 22 barn och 53 vuxna genomgick operativ behandling. De vuxna patienterna i studien har utöver klinisk undersökning också genomgått neuropsykologiska- och sjukgymnastiska tester före och efter operation. AC volym har beräknats på utförda MR undersökningar.

Cystornas morfologi har undersökts med ljus- och elektron mikroskopisk undersökning.

Prevalensen av AC i vårt material är 2.3 % och lika hos män och kvinnor. AC har heller ingen relation till de vanligaste symptom som vanligen tillskrivs AC.

Hos de opererade barnen förbättrades 59 % efter 3 månader och 77 % efter 8.6 år. Kvarstående subjektiva symptom fanns hos 59 %. Hos de vuxna patienterna fanns ingen skillnad i test resultaten av patienter som erbjöds operation och patienter där symptomen inte var relaterade till AC. Det fanns ingen relation mellan postoperativ minskning av AC volym efter operation och kliniks förbättring.

AC har indelats i tre olika grupper baserad på den morfologiska studie som gjordes av cystmembranet.

Studierna i denna avhandling visar att AC är ett relativt vanligt fynd vid radiologiska undersökningar och att AC har mycket varierande morfologi. Operativ behandling av patienter med AC bör begränsas i första hand till de patienter som har en obstruktion av likvorvägar dvs hydrocephalus.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.  Prevalence and Symptoms of Intracranial Arachnoid Cysts. A Population-based Study

    *Rabiei K, Jaraj D, Marlow T, Jensen C, Skoog I, Wikkelsø C.*

    Journal of Neurology, 2016 Apr; 263 (4), 689-694

II. Does Subjective Improvement in Adults with Intracranial Arachnoid Cysts Justify Surgical Treatment?

    *Rabiei K, Hellström P, Johansson-Högfeldt M, Tisell M.*

    Submitted

III. Surgery for Intracranial Arachnoid Cysts in Children- A Prospective Long-term Study

    *Rabiei K, Johnasson-Högfeldt M, Doria-Medina R, Tisell M.*

    Child's Nervous System, 2016 March 21, Epub ahead of print, Doi 10.1007/s00381-016-3064-8

IV. Diverse Arachnoid Cyst Morphology Indicates Different Pathophysiological Origins

    *Rabiei K, Tisell M, Wikkelsø C, Johansson B. R.*

    Fluids and Barriers of the CNS, 2014 March 3; 11 (1): 5

# CONTENT

# ABBREVIATIONS

AC        Arachnoid Cyst
CSF       Cerebrospinal Fluid
CT        Computer Tomography
FES (S)   Falls Efficacy Scale, Extended or Swedish version
FLAIR     Fluid Attenuation Inversion Recovery (sequence of MRI)
HRU       Hydrocephalus Research Unit
IQ        Intelligence Quota
MMSE      Mini Mental State Examination
MRI       Magnetic Resonance imaging
RAVLT     Rey Auditory Verbal Learning Test
ROCF      Rey Osterrieth Complex Figure
SEM       Scanning Electron Microscopy
SHH       Sonic Hedghog (a morphogen)
TEM       Transmission Electron Microscopy th

# INTRODUCTION

The objective of this thesis was to examine the prevalence, morphology and surgical outcome of intracranial arachnoid cysts.

## GENESIS OF THE NERVOUS SYSTEM

In order to understand the complexity of the nervous system and its various congenital defects, it is necessary to begin at its inception. Embryogenesis starts with the division of one fertilised egg into two, four, eight and sixteen cells, at which point the embryo has reached the so-called "morula stage".

After this stage, an inner cell mass will form, surrounded by cells that will help the cell mass implant itself in the uterus and build the future placenta. The inner cell mass will develop into a bilaminar plate during the second week. In the middle of the upper cell layer (epiblasts), a groove called the primitive streak forms. A massive proliferation of cells takes place along the primitive streak with downward migration of cells, a process referred to as gastrulation, which will turn the bilaminar plate into three cell layers: the ectoderm, the mesoderm and the endoderm. Multiple signalling molecules and genes, such as bone morphogenic protein, fibroblast growth factor, *Wnt* and sonic hedgehog (SHH), are involved in this complex process. Defects in gastrulation may give rise to many abnormalities, including split cord formations, dermoids, epidermoid cysts and neural tube defects, such as anterior and posterior spina bifida.[1, 2]

A group of cells proliferating along the primitive streak will migrate forward instead of downward. This cell group will form a structure called the notochord, which will play a central role in the formation of the nervous system; neurulation, Figure 1.
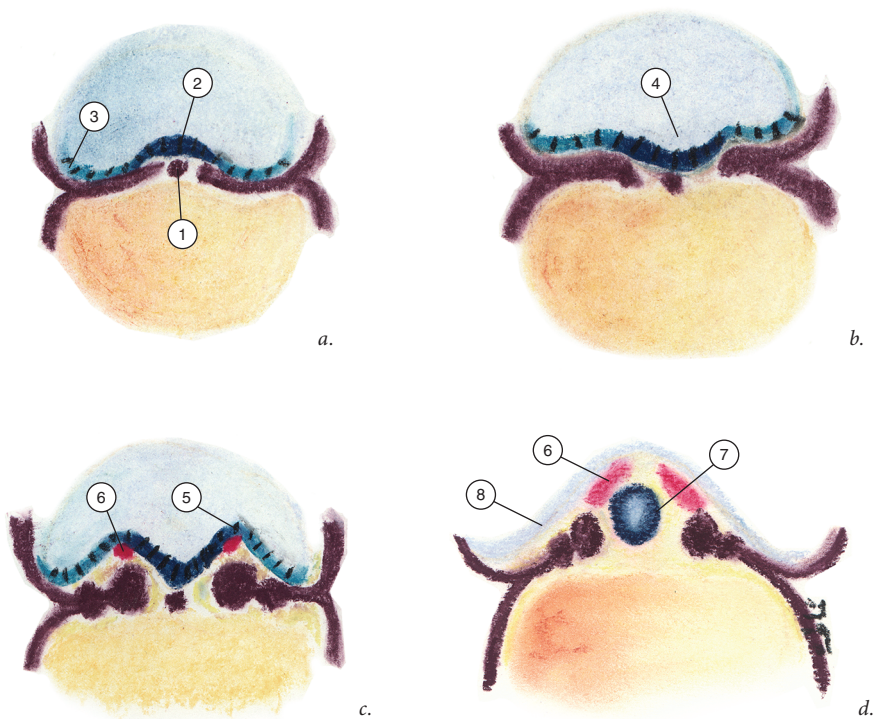
*Figure 1 - Genesis of the nervous system*
*a) The notochord induces the thickening of the overlying ectoderm b) The neural groove is formed c) Hinge points form on the edges of the ectoderm d) The neural tube is fused and the neural crest is separated.*
*1) Notochord, 2) Neural plate, 3) Ectoderm, 4) Neural groove, 5) Hinge points, 6) Neural crest, 7) Neural tube, 8) Epidermal layer*

The notochord induces the ectodermal plate to form the neural plate by secreting the morphogen SHH. The secretion of mainly SHH, but also hyaluronic acid, from the mesodermal layer is involved in raising the ectodermal and neural plate.[3] SHH also contributes to the formation of lateral edges and hinge points along which the neural plate is eventually folded into the neural tube and fused. The fusion of the neural tube is a bidirectional process that runs craniocaudally and fuses the cranial part before the caudal part. Populations of specialised cells at the edge of the folding neural tube, the neural crest, will dissociate from the neural tube and form parts of the peripheral nervous system and the leptomeninges. Both the nervous system and the epidermal layer of the skin originate from the ectoderm.

And so, when the fusion of the neural tube starts, neuroectodermal cells organise to form the roof of the neural tube while the overlying ectodermal cells form the epidermal layer of the skin. The fusion of the neural tube and the concomitant release from the epidermal cell layer are completed by the end of the fourth week.[2, 3]

Massive and rapid cell proliferation takes place at the cranial part of the neural tube, leading to the development of three brain vesicles: the prosencephalon, the mesencephalon and the rhombencephalon. The prosencephalon will differentiate to form the telencephalon, the future brain hemispheres, and the diencephalon that form the thalamus and hypothalamus. The central cavity inside the diencephalon will form the 3rd ventricle and the cavity inside the telencephalon will give rise to the lateral ventricles. The rapid growth of the telencephalon makes it cover the diencephalon, mesencephalon and rhombencephalon. The growth of the cerebral hemispheres, including the temporal lobe, will give the lateral ventricles their classic "C shape", Figure 2.[2]



*Figure 2 - Development of the brain vesicles*

## ORIGIN OF THE MENINGES

The human brain is wrapped in covers of both tougher (dura mater) and softer (arachnoid and pia mater) meningeal tissue. The first known anatomical description of the meninges is found in Egyptian manuscripts from Imhotep, 2600 B.C.[4] The embryological origin of the meninges is as complicated as that of the nervous system. Both mesodermal cells and neural crest cells are involved in the formation of the meninges, and while the dura mater appears to have a pure mesodermal origin, the origin of the arachnoid and pia mater seems to be a more complicated matter. It appears that the leptomeninges of the cerebral hemispheres have a neural crest origin, while the lower parts of mainly arachnoid membrane in the posterior fossa have a mesodermal origin.[5, 6] In addition, the inner surface of the dura mater and the outer surface of the arachnoid membrane originate from a common precursor cell that also has two sources; a mesodermal origin at the skull base and midbrain level and a neural crest origin in the cerebral hemispheres.[7]

For centuries, the meninges have been considered to constitute the protective cover of the brain and spine, but current research suggests that meningeal function and development are more intricate than previously known. The brain and the skull use common signalling pathways during the embryogenesis, making their development highly intertwined and tightly synchronised.[8]

The meninges play a crucial role in both the corticogenesis and the formation of the cranial bones by producing trophic signals.[9, 10] The meninges harbour cells forming the endosteum of the cranial vault, as well as cells with neuronal differentiation potential.[10, 11] Hence, the formation of the cranial bones is controlled by the meninges to accommodate the brain and the development of the two goes hand in hand during the embryogenesis.[8, 9]

A multilayered membrane consisting of astrocyte processes, known as glia limitans, located directly underneath the pia mater and attached to its basal lamina, surrounds the developing brain.[12, 13] Based on animal research, the leptomeninges are suggested to stabilise the surface of the parenchyma and glia limitans during a critical postnatal period. Destruction of meningeal cells has been shown to interrupt the normal foliation process in the cerebellum in rats. However, after the maturation of the glia limitans, the destruction of the meningeal cells could not interfere with this process.[14] Hence, the meningeal covering of the brain seems to play a crucial role in the neuronal development.[8, 15]

The primitive meningeal tissue is also believed to be the origin of the complex vascular plexus that forms the brain vasculature. Arachnoidal arteries and veins covering the surface of the brain and the pial vascular compartment are the first to develop. Vascular elements from pial capillaries perforate through the glia limitans and establish the intracerebral microvasculature. Hence, a perivascular space is formed between the basal lamina of the vasculature and the glia limitans, the Virchow-Robin space. The pial microvascular capillaries are an important part of the brain vasculature and are able to remodel according to the functional demands and needs of the brain, throughout life.[16]

In conclusion, in the adult CNS, the meninges both cover and form projections between main brain structures, form covering sheets around the vasculature of the brain, form the stroma of the choroid plexus and play a vital role for neuronal developement.[5, 17, 18]

## CEREBROSPINAL FLUID

The fluid surrounding the brain and spinal cord, called cerebrospinal fluid (CSF), is ultrafiltrated plasma, and was hypothesised to be produced by various structural parts of the brain, until Hubert Luschka studied and described the role of the choroid plexus in the production of CSF in 1855.[19] But even during that time, pia and the brain parenchyma were also considered to participate in production of CSF. However, later on, experiments performed by Frazier, and Dandy, led to the belief that the choroid plexus produced almost all CSF.[20, 21] Although the experiments were controversial and questioned, the choroid plexus was considered for a long time to be the sole producer of CSF. Today, the choroid plexus, brain parenchyma and ependyma are all considered to participate in the production of CSF.[5] The function of the CSF has been shown to stretch beyond maintaining the buoyancy of the brain. Aside from clearing waste products from the brain and carrying nourishment, the CSF plays an important role in carrying proteins that regulate the neurogenesis and axon pathfinding.[22] Recent findings suggest that microvesicles released from cells in the ventricular wall contain intracellular and signalling proteins, which are carried to their target in the brain by the CSF.[23-25]

The classic description of the CSF flow pathway was a result of several publications in 1914 and includes CSF production from the choroid plexus, mainly in the lateral ventricles, and flow through the foramina of Monroe into the third ventricle and through the aqueduct of Sylvius to the fourth ventricle. The outflow from the fourth ventricle runs through the foramina of Luschkae and Magendie into the subarachnoid space. The CSF is then absorbed from the arachnoid villi to the venous system[20, 26-28] ,Figure 3.
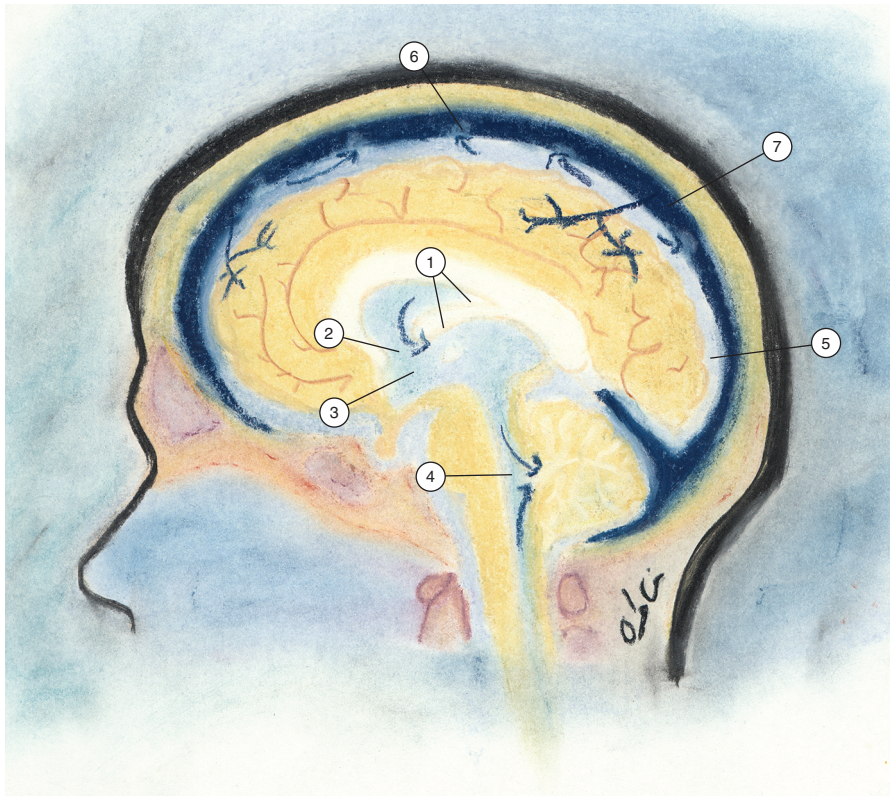
*Figure 3 - The classic CSF flow pathway*
*CSF is produced by choroid plexus in the ventricles and escape through foramina of Luschkae and Magendie into subarachnoid space where it is eventually absorbed into the venous system.*
*1) Choroid plexus, 2) Foramen of Monroe, 3) Third ventricle, 4) Fourth ventricle, Foramina of Luschkae and Magendie, 5) Subarachnoid space 6) Arachnoid granulations, 7) Sagittal sinus*

