Adult Chiari I malformation

Clinical presentation and surgical outcomes

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This thesis is dedicated my beloved and dearest people.

To the best thing that has ever happened to me, my brilliant, loving and supportive soul mate and dear wife Asma, who is my true inspiration and motivation for learning and moving forward.

To the pride and joy of life, my son, Salem.

To my heavenly parents (Salem & Maha), who gave their unconditional love and always encouraged me to become the person who I am today. I love you more than anything.

ABSTRACT

Background

Chiari I malformations (CMIs) are hindbrain anomalies that are characterized by cerebellar tonsillar ectopia. The typical presentation is an occipital headache that worsens with exertion. In this thesis, I focus on the following three atypical presentations of CMI: swallowing difficulty, neuropsychological (NP) dysfunction and acute deterioration. In addition, I address the impact of CMI on patient quality of life (QOL). The preoperative factors that predict cerebrospinal fluid disturbance (CSFD) after surgery for CMI have rarely been reported and will be discussed and investigated in this thesis.

Patients and methods

In the first two studies presented in this thesis (studies I & II), patients were prospectively included over a two-year period. Patients underwent both subjective and objective assessments of swallowing function in Study I and of NP functions and QOL in Study II. The total number of patients included were 11 and 14, respectively. All patients were assessed both before and at 3 months after surgery.

In the last two studies presented in this thesis (studies III & IV), patients were retrospectively included over two overlapping 10-year periods. The total number of patients included were 52 and 65, respectively. In Study III, I explore the preoperative radiological factors that indicate a risk of acute deterioration in CMI patients. In Study IV, I investigate preoperative patient characteristics that might determine the risk of postoperative CSFD.

Results

In Study I, four patients (36%) reported varying degrees of swallowing complaints (mean Watson Dysphagia score, 16). In two of these patients, there was substantial penetration of contrast on videofluoroscopy, and in the other two patients, minor disturbances were observed. None of the patients reported remaining symptoms after surgical decompression.

In Study II, the majority of included patients demonstrated cognitive functions within the normal range. However, their postoperative performance on some of the tested NP assessment tools significantly improved.

There was a lower level of satisfaction with QOL both before and after surgery in patients than in healthy subjects In addition, the 5-level Euroqol-5 dimensional questionnaire (EQ-5D-5L) indicated that patient QOL was significantly better after surgery.

In Study III, three patients (4.6%) presented with acute deterioration of symptoms. Additionally, the length and size of the syrinx were higher and it was extended more rostral (above C1 level) in these acute patients than in non-acute patients with CMI.

In Study IV, six patients developed CSFD after occipitocervical decompression (OCD) and subsequently underwent cerebrospinal fluid (CSF) diversion procedures. All of these patients were females, and they had a mean body mass index (BMI) of

32.3, whereas the mean was 24.3 in patients without CSFD (p=0.0011). There was no difference between the two groups in other examined patient characteristics.

Conclusion

Symptoms of dysphagia are not uncommon in CMI patients. A preoperative NP assessment of adult patients with CMI showed that there was a statistically significant improvement in four of the nine tasks tested after surgery. Furthermore, preoperative QOL was poorer in CMI patients than in healthy individuals. Surgery can potentially remedy the causes underlying dysphagia and NP dysfunctions, thereby relieving their symptoms.

Study III shows that it is important to assess the preoperative size, length and rostral extension of the CMI-associated syrinx because changes in these parameters could indicate acute deterioration, and affected CMI patients should be assigned for early surgical decompression.

All patients with postoperative CSFD were female, and their mean BMI was significantly higher than that of patients without this complication. Pseudotumor cerebri must be excluded in this group of patients.

Keywords

Arnold-Chiari Malformation, Deglutition Disorders, Deglutition, Surveys and Questionnaires, Decompressive Craniectomy, Treatment Outcome, Cognitive Dysfunction, Executive Function, Patient Satisfaction, Psychological Tests, Quality of Life, Syringomyelia, Emergencies, Postoperative complications, Hydrocephalus, Body mass index

Sammanfattning på svenska

Bakgrund

Chiari I missbildning (CMI) är en sjukdom som drabbar lillhjärnan och vars radiologiska definition är en neddragning av lillhjärns tonsillerna i foramen magnum med minst 5 mm. Det typiska symtomet är huvudvärk i bakhuvudet som förvärras vid ansträngande aktiviteter. Denna avhandling diskuterar tre atypiska manifestationer av CMI; sväljningssvårigheter, neuropsykologisk dysfunktion och akut försämring av CMI. Avhandlingen omfattar också två andra frågor som tidigare studerats knapphändigt; sjukdomens och behandlingens inverkan på patienternas livskvalitet (QOL) samt preoperativa faktorers korrelation till likvorcirkulationsstörning efter operation av CMI.