Several different pathways seem to be involved in the CSF absorption. One of the most recently proposed pathways is along the perivascular spaces formed by astroglia cells. This so-called "glymphatic system" has been described in animals as a part of the lymphatic system[23, 29]; however, these studies and theory have been vehemently criticised.[30]

Perturbations in the CSF circulation cause hydrocephalus, a condition that leads to enlargement of the ventricular system. If a pathological process in the brain constricts or hinders the flow of CSF along any part of its pathway, it causes obstructive hydrocephalus. A number of conditions may also cause ventricular enlargement, despite no apparent blockage along the CSF pathways, so-called communicating hydrocephalus.[31]

# ARACHNOID CYSTS

Arachnoid cysts (ACs) are fluid-filled benign pouches in the arachnoid membrane, found throughout the cerebrospinal axis. ACs usually overlie the surface of the brain, contain clear fluid and are unilateral (although bilateral ACs have also been described).[32-34]

ACs were first described by Bright in 1831.[35] Later, the British anatomist Cunningham published his findings following an autopsy of an acromegalic patient. Beside the pituitary adenoma, he also found a right hemispheric arachnoid cyst with an impression and thinning of the inner table of the skull, Figure 4.[36]
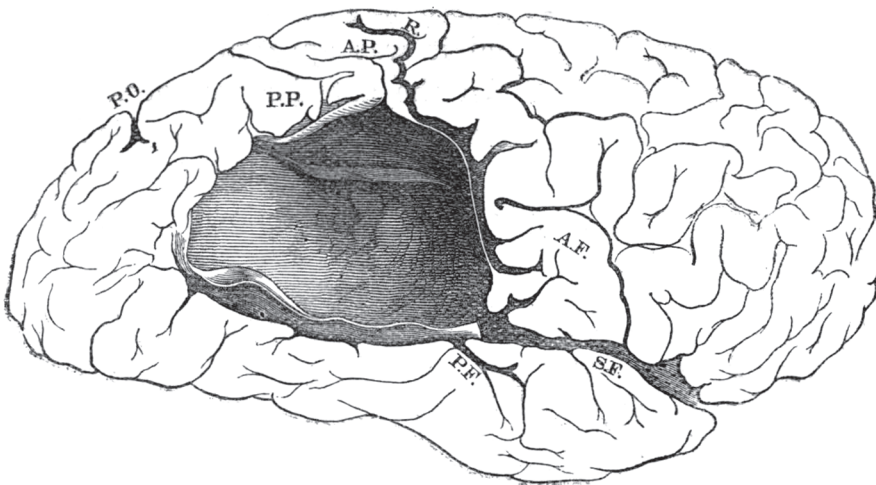


*Figure 4 - Original drawing by D. J Cunningham 1879[36]*

More than 50 years went by before the first suprasellar cyst was described by Hertage in 1937.[37] After the introduction of X-ray, pneumocephalography and cerebral angiography, more reports were published on cystic lesions of various kinds in the brain, probably not all of them were true arachnoid cysts. With the introduction of more advanced radiological methods, cysts were discovered more frequently.

Arachnoid cysts are described in various animals in the scientific literature. Dogs, cats, chimpanzees and cows are some of the species in which these cysts can be found.[38-40] There are also descriptions of treatments for arachnoid cysts in animals when causing obstructive hydrocephalus or hindbrain herniation.[41]

The following section will describe the location, prevalence, diagnostic methods and the natural history of ACs, as described in the literature.

## LOCATION OF INTRACRANIAL ARACHNOIDS CYSTS

Rengachary and Watanabe reported on 208 cases of arachnoid cysts in 1981. They found 49 % of the cysts to be located in the Sylvian fissure, 11 % in the posterior fossa (cerebellopontine angle), 10 % in the supracollicular area, 9 % in the vermian area, 9 % in the sellar and suprasellar area, 5 % in the interhemispheric fissure, 4 % over the cerebral convexity, and 3 % in the clival and interpeduncular area. Seven of these sites were related to subarachnoid spaces.[34, 42] Middle fossa ACs have a preponderance for the left side in most series.[43, 44] In a large series in children, the middle fossa, followed by the posterior fossa, were the most common locations for ACs in children.[44] In adults, however, the middle fossa and the posterior fossa were each occupied by ACs in about 30 % of the cases.[43] Interestingly, a study describing ACs in foetuses described the majority of the cysts being located in the interhemispheric region (30 %) followed by infratentorial locations (22 %), Table 1.

| Location | Prenatal (%) (n= 54)[45] | Children (%) (n= 309)[44] | Adults (%) (n= 696)[43] |
|---|---|---|---|
| Middle fossa | 1 (2) | 145 (47) | 237 (34) |
| Interhemispheric | 16 (30) | 4 (1) | - |
| Convexity | 1 (2) | 12 (4) | 98 (14) |
| Sellar/Suprasellar | 5 (9) | 5 (2) | 9 (1) |
| Skull base | 7 (13)‡ | - | - |
| Intraventricular | 5 (9) | 1 (0.3) | - |
| Infratentorial/retrocerebellar / supracerebellar | 21 (38) | 98 (32) | 264 (38) |
| Cerebropontine angle | 1 (2) | 20 (6) | 48 (7) |
| Quadrigeminal | - | 18 (6) | 20 (3) |
| Other | - | 6 (2)* | 20 (3) |

‡ At the level of temporal lobe, * Anterior Fossa

Table 1.
*Location of arachnoid cysts during prenatal diagnosis, in children, and in adults*

## DIAGNOSTIC METHODS

The invention of computer tomography (CT) and magnetic resonance imaging (MRI) during the 1970s made a substantial contribution to the diagnosis of conditions in the brain. On CT, arachnoid cysts appear as a homogeneous hypodense space occupying lesions in the subarachnoid space, often with compression of the adjacent brain parenchyma and thinning of the overlying bone[31], Figure 5.
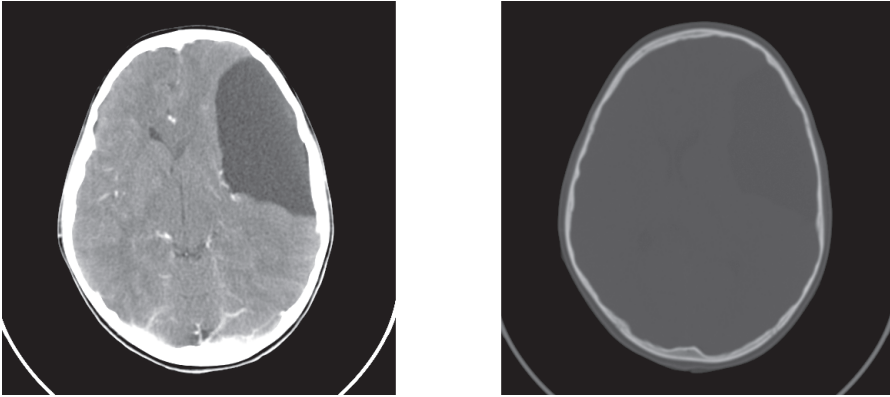
*Figure 5.*
*Contrast enhanced CT image of the brain a) Arachnoid cyst compressing the adjacent brain parenchyma b) Thinning of the inner table of the skull, where the arachnoid cyst resides.*

MRI is based on the inherent property of many atomic nuclei called spin. MRI for medical purpose is based on the detection of the nuclear spin of the hydrogen atoms. Roughly, the spatial distribution of water in tissue is measured. The MRI signal of ACs, which mainly contain water, parallels the signal intensity of cerebrospinal fluid, on all pulse sequences, e.g. low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The MRI appearance of epidermoid cysts, which are ectodermal/epidermal intracranial tumours, resembles AC on T1- and T2-Weighted images. However, epidermoid cysts can be distinguished from ACs using diffusion-weighted sequence of MRI, Figure 6[46-48].
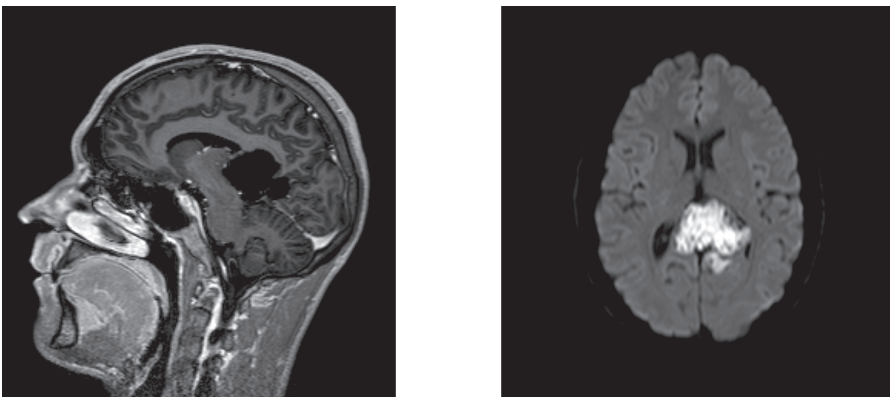


*Figure 6.*
*MRI image of epidermoid cyst a) Contrast-enhanced T1-weighted sagittal image where the epidermoid cyst appears hypointense b) Diffusion-weighted axial image illustrating increased signal (due to a combination of true restricted diffusion and T2 shine through) which is not seen with AC.*

With advances in ultrasound quality, ACs can also be discovered by routine ultrasound during the prenatal period.[45]

## PREVALENCE OF ARACHNOID CYSTS

Robinson estimated the prevalence of AC in 1971, based on his own personal experience, to be around 1 % of intracranial lesions, an opinion that is widespread also in modern era.[49] However, contemporary hospital-based and clinical studies report a prevalence of 0.2-2.6 %, with a two-to-three times higher occurrence among men than women. Eskandary et al. studied incidental findings on CT scans from 3000 trauma patients and reported only 30 cases of incidental findings, of which only seven cases were ACs (0.23 %).[50] Similarly, Katzman et al conducted a retrospective study of MRI images obtained from 1000 healthy asymptomatic volunteers, for various studies, and found only three arachnoid cysts (0.3 %).[51] Al-Holou performed a hospital-based retrospective study of nearly 12000 children and over 47000 adults who had undergone MRI of the brain for various reasons. ACs were found in 1.4 % of the adults and 2.6 % of the children.[43, 44]

Only a few studies have examined the prevalence of AC in samples from the general population. The Rotterdam Study studied the prevalence of incidental findings on MRI in persons 46-97 years old and found an AC prevalence of 1.1 %.[52] Another study, also aiming to describe the prevalence of incidental findings on MRI, included about 2500 healthy young men, 17-35 years old, from the German Air Force. The authors found an AC in 1.7 % of the subjects.[53] A recent population-based study found a prevalence of 3.6 %.[54] The studies mentioned are described in Table 2.

| Study | Method/ Objective | Type of study | Number of subjects | Type of Examination | Age group (yrs) | Prevalence |
|---|---|---|---|---|---|---|
| Hagberg[54] | Prospective/ Incidental findings | Population-based | 1006 | MRI | 59.2+4.2 | 3.6% |
| Al-Holou[44] | Retro-spective/ AC prevalence | Hospital-based | 11738 | MRI | 1-18 | 2.6% |
| Al-Holou[43] | Retro-spective/ AC prevalence | Hospital-based | 48417 | MRI | 19-100 | 1.4% |
| Eskandary[50] | Introspective/ Incidental findings | Hospital-based Trauma patients | 3000 | CT | 32+17.8 | 0.23% |
| Katzman[51] | Retro-spective/ Incidental findings | Healthy volunteers | 1000 | MRI | 3-83 | 0.3% |
| Vernooij[52] | Prospective/ Incidental findings | Population-based | 2000 | MRI | 63.3 (46-97) | 1.1% |
| Weber[53] | Prospective/ Incidental findings | German air force | 2536 | MRI | 20.5 (17-35) | 1.7% |

Table 2.
Prevalence of Arachnoid cysts according to different studies

## NATURAL HISTORY OF ARACHNOID CYSTS IN CHILDREN AND ADULTS

The natural behaviour of a condition is of great importance when deciding on the best course of treatment for it. This is especially important when dealing with a benign condition, often found as an incidental finding.[43] Pierre-Kahn et al. followed 56 foetuses diagnosed with AC during routine ultrasound screening and described their outcome. They found 55 % of the cysts between week 20-30 of gestational age and 45 % after week 30. The cases were followed after detection with ultrasound and MRI. They found an *in utero* growth of AC in 20 % of their cases, while 76 % remained stable and 4 % decreased in size. After delivery, 24 % decreased and 24 % increased, while 52 % remained stable in size.[45]

Al-Holou et al studied the MRI of 11738 children admitted to their institution during 11.5 years and found 309 ACs. Of these patients, 111 who were followed up with imaging over a mean follow-up period of 3.5 years. The ACs increased in size in only 10% of the cases, while a decrease in size was found in 12 %, and in the rest of the subjects, the size remained stable. Only three of the 111 patients who were followed developed symptoms during the follow-up period that could be related to the AC and underwent surgical treatment. Interestingly, none of the patients who had an enlarging AC or who underwent surgery was older than four years old.[44] Also in adults, most ACs remain stable in size.[55] The same research group performed a study including 48417 adults who underwent MRI for various reasons, and studied the natural history of 213 ACs that were followed up with serial imaging over more than six months (0.5-11.8 years). During the follow-up period, two cysts decreased, five increased and the rest remained stable in size. Of the five ACs that increased, three were small (Galassi 1), temporal ACs. They also found that the five patients with initial symptoms that could be related to the AC (headache, vertigo, seizure and hearing loss) improved spontaneously over the follow-up period. Only two patients developed new symptoms and cyst enlargement and were operated on. In one of these two patients the symptoms did not completely resolve.[43]

In addition to the fairly large studies described above, there are various case reports of ACs both decreasing and increasing in size. There are many reports on the disappearance of ACs and their rupture into the subarachnoid space. Some of these events have been described in relation to trauma[56, 57] but most reports concern a spontaneous disappearance[58-63] or decrease in size and resolution of symptoms.[64, 65] Nevertheless, rupture of ACs may cause subdural and intracystic haemorrhage.[66] It has been shown that rupture occurs more often in larger ACs and in connection with head trauma.[67] For this reason, harbouring an AC is traditionally considered to entail a slight increase in the risk of subdural haematoma, which has been used as an indication for surgical treatment by some neurosurgeons. However, a recent study found the incidence of subdural haematoma to be low in children with ACs.[68] Furthermore, another study did not find a decrease in the risk of subdural haematoma after decompression of ACs.[69]

> *In summary, ACs are common and most are found incidentally with a benign natural history.*

# THEORIES ON PATHOGENESIS

The mechanisms behind the formation of ACs are not fully understood. Several different mechanisms have been proposed to explain their genesis, many of which were introduced at the beginning of the 20th century after publications of case reports of cystic lesions. A congenital malformation of the nervous system in either the arachnoid membrane or the brain was introduced already in 1952, by the American neurosurgeon William Trowbridge, as a possible mechanism behind the formation of ACs.[70] Later, Rengachary and Watanabe studied ACs with light and electron microscopy and described a splitting of the arachnoid membrane at the margin of the cyst wall.[34] Since then, the ultrastructure of ACs and, later on, the genetics in patients with ACs have been investigated in various studies.

The following section will describe the evidence behind the existing theories on the formation of the AC.

## INFLAMMATION

In 1909, after having operated on a meningeal cyst involving the spinal cord and the cauda equina, Spiller proposed inflammation/arachnoiditis as a mechanism behind the formation of ACs, although no pathological examination of his specimen was performed.[71] His idea was supported by Sir Victor Horsley, who called the condition "chronic spinal meningitis".[72] Although Horsley points out in his publication from 1909 that when a new disease entity is introduced in the medical literature, it is likely that several conditions with different pathogenesis are all mistakenly explained by the novel disease entity. Nevertheless, inspired by his earlier work on syphilis, Spiller believed that the cyst he called "circumscribed serous spinal meningitis" was caused by syphilis or gonorrhaea.[71, 73] The term chronic cystic arachnoiditis was the usual description of cystic lesions in the reports to follow, but now, trauma was also introduced as an underlying mechanism.[74] It was hypothesized that blood and/or infection in the subarachnoid space could cause inflammation that, in turn, would cause scarring and thickening of the meninges, leading to obstruction of the CSF flow. Trauma was also considered to give rise to scarring, due to haemorrhage in the subarachnoid space, and cyst formation.[74, 75] Later on, several pathological examinations performed on cyst walls confirmed this hypothesis by describing thin fibrous tissue, in some cases accompanied by an occasional leukocyte or numerous small vessels in the cyst wall.[74-76]

## TRAUMA

Just like inflammation, trauma was among the first theories related to the AC pathogenesis. Horrax collected 28 cases, some of which were operated on by Cushing, and published these in 1924, proposing trauma and inflammation as potential mechanisms underlying the development of AC.[74] When reviewing the early literature, it is apparent that ACs were not distinguished from leptomeningeal cysts with growing fracture in children and often mistaken for the same entity.[75, 77-79] This is probably the reasoning behind the theory that ACs may have a traumatic cause.[79] Head trauma up to 50 years before the onset of symptoms in patients has been assumed as the cause of AC.[80-82] Choi reported on suprasellar cysts causing hydrocephalus after head trauma.[81] Some ACs may also become symptomatic after head trauma related to subdural haematomas or intracystic haemorrhages. However, considering the prevalence of both AC and head trauma, most authors contributing to the contemporary medical literature have mainly abandoned trauma as a cause of AC.[43, 44]

## CONGENITAL AND DEVELOPMENTAL CAUSES

It was not until the late 1950s that both Leslie Oliver and Starkman proposed an embryonal or congenital basis for AC.[83, 84] Oliver operated on two cases without any history of infection or trauma and included a pathological examination of the cyst wall in his report. From these publications it is apparent that the term AC was also used at the time for the cystic part of tumours, such as acoustic neurinomas. Hence, Oliver used the term "Primary Arachnoid Cysts" for his cases.[83] In the publications following these reports, a pathological examination of the cyst wall was often included. Judging from the light microscopy images in these publications, not all of them were true ACs; nevertheless, these examinations provided further support of a developmental theory for the formation of ACs.[85, 86]

Based on the publication of Rengachary et al., describing a splitting of the arachnoid membrane at the margin of the AC, a congenital duplication of the arachnoid membrane, together with a ball valve mechanism, was proposed as underlying the formation and expansion of AC.[34]

Several studies have described how the cyst wall morphology in AC differs from that of the normal arachnoid membrane, which may further support a developmental origin of AC.[33, 87-89]

## GENETIC AND HEREDITARY MECHANISMS

Hereditary mechanisms for the formation of AC have been proposed, mainly on the basis of case reports of ACs in siblings and twins,[90-94] as well as reports on several family members in one family harbouring ACs.[95, 96] Genetic investigations in these families have not shown a simple genetic explanation; deletion of chromosome 16 was found in one, while a connection to chromosome 6q22.31-23.2 and chromosome 11p15 was found in others.[95-97]

Global gene expression was studied in eleven ACs compared with arachnoid membrane from tumours, with the main finding being an almost complete similarity between the gene expression in these tissues; however a dubious connection to nine genes was found.[98] Another study by the same authors found a different gene expression in 17 different genes in the AC membrane compared with arachnoid membrane from four tumour patients. Both up and down-regulation of different genes in the AC membrane was found, of which Na-K-Cl-transporter 1 (NKCC1) was one.[99] According to the authors of the study, this would support the secretory function of the AC membrane. However, NKCC1 is widely expressed in the human body, especially by the epithelial cells of the nervous system and its precise role is a subject of controversy.[100] NKCC1 has been shown to be involved in the neurogenesis, in neuronal differentiation and in process formation, and plays an important role in GABA receptor polarity.[100-102]

AC has been described in several different syndromes and conditions and bilateral ACs have been described in glutaric aciduria type I[103, 104]; however, the strongest link has been shown to autosomal dominant polycystic kidney disease.[105]

> *In summary, the formation of AC has not been linked to one specific gene. A traumatic and inflammatory cause of AC has gradually been abandoned. A congenital or developmental mechanism behind cyst formation is accepted as the most probable cause of AC formation.*

# MORPHOLOGY

Morphology of a specimen is normally examined with light or electron microscopy. Modern light microscopes can magnify up to 1000-2000 times (often with oil immersion). In electron microscopy, beams of charged electrons are focussed on the object, which can thus be examined in nanoscales. Cell organelles can be examined in a transmission electron microscope (TEM). To be able to use specimens for TEM, they are fixated with aldehyde and stained with a heavy metal, often osmium, which absorbs or scatters electrons. The specimen is then dehydrated and embedded in plastic. After it has hardened it is cut into 60-90 nm thick slices using a diamond knife.[106] Areas of a specimen that bind more of the heavy metal absorb more of the electron beam, and are called electron-dense regions and, vice versa, areas that bind less of the heavy metal and hence absorb less of the electron beam are called electron-lucent regions.

Scanning electron microscopy (SEM) produces images of the surface of the specimen with less magnification than TEM. Specimens used for SEM are coated with vaporised gold or palladium. As an electron beam sweeps the surface, it discharges electrons from the metal-coated surface and these electrons produce the image of the surface. With electron microscopy, a magnification of up to 100 000 times can be achieved.

The morphology of the AC has been compared with and found to be similar to that of the arachnoid membrane.[33] However, not all cysts classified as AC have the arachnoid-like morphology.[107]

Below follows a description of the ultrastructure of the arachnoid membrane, arachnoid cyst and other cystic malformations found in the subarachnoid space.

## ARACHNOID MEMBRANE

In adults, the arachnoid membrane consists of three layers. The first one, the outer mesothelial layer, consists of up to six layers of closely packed flattened meningeal cells with a barrier function.[108] This layer is lined with a continuous or relatively continuous basement membrane, and the cells here are connected by desmosomes. The thickness of the outer cell layer varies greatly in different regions of the CNS. In areas where this layer is particularly thick, so-called "meningothelial nests", cystoplasmic whorls and psammoma bodies are found. Arachnoid cells of this layer have a myriad of branching cystoplasmic processes, which form concentric whorls.

The processes are separated by intercellular spaces and connected by gap junctions and desmosomes. The second layer consists of trabecular connective tissue. This layer also varies in thickness and fibre density in different areas. There are usually very few cells in this layer and fibroblasts are absent. Traversing trabeculae arise from this layer and attach the arachnoid to the pia. The inner membrane of the arachnoid, the reticular layer, consists of more loosely arranged, more electron-dense, and less flattened cells.[33, 109] These cells are linked by gap junctions and desmosomes, which also link the cells of this layer to the cells of the outer layer. Another layer of elongated cells lines the inner aspect of this layer.[5, 110]

Examined with scanning electron microscopy, the subdural arachnoid cell layer is seen to be arranged like cobble-stones, while the inner cell layer has a cobweb appearance because of the cell processes, Figure 7[33].
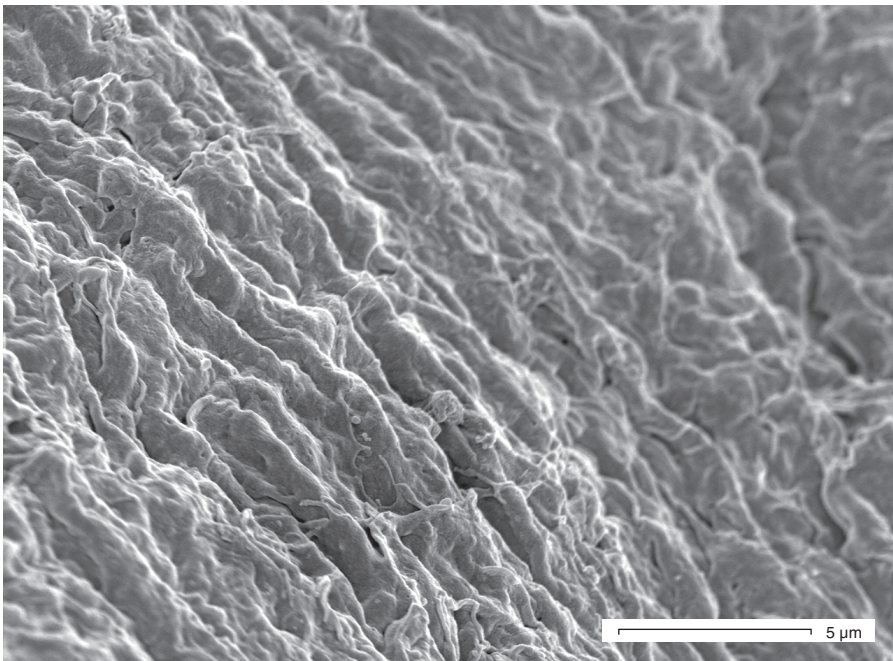


*Figure 7a.*
*SEM image of the dural and the luminal side of the arachnoid membrane.*
*a) Dural side with cobble-stone like surface*
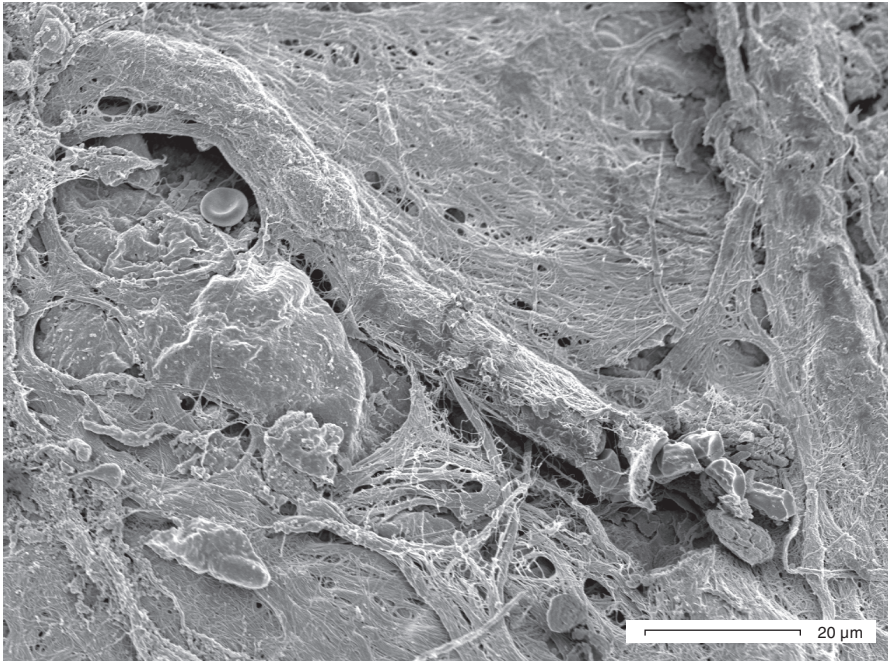
*Figure 7b.*
*SEM image of the dural and the luminal side of the arachnoid membrane.*
*b) Luminal side with cob-web appearance*