Patienter och metoder

I de två första studierna i denna avhandling (studier I & II) inkluderades patienter prospektivt under en tvåårsperiod. Patienterna genomgick både subjektiv och objektiv bedömning för sväljningsfunktionen i studie I och neuropsykologisk funktion och QOL i studie II. Totalt inkluderade patienter var 11 respektive 14. Alla patienter bedömdes både före och 3 månader efter operationen.

I de två sista studierna av avhandlingen (studier III och IV) inkluderades patienter retrospektivt under två överlappande 10-års perioder. Totalt inkluderade patienter var 52 respektive 65. Studie III belyser de preoperativa radiologiska faktorer som indikerar risk för akut försämring av CMI-patienter. Studie IV undersöker preoperativa patientfaktorer som kan avgöra risken för postoperativ likvorcirkulationsstörning.

Resultat

I studie I rapporterade fyra patienter (36%) olika grader av sväljningsbesvär (medelvärde för Watson Dysphagia, 16). I två av dessa fanns betydande penetration av kontrast på Videoflouroscopy, och i de andra två patienter observerades mindre störningar. Alla symtom förbättrades efter operation.

I studie II visade majoriteten av patienterna kognitiv funktion inom normalvärden. Ändå förbättrades deras resultat i vissa testade neuropsykologisk -test postoperativt signifikant.

Patienter rapporterade en lägre nivå av tillfredsställelse med sin livskvalitet både före och efter operation jämfört med friska försökspersoner. Däremot indikerade EQ-5D-5L-mätningarna att deras livskvalitet var signifikant förbättrad efter operationen.

I studien III uppvisade tre patienter akut försämring av symtomen (4,6%) och samtliga hade en ökad längd och storlek av syrinx och mer rostral förlängning av syrinx jämfört med icke-akuta patienter med CMI.

I studie IV hade sex patienter likvorcirkulationsstörning efter occipitocervikal dekompression (OCD). Samtliga dessa patienter var kvinnor med ett genomsnittligt kroppsmassindex på 32,3 jämfört med ett medelvärde på 24,3 hos patienter utan likvorcirkulationsstörning ($p = 0,0011$). Det fanns ingen skillnad mellan de två grupperna med avseende på de andra undersökta patientfaktorerna.

Slutsats

Dysfagi är inte ovanligt hos CMI-patienter men med en god postoperativ prognos. Trots att den preoperativa neuropsykologiska bedömningen av patienter med CMI var normal fanns statistiskt signifikant förbättring på fyra av de nio tester som gjordes efter operationen. CMI-patienter rapporterade en nedsatt QOL före operation jämfört med friska individer men även den förbättrades efter operation.

En stor CMI-associerad syrinx som sträcker sig över C1 är en riskfaktor för akut försämring och därigenom en indikation för tidig kirurgisk dekompression.

Alla patienter med postoperativ likvorcirkulationsstörning var kvinnor och deras genomsnittliga BMI var signifikant högre än patienter utan denna komplikation. Pseudotumör cerebri bör uteslutas i denna patientgrupp.

List of papers

I. Swallowing dysfunction in adult patients with Chiari I malformation; Fawaz S. Almotairi, Mats Andersson, Olof Andersson, Thomas Skoglund, Magnus Tisell. Submitted.

II. Chiari I malformation - neuropsychological functions and quality of life, Fawaz S. Almotairi MD, Per Hellström PhD, Thomas Skoglund MD, PhD, Åsa Lundgren Nilsson PhD, Magnus Tisell MD, PhD, Submitted.

III. Acute deterioration of adults with Chiari I malformation associated with extensive syrinx, Almotairi FS, Magnus Tisell, Submitted.

IV. Cerebrospinal Fluid Disturbance In Overweight Women After Occipitocervical Decompression In Chiari Malformation, Almotairi FS, Magnus Tisell , Acta Neurochirurgica: 2016 Mar; 158(3): 589-94; discussion 594. .

CONTENTS

ABBREVIATIONS

ADL	Activities of daily living
BMI	Body mass index
BVMT-R	The brief visuospatial memory test-revised
CMI	Chiari I malformation
CSF	Cerebrospinal fluid
CSFD	Cerebrospinal fluid disturbance
CT	Computed tomography
DTI	Diffusion tensor imaging
EQ-5D	Euroqol 5-dimensional
HAD	Hospital anxiety and depression scale
IAP	Intra-abdominal pressure
ICP	Intracranial pressure
MRI	Magnetic resonance imaging
NP	Neuropsychological
OCD	Occipitocervical decompression
PAS	Penetration-Aspiration scale
PFD	Posterior fossa decompression
PTC	Pseudotumor cerebri
QOL	Quality of life
RAVALT	Rey auditory verbal learning test
VFS	Videoflouroscopy
WDS	Watson dysphagia scale

INTRODUCTION

INTRODUCTION

Chiari I malformations (CMIs) are hindbrain anomalies that manifest radiologically as a descent of the cerebellar tonsils ≥ 5 mm into the foramen magnum, as shown in figure 1 [7].