## ARACHNOID CYST

Rengachary and Watanabe described the ultrastructure of the AC to be very similar to that of the normal arachnoid membrane, except for a collagenous reinforcement of the connective tissue layer of the AC.[33] However, other authors have described ACs with a morphology that is different from the above description.[87, 111]

## DIFFERENTIAL DIAGNOSIS

Ependymal cysts, choroid plexus cysts and neuroependymal or glioependymal cysts are all intracranial cysts, constituting differential diagnoses of AC. Ependymal cysts have been described as being located deep in the brain parenchyma and lined with cuboidal epithelium.[112] Most ependymal cysts are asymptomatic and only very few become symptomatic.[113]

Choroid plexus cysts are located intraventricularly or originate from the ventricle and extend into the parenchyma. They contain tissue from the choroid plexus and are mostly bilaterally located. Symptomatic choroid plexus cysts are rare.[113]

Glioependymal cysts are also called neuroectodermal cysts or neuroglial cysts and are lined with epithelial lining or endodermal epithelial lining.[111, 112, 114, 115]

Many of the cysts described in the literature share some morphological characteristics with colloid cysts of the third ventricle.[116, 117] Glioependymal cysts are described as rare but present along the entire neuroaxis. These cysts are mostly located within the brain parenchyma but have also been described in the subarachnoid space.[111, 113, 118] Friede and Yasargil postulated that these cysts originated from the wall of the neural tube.[117]

> *In summary, the morphology of most ACs is similar to that of the arachnoid membrane. However, a divergent morphology has been described for some ACs.*

# THEORIES BEHIND CYST GROWTH

Theories about the mechanisms of cyst growth have developed in parallel with those related to cystogenesis and this subject is extensively debated. The onset of symptoms is ascribed to a probable progress in cyst size. However, ACs are often discovered as incidental findings and their size is therefore not known before the diagnosis. Pierre-Kahn et al. described cysts found during prenatal diagnostic work, with a follow-up time of four years.[45] Their study shows that progression of cyst size over time is rare. The most frequent event is, in fact, stabilization in size or regression of cyst size. Al-Holou's study confirms these results in both children and adults.[43, 44]

The following section will explain the existing theories behind cyst growth.

## OSMOSIS

Intracystic haemorrhage and blood products building an osmotic gradient have been proposed as a possible mechanism for cyst expansion. One study has found differences in the protein content in cyst fluid compared with CSF[119] while another has found a similar protein content in CSF and cyst fluid.[120] Considering the natural history of AC, osmosis as a mechanism of expansion is rare and therefore not considered to constitute the main mechanism of expansion of ACs.

## ACTIVE SECRETION FROM THE CYST WALL

The difference in protein content between AC fluid and CSF might be explained by active secretion from the AC wall.[119] Go et al studied the ultrastructure of AC and described similarities between the AC membrane and both the subdural neurothelium and arachnoid granulations. They proposed that these similarities could indicate a secretory capacity of the cyst wall.[32, 121] The same research team described $Na^+$-$K^+$-ATPase in the AC membrane as another clue to the secretion by the cyst membrane.[122, 123] The existence of aquaporines (proteins acting as water channels), mainly Aquaporine 1, has been demonstrated in several secretory parts of the CNS, such as the choroid plexus, and also in cystic tumours, such as hemangioblastomas.[124-126] However, the immunohistochemistry of the cyst wall has failed to show the existence of Aquaporine 1 in the AC membrane.[127]

## BALL VALVE MECHANISM

The ball valve hypothesis states that a one-way valve between the AC and the subarachnoid space leads to entrapment of CSF inside the cyst when positive extracystic versus intracystic pressure exists, and subsequently causes the expansion of the AC. Such a mechanism has, in fact, been observed in several cases during surgery,[128, 129] but the presence of this valve has not been observed in all cases.

*In summary, none of the above theories is probably true for all ACs; rather, it is likely that not all ACs have the same expansion mechanism.*

# CLINICAL SYMPTOMS

There are two types of clinical signs and symptoms of AC: symptoms from compression and obstruction of CSF pathways and the subsequent development of hydrocephalus, and symptoms caused by compression of the adjacent brain parenchyma.[130-132] The most common symptom associated with AC is headache followed by dizziness and cognitive impairment.[133] The relationship of these symptoms with AC and the surgical outcome for the patients operated on for these symptoms are a subject of controversy in the neurosurgical world. Some authors argue that most ACs are symptomatic and should be treated, while others suggest a restrictive approach.[43, 134-137] Some of the most common symptoms and signs, along with their relation to the AC location, are discussed below.

## HEADACHE

Headache, one of the most common ailments known to mankind and one of the conditions causing the most disability in the world, is also the most common symptom of patients with AC.[5, 138-140] Headache is a complex and multifactorial symptom, and many forms of headache, from exertion headache to complex cluster headaches and headaches related to overmedication with prescription-free drugs such as paracetamol, are well known. Sleep disorders, bullying, psychological stress, and psychiatric co-morbidity in both adults and children may also cause headache.[141-144] An overall prevalence of 54.4 % of any type of headache has been found in children and adolescents.[145, 146] A study comprising populations in ten different European countries described the overall one-year prevalence of headache to be 79.6 % in adults, with women predominating. The prevalence of headache 15 days per month or more was 7.6 %.[147]

Despite its mostly self-terminating nature, headache can also be an alarming symptom of raised intracranial pressure. An increase in intracranial pressure often leads to headache in combination with vomiting, double vision or impaired vision. In its most acute form, these symptoms progress to a decreased level of consciousness and may be fatal, making the evaluation of headache particularly challenging.

The international headache classification (IHS-ICHD3 beta) describes headache related to non-vascular intracranial disorder and space-occupying lesions as progressive, localised, worse in the morning, and aggravated by coughing, bending forward or the Valsalva manoeuvre.[148]

There is no specific description of headache caused by AC. Case reports describe various different types of headache in relation to AC.[149, 150] Some authors describe a good response in patients with AC and headache when their AC is treated surgically. Others argue that headaches often have a different cause in these patients and may be worsened by the anxiety provoked by the diagnosis of an intracranial lesion, and that the high prevalence of a condition like headache contributes to its coexistence with AC.[43, 151]

## DIZZINESS AND IMBALANCE

Balance is achieved by the complex synthesis of several different senses and is one of the most elaborate tasks performed by the nervous system. Vision, inner ear function and proprioception (a product of signals from muscle spindles and joints carried by the dorsal column in the spinal cord) are the main components of this refined task. Unequivocal and precise information from these organs is unified in the cerebellum, which, through a complex set of connections to the cerebrum, maintains the sense of balance and postural function in humans. Hence, the sense of imbalance may have several causes, including psychological factors, pain, muscle weakness, impaired motor function, altered tonus of the musculature, reduced joint movement, impaired sensation, proprioception, vision and inner ear function.[152-154] Much like headache, dizziness and imbalance are a frequently encountered condition among the general population.[155, 156] The estimated prevalence of vertigo and imbalance is up to 30% in the general population.[155]

Imbalance and gait difficulties are also symptoms of hydrocephalus, which can be caused by AC. When combined with hydrocephalus, these symptoms can be successfully treated by decompression of the AC or by both decompression and shunting.[130] Imbalance can also be caused by a focal neurological impairment caused by a convexity AC in the proximity of the motor or sensory cortex.[157]

Besides the combination with hydrocephalus or motor/sensory symptoms, the sense of dizziness and imbalance is the second most common symptom in patients with AC.[158]

### ASSESSMENT OF BALANCE

An assessment of balance can be performed using different methods. The most widely used clinical test of balance is probably the Romberg test, in which the individual stands with the feet together, arms resting by the side and with the eyes closed. The number of seconds up to 60 seconds is counted. Similar to this, the sharpened or tandem Romberg test was performed with the eyes open and closed.[31] In sharpened Romberg, the subject puts one foot in front of the other

and, similar to the Romberg test, the number of seconds the person stands is counted. The test was performed with the eyes open and closed, in Study II. In both tests, the subject holds the arms by the side.[31] In addition to these tests, the extended version of the Falls Efficacy Scale was used for patient evaluation in this thesis and is described below.[159]

Originally developed by Tinetti et al., the Falls Efficacy Scale (FES) assesses perceived self-efficacy in performing ten activities of daily living, rated on a scale of 1-10. The activities included in the scale are preparing simple meals, taking a bath or shower, getting in and out of a chair, getting to the door, walking around the house, going up and down the stairs, reaching into cabinets or closets, getting dressed and undressed, light housekeeping and simple shopping.[160]

The original set of tests described by Tinetti included three additional items that were eventually replaced, as a few subjects expressed poor self-confidence in performing them. The extended version of the FES (S) includes these activities, namely getting on and off the toilet, getting in and out of bed and personal grooming, and has been shown to be associated with the Berg balance scale.[153, 159, 161]

## COGNITIVE DISTURBANCE

Cognition is a mosaic of several different functions of the human brain and various different regions of the brain participate in this function. Therefore, cognitive disturbances have as many different causes as the previously discussed symptoms.[31] Cognitive impairment is one the most common symptoms of hydrocephalus and reversible if the hydrocephalus is treated.

Cognitive impairment is also one of the common symptoms in conjunction with AC. In fact, it has been described that patients with temporal AC suffer from dyscognition that is reversed by surgical treatment.[134, 158, 162, 163] A study testing children with AC failed to show that they suffered from dyscognition or had a lower IQ.[164]

### NEUROPSYCHOLOGICAL TESTING FOR ASSESSMENT OF COGNITIVE FUNCTION

Cognitive function is assessed through neurocognitive testing, the simplest form of which is the widely used Mini Mental State Examination (MMSE). However useful for the detection of dementia, the MMSE is a rather blunt instrument when measuring cognitive function in individuals without dementia.[165] Therefore, other neuropsychological testing methods are used to detect mild cognitive dysfunction.

The tests used in this thesis are described below. They collectively measure different aspects of cognitive function and involve many brain structures, including the temporal lobe region, the anterior cingulate, and the dorsolateral prefrontal cortex.[166-169]

The Rey Auditory Verbal Learning Test (RAVLT) measures verbal learning, memory and recall. The subject is instructed to remember as many as possible of fifteen words read out in five consecutive trials. These five learning trials are followed by one trial with words from a second list, which serves the purpose of distracting the subject. After this, the subject is asked to remember the words from the original list again. Another recall trial is made after a delay of 20-30 minutes. The variable used, in Study II, was the total sum of words recalled over the five trials and the delayed recall. The test value used was a T-value calculated on the basis of the subject's age.

The Rey Osterrieth Complex Figure (ROCF) is a visuospatial learning and recall test. It starts with the task of copying a complex figure (that has to be remembered), and thus, assesses both visuospatial and visuoconstructive abilities as well as recall.[170]

The Target Reaction Time and the Swedish Stroop Test measure cognitive control against interference. The Swedish Stroop Test consists of two tasks: colour-naming and interference. The test begins with colour-naming, in which the subject is instructed to name the colours of 100 rectangles (in blue, red, yellow and green) as fast as possible. This is followed by the interference task, in which the subject must name the colour of the ink of 100 words written in colour. The measured variable in Study II was time in seconds to perform the tasks. A T-value based on the subject's age was used.

Target reaction time is a computerised task developed at the HRU. The subject is asked to fix a white cross on a black screen and to press the space bar as soon as the screen turns white but avoid pressing if the screen turns red. The white and red screens are presented in random order. The length of the fixation intervals also varied between two and six seconds. The variable used, in Study II, was the mean reaction time of the subject in the go-no-go condition.

The grooved pegboard test performed with the dominant and non-dominant hand measures manual dexterity. The subject is instructed to fit 25 pegs into holes with randomly positioned slots as quickly as possible.[171] The test is performed with both the dominant and the non-dominant hand. The variable used, in Study II, was a T value based on age and the time in seconds to perform the task with the dominant and non-dominant hand.

## EPILEPSY AND SEIZURES

Epilepsy and seizures may coexist with AC, especially in complicated paediatric cases involving brain malformations.[172, 173] Several case

reports relate good seizure control after surgical decompression of an AC, which, seemingly and anatomically, cannot explain the seizures, while others have failed to show a connection between seizure foci and the AC. No connection has been found between temporal lobe AC and temporal lobe epilepsy.[174-176] It should be kept in mind that an isolated seizure episode may have many causes and may be unrelated to the AC. It is likely that seizures can be caused by AC in some cases and the treatment of the AC may therefore lead to complete resolution of symptoms or a reduced frequency of seizure episodes in a selected group of patients.[177]

## FOCAL NEUROLOGICAL SYMPTOMS

Focal neurological signs and symptoms in AC are mainly related to convexity AC overlying the functional areas of the cortex. Progressive hemiplegia caused by convexity AC is described and, although uncommon, surgery usually results in the resolution of symptoms.[178, 179] Other than an AC overlying the eloquent cortex, visual impairment has also been described in connection with a temporal AC.[180, 181]

Infratentorial ACs may have specific symptoms and signs. Aside from compression of the CSF pathways and hydrocephalus, these cysts can also cause symptoms related to compression of the brainstem and cranial nerves. An AC compressing the cerebellum can cause gait or balance disturbances.[182, 183] Focal symptoms of cerebropontine angle AC include hearing loss, trigeminal neuralgia, hemifacial spasm, diplopia, hoarseness and dysphagia.[184-189] Surgical treatment of these rather unusual cases can either lead to complete resolution of symptoms or a halt in the progression of symptoms.[43, 190]

## ENDOCRINE DYSFUNCTION

An AC located in the basal cistern, above or inside the sella (where the pituitary gland resides), can cause several different types of symptoms, due to the proximity to and compression of the pituitary and its stalk, the hypothalamus, mesencephalon, optic nerve or foramen of Monroe. The latter causes obstructive hydrocephalus, as described earlier.[131, 132] Symptomatic suprasellar ACs present usually in the paediatric population, and in most of the cases, with precocious puberty. Suprasellar ACs, with or without hydrocephalus, generally have a good surgical outcome and the patient's symptoms are usually either resolved or the progression of symptoms is halted.

Rare cases of precocious puberty are also described in giant temporal AC extending in and above the sella,[191] but temporal ACs do not normally cause endocrine symptoms.

## SYMPTOMS RELATED TO HYDROCEPHALUS

ACs in various locations can cause obstruction of the CSF flow. The main locations in which AC can cause hydrocephalus are the suprasellar region, the posterior fossa and the intraventricular location. Albeit unusual, especially in adults, AC can exist inside the ventricular system and cause a direct obstruction of the CSF flow. Obstruction of the CSF pathways may cause acute hydrocephalus with headache, vomiting and papilloedema. Symptoms may also develop gradually, leading to gait and balance disturbances along with developmental delay in children. Hydrocephalus in infants and small children can also cause head enlargement (macrocephaly). However, macrocephaly or an abnormal head shape might persist despite successful decompression of the AC.[137]

Hydrocephalus can be both a life-threatening and permanently disabling condition that is reversible with excellent outcome, if treated in time. For this reason, AC causing hydrocephalus should be treated urgently.

*In summary, many symptoms are ascribed to AC, the most common of which are headache, dizziness/imbalance and cognitive disturbances. AC may also cause seizures, focal neurological symptoms, endocrine disturbances and hydrocephalus.*

## SURGICAL TREATMENT METHODS

The surgical treatment methods in AC include fenestration surgery or the placement of a shunt. Fenestration surgery involves opening the membrane of the AC on the dural side and toward the basal cistern to ensure the flow of CSF through the AC. Fenestration surgery can be performed both as open microsurgical fenestration and endoscopic fenestration. The different methods are chosen depending on the location of the AC and the surgeon's experience. A brief description of the surgical methods as well as their complications follows below.

## OPEN MICROSURGICAL FENESTRATION

Open microsurgical fenestration involves a rather large opening in the skin and a craniotomy. The dura is opened, after which the outer membrane of the AC is excised. The inner membrane of the AC, usually toward a cistern, is then opened. The open procedures are performed by most neurosurgeons using a surgical microscope and provide the surgeon with excellent visibility of the surgical area. In temporal AC, the inner membrane is opened toward the basal cistern in the vicinity of the main vasculature of the brain and cranial nerves, namely the middle and anterior cerebral artery, and the optic, abducens and oculomotor nerve. Oculomotor nerve palsy and stroke are therefore rare but known complications of this procedure.[192]

In the posterior fossa, the standard procedure of choice is open microsurgical fenestration. This involves craniotomy of the posterior fossa and opening and excision of the AC membrane. A well-known complication of surgery in the posterior fossa is CSF leakage, which, if not treated, can cause meningitis and symptoms of intracranial hypotension.[31]

The complications of open microsurgical fenestration are much similar to the complications involving craniotomies for other indications. Subdural, epidural and intracerebral haemorrhage (ICH), infarction, vasospasm, superficial and deep wound infections, meningitis, CSF leakage, seizures, cranial nerve damage and neurological deterioration and sequelae are all well-known complications of neurosurgical procedures. Some of these complications require only minor interventions, such as extra sutures in the case of CSF leakage or prescription of antibiotics for minor wound infections. Others might lead to major disability, such as infarction and ICH, or require surgical intervention, such as deep wound infections and evacuation of subdural and epidural haematomas causing mass effect. All these complications are described in reports on open microsurgical fenestration of AC.[135, 178, 193, 194] The complication rates in most of the surgical series are about 20%. Some of the studies presenting their complications along with their rates are presented in Table 3 below.

## ENDOSCOPIC FENESTRATION

Endoscopic surgery is a minimally invasive technique that provides rapid access to the target via a small burr hole. Lespinasse performed the first endoscopic surgery in 1910. Since then various endoscopic methods have been developed and used in neurosurgery.

The technique had many limitations in the past, which have been overcome by the development of better optical techniques and instruments. The widespread use of frameless navigational systems have further contributed to making this technique a safe and non-invasive method in neurosurgical practice.[195] Nevertheless, experience from endoscopic techniques and thorough patient selection, are prerequisites for a good outcome with endoscopic surgery.[69] Endoscopic fenestration is usually used for the treatment of intraventricular- and suprasellar AC, especially in children, with excellent outcomes.[196-200] Treatment of AC in the quadrigeminal cistern, temporal location and posterior fossa is also performed endoscopically in different series with good outcome.[190, 201, 202]

Complications of this treatment involve haemorrhage, infection, CSF leakage and damage to nervous structures. Turhan et al. describe the open neurosurgical treatment as a safer and more effective treatment of temporal ACs.[203] However, a lower rate of success and higher complication rate for temporal ACs have also been described.[204] Other authors report an excellent outcome of endoscopic treatment, regardless of the location of the AC, with low complication rates.[202, 205-212]

## CYSTOPERITONEAL SHUNTING

Shunting is the main method for CSF diversion in hydrocephalus. Shunting can be used for diversion of cyst fluid inside the AC cavity and usually leads to complete effacement of the AC. The main drawback of shunts is the implantation of a foreign material in the body and the subsequent life-long risk of infection, malfunction, disruption and obliteration.[213] In addition to these, specific complications, such as Chiari type 1 malformation and shunt dependency based on CSF over-drainage, have been described in patients with cystoperitoneal shunts in the absence of hydrocephalus.[177, 214-216] Attempts to reduce these complications have been made by placing internal shunts between the lumen of the AC and the subdural compartment.[217]

| Author (Number of patients) | Type of study | Population | Procedure (endoscopy, open, shunt) | Complication rate |
|---|---|---|---|---|
| Ali[218] (27) | Retrospective | Paediatric | All three | 33% |
| Choi[137] (75) | Retrospective | Infants ≤1 yr. | Endoscopic and open | 55% |
| Couvreur[211] (34) | Retrospective | 21.4 (16d-77.9) | Endoscopic | 29.4% |
| Gui[205] (32) | Retrospective | 8-73 months | Endoscopic | 18.8% |
| Helland[217] (31) | Retrospective | Adults | Internal shunt | 22.5% |
| Helland[219] (48) | Retrospective | ≤16 yrs. | Mixed | 6% |
| Helland[158] (156) | Retrospective | Adults | Mixed | 17% |
| Spacca[69] (40) | Retrospective | 7.8 yrs. (3m-30y) | Endoscopic | 20% |
| Wang[179] (63) | Retrospective | Adults | Mixed | 11.1% |

*Table 3.*
*Complication rate of different treatment modalities for intracranial arachnoid cysts*

*In summary, there is no consensus on the best surgical treatment strategy for AC. Studies comparing open and endoscopic fenestration surgery show similar results for these treatment modalities.[203, 207]*

# SURGICAL OUTCOME AND MEASURES

A high improvement rate following surgical treatment is reported in many studies, although the definition of improvement and its evaluation often differ in surgical series. Surgical success can also be reported as decreased AC volume or radiological evidence of successful fenestration in the absence of a clinical evaluation of the patients. The two different evaluations may also be intermingled.[208, 220]

Even when patients are clinically evaluated, improvement is often vaguely defined and the follow-up times vary. In some series, improvement has been defined as improvement of at least one preoperative symptom, while other series present a general improvement of the patients' symptoms. Most studies describing surgical outcome have been retrospective, based on patient charts from follow-ups by the treating surgeon. In the case of hydrocephalus and objectively verified neurological symptoms and signs, it is often easier to evaluate improvement. However, in the case of purely subjective symptoms, the evaluation is often based on the patient's experience and is difficult to objectify.

It has not been proven that the surgical outcome is based on the surgical method of choice. Improvement may, however, be based on the cyst location or symptoms leading to surgery. It is generally accepted that ACs in combination with symptoms that may anatomically be related to the AC have a better outcome than ACs with diffuse sympotms.[137, 186, 187, 190] The surgical outcome of several studies is presented in Table 4.

| Author | Method | Population/ AC location | Aim of study | Improvement criteria | Improvement rate |
|---|---|---|---|---|---|
| Levy[178] | Retrospective | Paediatric/ Temporal | Evaluation of treatment modality | At least one symptom | 95% |
| Choi[137] | Retrospective | Paediatric/ Mixed | Surgical outcome | Improvement after 1 year | 28% |
| Couvreur[211] | Retrospective | Adults and children/ Temporal | Evaluation of endoscopy | At least one symptom | 76.4% |
| Gangemi[207] | Retrospective | Adults and children/ Mixed | Evaluation of endoscopy | Overall improvement | 83.3% |
| Gui[205] | Retrospective | Adults and children/ Temporal | Evaluation of endoscopy | Overall improvement | 92.6% |
| Helland[217] | Retrospective, Questionnaire | Adults/ Mixed | Evaluation of Internal shunts | Overall improvement | 83% |
| Helland[219] | Retrospective, Questionnaire | Paediatric/ Mixed | Surgical outcome | Overall improvement | 82% |
| Helland[158] | Retrospective, Questionnaire | Adults/ Mixed | Surgical outcome | Overall improvement | 82% |
| Spansdahl[151] | Retrospective, Questionnaire | Adults/ Mixed | Surgical outcome | Overall improvement | 84% |
| Wang[179] | Retrospective | Adults/ Mixed | Indication for surgery | Overall improvement | 80.9% |

*Table 4.*
*Surgical outcome in different studies*

*In summary, the symptoms leading to surgery, as well as the different ways of measuring surgical success, make it almost impossible to compare different studies or to decide on acceptable surgical results.*

# AIMS

The aim of the current thesis was to contribute to the knowledge on arachnoid cysts by examining their prevalence and their relation to the most common symptoms, their morphology, in order to understand their pathogenesis, and to examine the surgical outcome in both children and adults undergoing surgery for an arachnoid cyst. The specific aims of each study were the following:

### STUDY I:

To investigate the prevalence of AC in the general population and examine whether an association with the most common symptoms of AC could be detected on a population basis.

### STUDY II:

To evaluate the clinical effect of surgery in symptomatic adult patients with AC and to examine the correlation of the reported symptoms and anatomical locations of AC with objective test results. Further, to examine the relationship between clinical- and radiological improvement using volumetrics.

### STUDY III:

To evaluate the clinical effect of surgical treatment of intracranial arachnoid cysts in children, in a prospective long-term series. We also studied whether the postoperative cyst volume was correlated with clinical improvement.

### STUDY IV:

To study the morphology and ultrastructure of surgically treated arachnoid cysts.

# PATIENTS AND METHODS

## PATIENTS

### STUDY DESIGN

All four studies in the thesis were prospective studies. Study I was a population-based cohort and nested case control study, and Study II and III were observational studies. Study IV was an explorative study.

### PATIENTS AND PARTICIPANTS

The participants in Study I consisted of probands included in several population-based studies conducted on elderly persons in the Gothenburg region in Sweden. The following studies were included: H85, the NORA, the Prospective Population Study of Women (PPSW), and The Gerontological and Geriatric Population Studies (H70).[221-226] The participants were aged 70 years and above and were systematically retrieved from the Swedish population register based on their date of birth. The cohorts included both people living in private households and in residential care. A total of 1235 individuals underwent both clinical and radiological examination with head CT.[227]

The patients in Study II were 125 adults (57 females and 68 males) with AC, all from the western region of Sweden and between 18 and 83 years of age (mean age, 43 yrs.). After an initial evaluation of images and referrals by two senior neurosurgeons, one patient was diagnosed with an epidermoid cyst and one patient was found to have a mega cisterna magna. Both were excluded from the study. Fourteen patients were excluded from further investigation due to the combination of a lack of symptoms associated with AC and a small cyst, leaving 109 patients for further evaluation by the Hydrocephalus Research Unit (HRU). After this evaluation, two more patients were excluded based on a diagnosis of vascular and Parkinson's dementia, leaving 107 patients in this study, Figure 8.
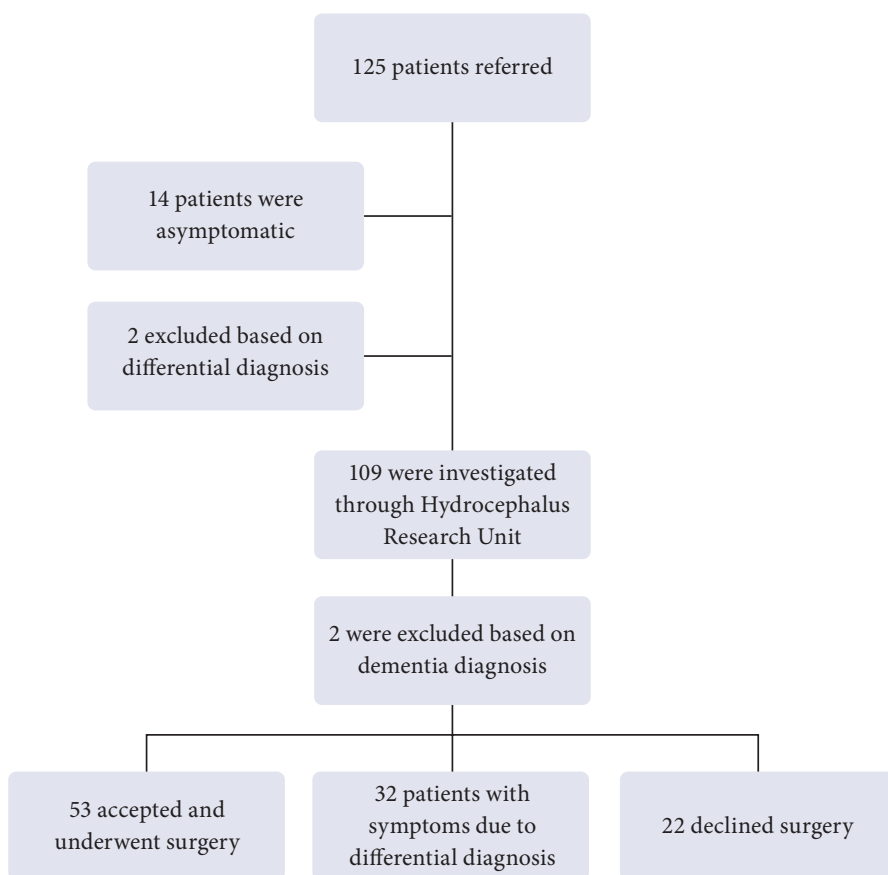
*Figure 8.*
*Flowchart of the patients in Study II*

Seventy-five patients were considered symptomatic and offered surgical treatment, of which 53 patients accepted surgical treatment and 22 declined. In the remaining 32 patients, the symptoms were considered to have other causes than AC.

In Study III, 27 children (13 females and 14 males, age 2 months-17 years) with arachnoid cysts, from the western region of Sweden, were consecutively included. Of these, one child was found to have a desmoplastic infantile ganglioglioma and was excluded from the study. Three patients were asymptomatic and one refused further investigation, leaving 22 patients who were clinically evaluated.

The patients in Study IV were 24 patients included in Study II and III (12 females and 12 males, age 10-79 years). Arachnoid membrane from five patients with Chiari I malformation operated on for the first time was used as control material.

# ETHICAL CONSIDERATIONS

## STUDY I

The Ethics Committee for Medical Research at Gothenburg University approved all studies included in Study I. Informed consent was obtained from the participants or their closest relatives, or both. The medical risks involved in the examinations performed were considered low. However, aside from exposing the patient to radiation, computer tomography may also have led to the discovery of incidental findings, which in some cases, may have benefitted the individual, but may also have led to added worry or anxiety for the individuals in the study.

## STUDY II, III AND IV

The studies were approved by the Ethics Committee for Medical Research at Gothenburg University and all patients gave their written consent to participation in the studies. Additional approval was obtained to include patients with Chiari I as controls and these patients also gave their written consent. In the paediatric cases, the patients' parents provided written consent. The thorough examinations performed in Study II were in no way harmful to the patients and may, in fact, have benefitted them, as symptoms occasionally were found to have other causes than AC.

# METHODS

## CLINICAL ASSESSMENT

The same research team examined all the subjects in Study I, using identical methods. The examinations included neuropsychiatric examinations, Computed Tomography (CT) of the brain and key informant interviews.[228] The clinical assessments of the individuals were performed by psychiatrists between 1986 and 1999, and in 2000 by specially trained psychiatric research nurses. Patient medication, medical history, hereditary factors, headache, including frequency and type, dizziness, including frequency and type, and head trauma were recorded. Cognition was measured with the Mini Mental State Examination (MMSE) and depressive symptoms with the Montgomery-Åsberg Depression Rating Scale (MADRS). Dementia

was diagnosed by psychiatrists, according to the DSM-III-R. Depression was diagnosed according to DSM-5. A nested case control design was used to examine the relationship between AC and clinical features. For each case having an AC on CT, ten matched controls from the same population were randomly selected, based on age, gender and cohort.

In Study II, the clinical interviews were structured according to a special protocol (see Appendix section). Besides medical history and neurological examination, the protocol included previous head trauma, surgical history or any hospital admission, complications during birth, trauma and history of extensive headache, including frequency, duration and intensity, and triggering and aggravating factors. The Mini Mental State Examination (MMSE), Bingley's Visual memory test and the Identical Forms Test were included in the neurological examinations. In Bingley's Visual memory test, a picture of twelve drawings of familiar objects is presented over a 30-second period. Recognition was tested immediately.[229] Each test was performed twice and the mean result was calculated. The identical forms test, which tests perceptual accuracy and speed, was used in this study.[230] At least two neurologists were involved in the evaluation of the patients.

The clinical evaluation of patients in Study III, specifically infants and small children (below 13 years old), was performed by paediatricians, paediatric neurologists and paediatric neurosurgeons at Drottning Silvias Barn och Ungdomssjukhus (The Queen Silvia Children's Hospital).

## FOLLOW-UP

The patients in Study II and III were followed with clinical and radiological follow-up at three to five months and one year postoperatively, on the latter occasion with radiological follow-up only. The follow-up in Study II was performed by the HRU according to the same protocol as the preoperative examinations. Patient-reported outcome was asked for and recorded (see Cyst protocol, Appendix section) by a neurologist who was not involved in the surgical treatment of the patients.

In Study III the patients were also followed up after 8.6 years with structured interviews (7-10.5 years), see the Appendix section.

## NEUROPSYCHOLOGICAL ASSESSMENT

The evaluation of the adult patients in Study II was performed using the RAVLT, the ROCF, the Grooved peg board test with the dominant and non-dominant hand, the Swedish Stroop test and Target reaction time, as described in the Introduction. Each test session started with an interview with the neuropsychologist (Per Hellström), in order to familiarise the patients with the testing situation and

and the examiner. The neuropsychological evaluation was part of the patient evaluation and the results were discussed in a multidisciplinary team conference along with the evaluation by the neurologists and physiotherapist involved. Patients who were operated on were followed up using the same test battery postoperatively.

### ASSESSMENT OF BALANCE

In Study II, balance was assessed using the Romberg test, the sharpened Romberg with open and closed eyes, and the extended version of the FES (S). The tests were performed twice and the result of the best performance was noted. All patients included in the study were examined and the results were discussed in a multidisciplinary conference, as described above. Patients who were operated on were followed up with balance tests at the postoperative follow-up.

## RADIOLOGICAL AND VOLUMETRIC ASSESSMENT

### STUDY I

CT was performed with axial scans without contrast media. CT scans between 1986 and 1992 were performed with 10-mm continuous slices (n = 383) and between 1995 and 2000 with 8-mm slices (n = 855).[227]

Three observers first assessed all scans collectively: a neurosurgery resident (Katrin Rabiei), a medical student (Daniel Jaraj), and a professor of clinical neurology (Carsten Wikkelsø). All cases with a suspected AC, or cases with uncertain findings, were re-evaluated by a senior neuroradiologist (Christer Jensen). Focal atrophy, postsurgical or post-ischaemic lesions, or other lesions that could mimic cystic AC, were excluded.

The length and width of the cyst were measured on the scan where the cyst appeared largest.

### STUDY II-III

Patients in Study II and III underwent MRI according to a fixed protocol including FLAIR, diffusion and T1-weighted sequences to exclude differential diagnoses and determine the cyst volume.

The cyst volume was measured on MRIs performed preoperatively, five months after surgery and one year postoperatively, using OsiriX® software version 6.5.[231, 232] The region of interest was manually outlined on each MRI slice of the FLAIR sequence and the AC volume was measured by the software.

## MORPHOLOGICAL ASSESSMENT

Light, transmission electron and scanning electron microscopy were used in Study IV. A part of the cyst wall sample collected at the time of surgery was sent for routine histopathological diagnosis. The other part of the sample was fixed in a mixture of formaldehyde, glutaraldehyde and sodium azide. The part of the sample that was used for TEM was post-fixed in osmium tetroxide and potassium hexacyanoferrate in 0.1 M calcodylate, stained *en bloc* with uranyl acetate and dehydrated in ethanol. The specimens were infiltrated with epoxy resin and heat-cured. Sections were cut with a diamond knife and the part intended for light microscopy was Richardson-stained. TEM sections were contrasted with uranyl acetate and lead citrate. For SEM sections, the fixation process was followed by repeated osmification according to the OTOTO protocol.[106] After dehydration in ethanol and hexamethyldisilazane, the sections were mounted on aluminium stubs and coated with palladium before examination with SEM.

## STATISTICAL ANALYSIS

Continuous variables were compared using the independent sample t-test and the Mann-Whitney U test. For comparison between two groups, Fisher's Exact test was used for dichotomous variables. The Chi Square test was used for non-ordered categorical variables. For comparison over time, the Wilcoxon Signed Rank test was used for continuous variables and the Sign test was used for categorical variables. For comparison between groups in Study I-II, the Mantel-Haenszel Chi Square test was used for ordered categorical variables and the Kruskal-Wallis test for continuous variables.

Mortality in Study I was examined by comparing time to death from the CT scan, using a Kaplan-Meier survival curve and the Log rank test.

All tests were two-tailed and statistical significance was assumed at $p < 0.05$. In Study I, SPSS version 20.0 (IBM, Chicago, IL) was used. In Study II and III, version 9.4 of the SAS system for Windows was used. Statisticians from Statistiska Konsultgruppen performed all statistical analyses.

# RESULTS

## STUDY I

The prevalence of AC was 2.3 % (n = 29), with no significant difference between men and women. There was no difference in prevalence between subjects in different age categories.

Individuals with and without AC had the same frequency of headache, dizziness, previous head trauma, cognitive impairment and depressive symptoms. No differences were found regarding the prevalence of dementia, depression, epilepsy, or previous hip fracture in individuals with and without AC. ACs were not associated with increased mortality.

## STUDY II

Headache was the most common symptom (60 %), followed by dizziness/imbalance (42 %) and cognitive impairment (17 %). Other symptoms present were seizures (9 %), visual disturbance (7 %), and focal neurological symptoms (6.5 %). Patients who accepted to undergo surgery (n = 53) did not differ from those who declined (n = 22) and those whose symptoms were due to differential diagnosis (n = 32), with regard to neuropsychological and balance tests. The performance of patients with temporal cysts was in the normal range for test results on the neuropsychological tests. Furthermore, patients who experienced cognitive disturbances did also not differ from those who did not display this symptom on neuropsychological tests.

Patients reporting dizziness/imbalance preoperatively exhibited worse results on Romberg (p= 0.004), sharpened Romberg with the eyes open (p = 0.012) and eyes closed (p = 0.0081), but not on FES (S) (0.085), compared with those who did not experience this symptom. These patients did not improve with regard to any of the tests performed postoperatively.

Patients with posterior fossa AC did not differ preoperatively on any of the performed balance tests from patients with AC in other locations. However, the test results were significantly worse postoperatively on both Romberg and sharpened Romberg with the eyes open (p = 0.0003, 0.015) compared with the results of patients with AC in other locations; however, the difference only reached statistical significance on Romberg (p = 0.050) within this group.

Eleven patients suffered 15 complications including extra cerebral haematomas/hygromas (n = 5), CSF leakage and pseudomeningocele (n = 4), meningitis and empyema (n = 2), transient aphasia (n = 1), transient occipital neuralgia (n = 1) and intracerebral haematoma (n = 1). Five reoperations were performed following these complications.

At the time of follow-up, 77 % of the operated patients who underwent surgery reported an overall improvement, while eight (15 %) considered themselves to be unchanged, and two (4 %) reported being worse. However, when evaluating improvement more objectively by looking at the complete disappearance of at least one preoperative symptom, only 43 % were improved, while 49 % were unchanged and 6 % had more symptoms than before the surgery. The outcome of Study II and III are presented in Table 6.

Furthermore, no differences in the test results of the operated patients were seen before and after surgery. Cyst volume decreased postoperatively (p < 0.0001); yet, there was no relationship between cyst volume and clinical improvement.

## STUDY III

Symptoms found preoperatively are presented in Table 5. In summary, the main symptom was headache (12/22), followed by imbalance and/or dizziness (6/22). However, seizures, cognitive impairment or developmental delay, endocrine dysfunction, visual disturbance, hydrocephalus, and macrocephaly were also found in the patients offered surgery. Two patients presented with signs of raised intracranial pressure. The ACs in the patients operated on were located in the temporal lobe (10), multilobular (2), suprasellar (3), intraventricular (3), ambient cistern (1) and the posterior fossa (3). Eighteen per cent experienced complications that did not cause any permanent morbidity and reoperation was performed in three patients during the study period (two due to hydrocephalus and one due to therapy resistant headaches). The average volume of the AC before surgery was 60.6 ml (5 - 225 ml). At the time of the short-term follow-up, at least one of the preoperative symptoms had ceased in 59 % of the patients and the cyst volume had been reduced to an average of 33.3 ml (0 - 145 ml, p < 0.001). We found no association between volume reduction and clinical improvement. At the long-term follow-up, the number of patients in whom at least one symptom disappeared had increased to 77 % (17/22). The average follow up period was 8.6 years (7-10.5 years). However, subjective symptoms remained in 59 % (13/22) of the patients.

| | Preoperative (N= 22) | 3 months postoperative (N=22) | P-value Preoperative to 3-months | Long-term follow-up (N=22) | P-value Preoperative to long-term | P-value 3 months to long-term |
|---|---|---|---|---|---|---|
| Headache | 12 | 7 | 0.13 | 8 | 0.22 | 1.00 |
| Dizziness and imbalance | 6 | 2 | 0.22 | 0 | 0.03 | 0.50 |
| Cognitive impairment/ developmental delay | 3 | 2 | 1.00 | 4 | 1.00 | 0.60 |
| Visual disturbance | 3 | 0 | 0.25 | 0 | 0.25 | - |
| Seizures | 5 | 2 | 0.25 | 1 | 0.13 | 1.00 |
| Endocrine dysfunction | 2 | 2 | 1.00 | 0 | 0.50 | 0.25 |
| Hydrocephalus | 5 | 1 | 0.13 | 0 | 0.06 | 1.00 |
| Number of remaining symptoms | | | 0.001 | | <0.001 | 0.34 |
| N=0 | 0 | 7 | | 9 | | |
| N=1 | 11 | 13 | | 13 | | |
| N=2 | 8 | 2 | | 0 | | |
| N=3 | 3 | 0 | | 0 | | |
| Cyst volume | 60.6 ml (5.3-225.2) | 33.3 ml (1-145) | <0.001 | 37.8 ml (0-202.6) | 0.004 | 0.13 |

*Table 5.*
*Symptoms and signs in children operated for intracranial arachnoid cysts in study II before and after surgery*

| | Study II (Adults) | Study III (Children) |
|---|---|---|
| Patient reported improvement | 77% | 68% |
| Complete disappearance of at least one preoperative symptom; short-term | 43% | 59% |
| Complete disappearance of at least one preoperative symptom; long-term | - | 77% |
| Complications | 15/53 | 4/22 |
| Permanent morbidity | 3.8% | None |

*Table 6.*
*Surgical outcome of study II and III*

The ACs were divided into three groups based on their microscopic features. Twelve ACs were composed of arachnoid-like tissue similar to the composition of the control material from Chiari I patients (Group I). Four specimens consisted mainly of a thick layer of connective tissue with very few meningothelial cells covering the connective tissue layer (Group II), Figure 9.
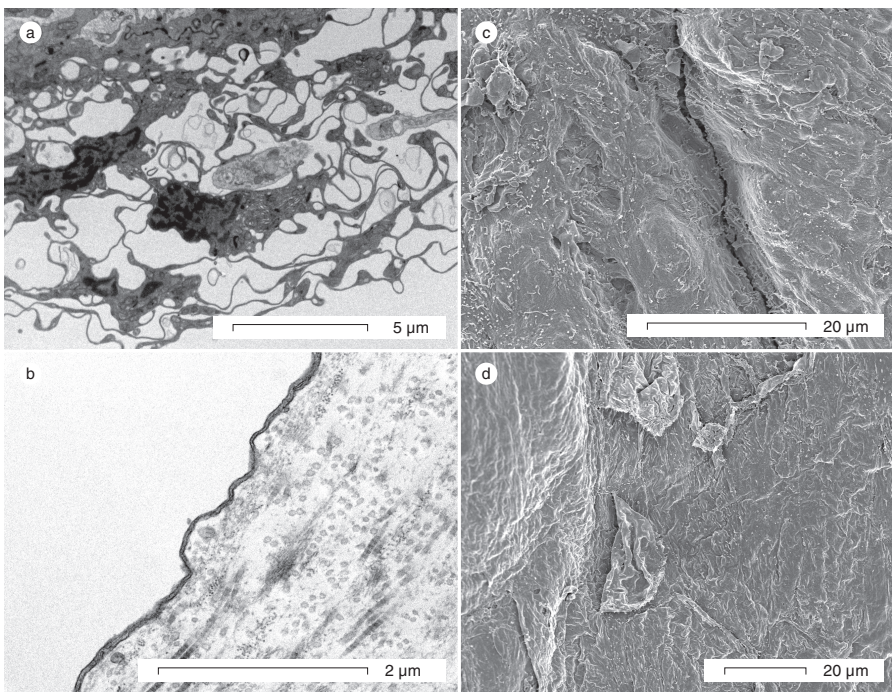


*Figure 9.*
*a. TEM image of a type I arachnoid cyst with a typical meningothelial epithelium on the outer layer of the arachnoid membrane. b. TEM image of the luminal side of a type II arachnoid cyst. c. SEM image of a type I AC with magnification of its left border. d. SEM image of a type II arachnoid cyst.*

Eight specimens made up a heterogeneous group of ACs, each with unique features despite some common characteristics (Group III). The thickness of the membrane varied, with a thickness of 20-150 μm in Group I, 30-800 μm in Group II, and 6-400 μm in Group III, Figure 10.
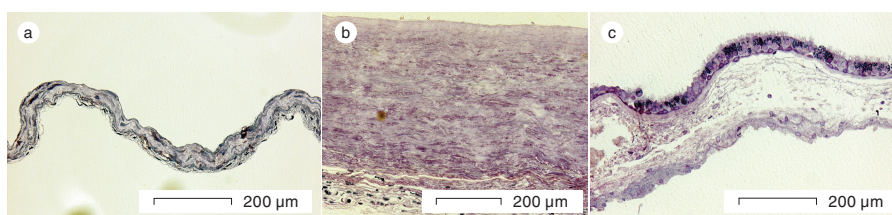


Figure 10.
Light microscopic view of the different types of cyst wall with Richardson's stain. a) Group I, arachnoid-like b) Group II, connective tissue type c) Group III, aberrant type of arachnoid cyst

The ACs in Group I and III were found in the temporal, frontal and posterior fossa locations and present in both adults and children. ACs in Group II were only located in the temporal fossa and only adults were represented in this group. Both men and women were represented in the different groups. All the cysts included in study IV were classified as ACs in routine pathological examinations performed by the neuropathologist.

The third group was composed of ACs of heterogeneous morphology although some characteristics were shared by all the ACs in this group. Four cysts on the luminal side contained ciliated epithelium. The apical cytoplasm of the ciliated cells was rich in mitochondria. One cyst had complex packing of unmyelinated nerve fibres. In three cases, condensed masses of cytoskeletal fibrils, resembling glia fibrils, formed a substantial part of the cyst wall, Figure 11 and Figure 12.
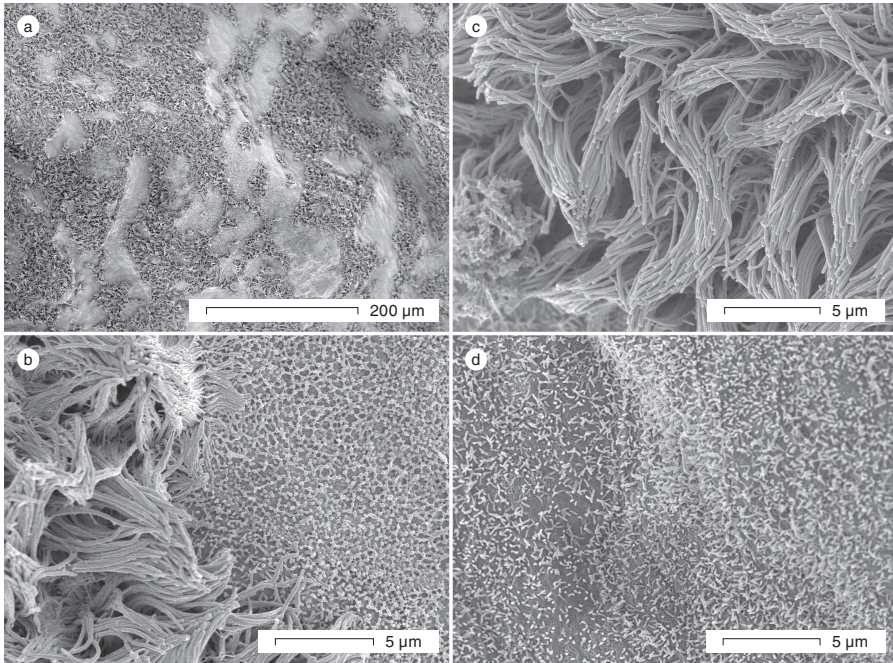
*Figure 11.*
*SEM image of the luminal side of the aberrant type of arachnoid cyst a) The epithelium exhibits a mosaic of two cell types, one with numerous cilia, and another with a myriad of microvilli b) Detailed image of the specimen (5000X magnification) c) cilia d) microvilli*
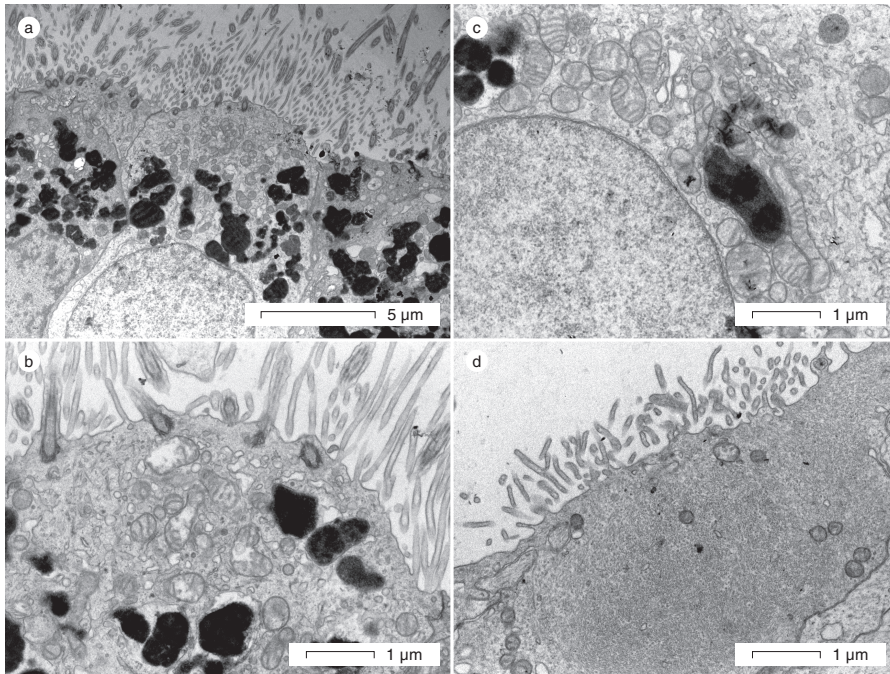
*Figure 12.*
*TEM images of the abarrant cyst type. a-c) Microvilli and cilia of the luminal side of the cyst. Numerous irregular vesicles with electron-dense content are seen in the cytoplasm. The cytoplasm is rich in mitochondria. d) Another cyst where the cystoplasm is almost completely occupied with masses of intermediate filaments. In this image, a filament-rich cell with brush border-like microvilli towards the cyst lumen is seen.*

# DISCUSSION

## EPIDEMIOLOGY (STUDY I)

Most ACs are discovered as incidental findings.[233] The increased availability and the reduced cost of radiological examinations, along with medico-legal issues, have resulted in an increase in radiological examinations.[234, 235] This will naturally lead to an increase in the number of incidental findings. When it comes to AC, its most common symptoms are frequently encountered in the general population.[147, 236, 237] We found a prevalence of 2.3 %, which is similar to that of a hospital-based study in children[44], but higher than that found in adults.[43, 50, 52, 53] The reason could be that the other studies, except the studies by Al-Holou, did not have as an aim to study AC. A recent population-based study has, however, found a prevalence of 3.6 % and reported that ACs were the most common incidental finding in the study.[54] Al-Holou et al. found different prevalences in adults and children. However, similar to our results, they did not find the prevalence to be age-related; thus, even if assuming that some of our cases may have been epidermoid cysts (prevalence of 0.04[53]), we believe that the true prevalence of AC is around 2-3 % in both adults and children.

AC is described as being to be more frequent in men.[238, 239] We found no gender differences in our study, which could be due to the fact that most of the cohorts in our studies included only women. Another reason could be that previous hospital-based studies also included trauma patients and trauma is more frequent in men than in women; hence, the gender difference seen in previous studies could be smaller or non-existent on a population basis.[240]

## SYMPTOMS (STUDY I-III)

To our knowledge, symptoms of AC have previously not been investigated in a population-based sample. In our study, we found that headache, dizziness, dementia, depression, epilepsy, hip fractures as a measure of falls, and history of head trauma, were not more prevalent in individuals with AC than in those without.

The multifactorial nature of headache, dizziness and cognitive impairment, discussed earlier, poses a special challenge to clinicians

when evaluating these symptoms in combination with AC, which is oftentimes incidentally found. A survey among neurosurgeons shows that a predictor of surgery for AC is its size.[218] Although the volume calculation in this study is based on the volume of a cube and therefore overestimates the AC volume, the study makes an interesting point. Despite the fact that AC volume or decompression has not been shown to be related to symptoms, and that large ACs occasionally are reported to be completely asymptomatic[241, 242], it is likely that the decision to intervene surgically is not solely based on objective symptoms but also on AC size. It is also possible that the patient's symptoms are aggravated by the anxiety of being diagnosed with an intracranial lesion.[151, 243]

Of the symptoms of AC, headache is perhaps the most disabling, just as it is among the general population.[139] In Study II, we found that headache was as prevalent in patients with AC as in patients in whom the symptoms were due to a differential diagnosis. On the other hand, headache was significantly less frequent in those who declined surgery. This difference was not found for any other symptom, making headache a likely reason for why some patients are willing to undergo surgery. Results from the Eurolight project on headache shows that 9.2 % of adults experiencing various types of headache find that the headache interferes with their education, and 7.7 % described that headache makes them less successful in their careers.[147]

Headache and dizziness were improved postoperatively in Study II. However, no long-term follow-up has been performed of the patients in Study II regarding headache, and no difference was noted in the balance test results of these patients before and after surgery.

In Study III, only dizziness and/or imbalance showed long-term improvement. The total number of symptoms was reduced in Study III, both at the short and the long-term follow-up. However, it should be kept in mind that the indication for treatment was perhaps somewhat different in children than in adults. As an example, there were cases of hydrocephalus presenting with headache, gait difficulties and developmental delay, where the symptoms were completely resolved.

Cognitive disturbances have been suggested in some studies to be an indication for surgical treatment of AC, especially in the case of a temporal AC;[163, 180, 244, 245] however, the cognitive impairment did not improve, either in Study II or in Study III. In Study II, we performed extensive neuropsychological testing in our patients and detected no difference between those experiencing cognitive impairment and those who did not. Furthermore, temporal AC did not affect the test results. Cognitive impairment therefore remains a highly subjective symptom, which, at least in our studies, could not be measured.

# SURGICAL OUTCOME (STUDY II-III)

As described in the Introduction section, the definition of improvement varies in different studies. We chose to use complete disappearance of at least one preoperative symptom as a measure of improvement in Study II and III, in order to make the evaluation of the patients more objective. This was of a particular importance in Study III in order to reduce recall bias. Further, to avoid potential partiality, the follow-up in Study II and the long-term follow-up in Study III were performed by a physician who was not involved in the surgical treatment of the patients.

We found a high rate of improvement in both Study II and III. In Study II, the reported improvement rate (77 %) could not be confirmed in most of the objective tests performed, and only 43 % of the patients had complete resolution of at least one preoperative symptom. In Study III, 59 % of the patients had complete resolution of at least one preoperative symptom at the short-term follow-up and 77 % at the long-term follow-up. However, 59 % still experienced subjective symptoms at the time of the long-term follow-up. One has to also keep in mind the strong placebo effect in surgery, which is specially pronounced in subjective symptoms and during shorter follow-up times.[246, 247]

Quality of life has recently been described to improve in patients who undergo surgery for AC.[135] However, a similar study found no differences between patients treated surgically and those who did not undergo surgery. The study suggested that anxiety and depression may occasion patients to undergo radiological examination and that their pre-existing symptoms are then aggravated after a diagnosis of an intracranial lesion.[151] Interestingly, in Study III, 21/22 patients or parents considered the surgery worthwhile, regardless of whether improvement was achieved. When asked to justify their answer, they unanimously replied that the surgery was worthwhile, as it removed the parents' worry about the AC.

Considering this, the best effect of surgery on symptoms appears to be the effect on the anxiety caused by the AC itself. If this is the case, then the role of the neurosurgeon in terms of providing the correct information about an AC as an incidental finding is of great importance, regardless of the AC size on the initial scan. Considering the complications of the procedures involved, surgical treatment should possibly be reserved primarily for patients with symptoms and signs of hydrocephalus in combination with AC, symptoms and signs of raised intracranial pressure, or symptoms that can be objectively verified.

## SURGICAL OUTCOME IN RELATION TO POSTOPERATIVE CYST VOLUME

The relationship between improvement and postoperative cyst volume has been investigated in several studies. Some authors have found a relationship between improvement of symptoms and postoperative volume,[219, 248] while others have failed to show such a connection.[137, 158] One of the main reasons may be the vastly different methods used for the calculation of the AC volume. The methods used include: calculation of the volume as a cube[218], as an ellipsoid[135], a reduction by more than 25 % in the section where the AC appears as largest on postoperative CT or MRI,[67, 137] or a visual evaluation of the cyst size and a rough estimation of the reduction in volume.[158, 219, 248] These methods are all subject to potential miscalculation. The calculation of the volume as a cube overestimates the volume of the AC, and calculation of the volume as an ellipsoid also leads to overestimation of the volume. However, these methods are simple and more objective than a rough evaluation of the postoperative size compared with the preoperative size, which is also dependent on the examiner. Another reason may be the different methods used for the evaluation of surgical outcome, as described earlier. In Study II and III, we measured the AC volume using a computer programme. All MRI sections with an AC present were outlined manually and the software calculated the AC volume. This offered a precise measurement of the volume. Both studies show a significant reduction in the AC volume postoperatively and further reduction after one year. To our knowledge, these studies are the first in which the AC volume has been measured using volumetric methods. Improvement defined as complete disappearance of at least one symptom was found in none of the studies to be related to the AC volume.

# DIVERSE MORPHOLOGY (STUDY IV)

As briefly discussed in the Introduction section, the process of formation of the nervous system is rather complex and its components are still not fully understood. Arachnoid cysts are pouches formed inside the arachnoid membrane. In Study IV, we found that the morphology of AC is diverse. This may reflect perturbations in the formation of the meninges during different stages of the development process. The findings in Study IV may indicate that cells of a mesenchymal or endodermal origin are incorporated in the arachnoid membrane at any stage of the embryogenesis or neural

tube folding, leading to the formation of the AC; in fact, AC has been reported to occur also in the brain parenchyma.[249]

From observational studies we know that the majority of ACs are stable or decrease in size over time; however, a few of them expand and cause symptoms.[43, 44] The underlying morphology of the AC may be a factor leading to this variation in expansion possibilities and the subsequent presentation of symptoms later in life.

The subarachnoid spaces covering the temporal lobes are quite wide in foetuses. These spaces normally regress in size, beginning at the end of gestation and continuing until a few months after birth. It is therefore possible that any perturbations in this process may cause the formation of an AC.[42, 45] Hence, vastly different pathophysiological mechanisms may lead to the formation of an AC and be reflected by the different AC morphologies seen.

Since the development of the meninges is closely intertwined with the development of both the cortex and the cranial bones[8], the thinning of the bone overlying the AC may not be an expression of pressure moulding of the cranium, but rather of the perturbation during the process of meningeal formation and, finally, formation of the overlying cranial bone.

Interestingly, during the 1960s, Robinson proposed agenesis of the temporal lobe as the cause of AC.[250] Although he later abandoned this theory,[49] a study measuring temporal lobe volume in five children found that the temporal lobe volume on the side of the AC was significantly lower than on the contralateral side in the same child.[251, 252] True temporal lobe agenesis, however rare, sometimes accompanies AC.[253] It is also notable that the destruction of the meninges overlying the cerebellum has been found to cause cerebellar hypoplasia.[14, 15] These findings may be clues to the complex process in which ACs are formed.

Finally, ACs are found in conjunction with many different malformations of the CNS, further supporting the theory that several different disorders during the development may cause the formation of ACs, rather than a single factor.[254-257]

# STRENGTHS AND LIMITATIONS

## STUDY I

The main strengths of the study include the population-based design and prospective data collection, involving extensive examinations and long follow-up periods. Cases were also matched with ten controls of the same age and gender and in the same cohort.

However, the diagnosis of AC was based on CT scans performed according to the standards at the time of performing the studies, with thicker slices and lower resolution compared with modern imaging. Furthermore, epidermoid cysts, if existing in this group, could not be distinguished from ACs. The small number of ACs detected leads to low statistical power, which may be the reason for the lack of association with clinical symptoms.

The fact that the participants only consisted of elderly persons may limit the inference of the results to younger persons. However, the signs and symptoms of AC are the same in the elderly as in the younger patient. Elderly patients could also be argued to be frailer and the signs and symptoms may therefore be more evident in them than in younger individuals.[258, 259]

## STUDY II, III AND IV

The strengths of study III are its prospective design, the long-term follow-up performed by a physician who was not involved in the surgical treatment of the patients, and the volumetric measurement of the AC volume.

The main limitation of both studies III and IV is the small sample size. In Study III, this made further analysis of the cyst location in relation to the surgical response impossible, and in Study IV, we could not draw any conclusions regarding symptoms or the risk of recurrence based on morphology. In Study III, this also meant that the number of patients who were conservatively treated was few.

The strengths of Study II include the prospective design, the extensive clinical, neuropsychological and physiotherapeutic evaluation and the volumetric measurements. Almost one-third of the patients in this study declined surgery, thereby providing us with a unique group of patients for comparison. The lack of long-term follow-up is the main weakness of Study II.

# CONCLUSIONS

✓ Arachnoid cysts are common intracranial findings, with a prevalence around 2 % and no relationship with the common symptoms ascribed to them, at a population basis.

✓ Dyscognition could not be objectified in patients reporting this symptom or in those with a temporal arachnoid cyst and cognitive test results did not improve among those patient groups after surgery.

✓ Adult patients experiencing balance problems did not improve postoperatively on balance scales nor balance tests.

✓ The reported improvement rate was as high as 77 %, during the short-term follow-up in adults, and the long-term follow-up in children who underwent surgery.

✓ Beneficial long-term results of surgery for intracranial arachnoid cysts were obtained in children.

✓ There was no difference in the test results before and after surgery in the adult patients operated on for an arachnoid cyst.

✓ There is no relationship between a postoperative reduction in cyst volume and clinical improvement, neither in adults nor in children.

✓ The results of the clinical studies support a restrictive approach to surgical treatment in the absence of verifiable objective signs and symptoms or obstruction of the CSF pathways.

✓ Arachnoid cysts have a diverse morphology with at least three subgroups, based on their ultrastructure: those with an arachnoid-like structure, those with a connective tissue structure, and the group of cysts with an aberrant and diverse morphology.

✓ The diverse arachnoid cyst morphology may reflect different mechanisms behind the cystogenesis.

# FUTURE PERSPECTIVE

The results of this thesis show that AC is a common condition in the general population and not associated with any of the common symptoms ascribed to it at population level. Based on the results of the clinical studies, the role of surgery in the treatment of AC in the absence of hydrocephalus may be questioned.

Indeed, incidental findings are discovered more frequently with increased use of radiological examinations. In accordance with this, and, perhaps, also based on publications showing promising results for AC surgery, the incidence of fenestration surgery for AC has almost doubled during the last five years compared with the study period. It is therefore of great importance to study AC further and examine the best treatment strategy for these patients.

We performed a long-term follow-up of the children operated on in this study; however, no long-term follow-up has been performed for the adults operated on at our department. Long-term follow-up would provide us with more information on whether or not the results on subjective symptoms, such as headache and dizziness/imbalance, are maintained in the long run.

Many patients improve spontaneously over time without surgical treatment, both in our series and in other studies that have included a natural history analysis. Based on this and the benign nature of AC, a randomised study evaluating the best medical and physiotherapeutic treatment for symptoms of AC versus surgical treatment, would be of great interest and importance. It would provide more solid evidence of the best treatment strategy for this condition and potentially shed more light on which patients benefit the most from surgery. Better studies of the natural history of AC would also be of great importance.

Finally, all ACs may not have the same pathophysiological or expansion mechanisms. Further research could perhaps also answer the question whether the AC morphology, symptoms, recurrence risk and surgical outcome are connected, and possibly show what types of AC truly benefit from surgical treatment.

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# APPENDIX

| NEUROLOGIST'S EVALUATION PROTOCOL – INTRACRANIAL ARACHNOID CYSTS | |
|---|---|
| **Specific instructions on how the form is filled out are given at the bottom of the protocol** | |
| 1 | Patient ID in the study |
| 2 | Name |
| 3 | Social security number |
| 4 | Age |
| 5 | Gender<br>1. Man 2. Woman |
| 6 | Height (cm) |
| 7 | Weight (kg) |
| 8 | Admitted from<br>1. Own residence 2. Serviced apartment 3. Nursing home 4. Hospital |
| 9 | Referral was from<br>1. Primary care 2. Hospital |
| 10 | Referring doctor<br>1. GP 2. Internist 3. Neurologist 4. General surgeon 5. Other specialty |
| 11 | Reason for radiological investigation (one or more options)<br>1. Headache 2. Seizure 3. Imbalance 4. Dizziness, 5. Trauma 6. Dyscognition/psychiatric reason 7. Visual disturbance 8. Endocrine disturbance 9. Other (specify) |
| 11a | If radiological investigation shows haemorrhage, was it<br>1. Spontaneous 2. Traumatic |
| 11b | Head trauma; grading of trauma  (see below)<br>1. Minimal 2. Mild 3. Moderate 4. Severe |
| 12 | Headache analyses Headache duration in months |
| 12a | Character<br>1. Sharp 2. Dull 3. Pulsating 4. Pressing |
| 12b | Intensity (see below)<br>1. Light 2. Moderate 3. Severe |
| 12c | Localisation<br>1. Unilateral 2. Bilateral |
| 12d | Localisation (one or several)<br>1. Frontal 2. Temporal 3. Parietal 4. Occipital 5.Difuse |
| 12e | Character<br>1. Episodic 2. Lasting 3. Lasting with exacerbation |
| 12f | If episodic (one or several)<br>1. Variation over the day 2. Exertional 3. Related to body position |

| | | |
|---|---|---|
| 12g | Variation over the day | |
| | 1. Morning 2. Day 3. Evening 4. Night 5. No variation | |
| 12h | Pharmacological treatment for headache | |
| | 1. Yes 2. No | |
| 13 | Anamnesis | |
| | 1.Stroke 2.Abscess/meningitis/CNS-infection 3. Head trauma 4. Birth trauma/traumatic birth | |
| 14 | Right/left-handed | |
| | 1. Right-handed 2. Left handed | |
| 15 | Hereditary disease/intracranial cysts in family (see appendix) | |
| | 1. Yes 2. No | |
| 16 | Does the patient have a twin | |
| | 1. Identical twins 2. Fraternal twin 3. No | |
| 17 | Radiological cyst location | |
| | 1. Temporal 2. Frontal 3. Parietal 4. Occipital 5. Suprasellar 6. Posterior fossa 7. Intraventricular | |
| 18 | Cyst character | |
| | 1. Homogeneous 2. Septations | |
| 19 | Cyst character | |
| | 1. Extra cerebral 2. Intra cerebral | |
| 20 | Cyst location | |
| | 1. Left 2. Right 3. Midline 4. Bilateral | |

| | **Date** | |
|---|---|---|
| 21 | Residential circumstances | |
| | 1. Home with no help 2. Home with help from relatives 3. Home with home care service 4. Home but stays in service apartments sometimes 5. Service apartment 6. Hospital | |
| 22 | Major complaint (one or several) | |
| | 1. Headache 2. Seizure 3. Imbalance 4. Dizziness 5. Dyscognition 6. Focal neurological symptoms 7. Visual disturbance 8. Endocrine disturbance 9. Other (specify: …………………) 10. No complaints | |

| **23** | **Cognitive Examination** | |
|---|---|---|
| | MMSE (number of points) | |
| | Identical forms test (number of correct answers– number of wrong answers/4) | |
| | Bingley's test (average of 2 trials) | |
| 24 | Reported outcome of surgery | |
| | 1. Unchanged 2. Better 3. Worse | |
| 25 | Cyst volume on MRI (ml) | |

INSTRUCTIONS

**Point 1-23**
Is filled out by the physician at HRU

**Point 24-28**
Is filled out by the physician who discharges the patient at HRU

**Point 11**
What was the reason the cyst was discovered?
11:9 e.g. hemiparesis or other focal neurological sign or symptom

**Point 11b**
Minimal head injury (did not loose consciousness or have amnesia for the event, GCS 15)
Mild head injury (loss of consciousness<5 min and/or amnesia for the event, GCS 14-15)
Moderate head injury (loss of consciousness>5 min, GCS 9-13)
Severe head injury (loss of consciousness, GCS < 9)

**Point 12**
Number of months; e.g. 2 weeks = 0.5 month

**Point 12b**
Light=VAS 0-3
Moderate=VAS 4-6
Severe=VAS 7-10

**Point 15**
Are there any intracranial cystic lesions in the family?

**Point 25, 26, 27, 28**
Is filled at when the examinations are performed

QUESTIONNAIRE FOR LONG-TERM FOLLOW UP OF CHILDREN OPERATED FOR AC (ENGLISH TRANSLATION)

1. In what way were you/your child affected by the symptoms?
2. Was the you/your child affected to a degree that you/he/she could not participate in playing with other children or in school?
3. If you/your child went to school at the time of the symptoms, were the school results or your presence at school affected based on your/hers/his symptoms?
4. The total negative impact of the symptoms on daily life
5. 0-100
6. After the surgery, was your participation in school affected to the better?
7. Were you school results improved after the surgery?
8. What symptoms were most improved by the surgery?
9. Was the operation worthwhile? Why so?
10. How long did it take before you noticed an improvement?
11. Do you experience any of the symptoms you had before the surgery?
12. Do you suffer from any additional symptoms since the surgery?
13. What type of symptoms do you have at the present time?
    a) Headache b) Seizures c) Imbalance d) Dizziness e) Cognitive- or memory disturbance f) Depression g) Visual disturbance h) Endocrine problems i) other (specify) j) No symptoms
14. If you have headache, how many days per month do you suffer from headaches?
15. Intensity of headache episodes: 1) Light 2) moderate 3) severe
16. Localization 1) frontal 2) temporal 3) parietal 4) occipital 5) Diffuse
17. Character 1) Occasional 2) All the time 3) All the time with exacerbations
18. Does the headache demand pharmaceutical treatment 1) Yes 2) No
19. What medications do you use? 1) Prescription free drugs such as paracetamol or ibuprofen 2) Prescribed medication (specify)
20. Are you worried the cyst might recur?