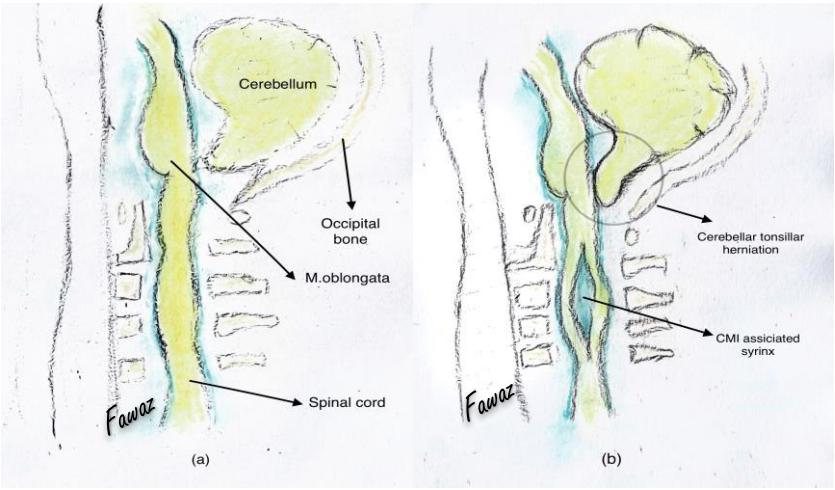


Figure 1: Illustrative comparison between (a) normal anatomy and (b) Chiari I malformation (CMI) showing the cerebellar tonsillar ectopia and CMI associated syrinx.

Hindbrain structures, including the pons, medulla oblongata and cerebellum, and the upper cervical spine are the most frequently involved anatomical areas [8]. In turn, most of the clinical signs and symptoms associated with CMI originate from these structures, as will be described later. CMI is incidentally found in 0.8-1% of the normal population [9,10] with a nearly equal gender representation [11]. However, females are more likely than males to present with symptoms (55-76%), and most patients present between the third and fourth decades of life [12].

One of the most common radiological findings associated with CMI is a syrinx (50-70%) [11,12]. A syrinx is defined as a fluid cavity located within the spinal cord tissue [13]. If it further extends into the medulla oblongata, it is called a syringobulbia (1-10% of cases) [14,15]. Another milder type of fluid filled-cavity in the spinal cord is "hydromyelia", which is a dilatation of the central canal [16]. In contrast to a syrinx, in a hydromyelia, the fluid is lined with ependymal tissue, and hydromyelia are not associated with spinal cord injury or symptoms [17].

In this thesis, the focus will be on Chiari I malformations (CMIs) in adults, which, in contrast to other types of Chiari malformations, lack a caudally displaced brainstem and are not associated with neural tube defects [1-4], as detailed in the sidebar.

Classification of Chiari Malformations

I: Tonsillar ectopia ≥ 5 mm into the foramen magnum. No neural tube defects.

II: Neural tube defect. Hydrocephalus and other anomalies.

III: Rare, a portion of the cerebellum and brainstem migrates out of the craniocervical junction.

IV: Uncommon, hypoplastic or absent cerebellum.

0: Crowded appearance of craniocervical junctions. No or minimal tonsillar ectopia.

1.5: Significant caudal descent of the cerebellar tonsils and brainstem. No neural tube defects.

HISTORY

Year/Scientist	Description
1593-1674, The Dutch physician and anatomist Nicholas Tulp [18]	Reported a myelodysplastic individual with hindbrain herniation
1883, The Scottish physician John Cleland [19]	Described a Chiari II malformation in a myelodysplastic individual with hindbrain malformation and hydrocephalus
1891, Hans Chiari, professor of pathological anatomy [20]	Published his description of what later became known as Chiari malformations
1894, Julius Arnold, professor of anatomy at Heidelberg [21]	Described a myelodysplastic patient with hindbrain malformation without hydrocephalus
1907 [22]	Chiari II malformations were labeled "Arnold Chiari malformations"

Table 1: A brief historical background of Chiari malformation.

PATHOPHYSIOLOGY

CMI and associated disorders

Morphometric studies have made comparisons between CMI and normal populations. These have shown that the posterior cranial fossa is smaller in CMI patients than in normal controls [23-26]. This phenotype could be secondary to mesodermal defects that lead to a tight foramen magnum and cerebellar tonsillar herniation [25,27]. A small posterior cranial fossa has also been observed in CMI cases associated with other conditions and syndromes. These include craniosynostosis [28,29], especially multisuture and lamboid types, familial vitamin D–resistant rickets (44%) [30], acromegaly [31] and neurofibromatosis type I (8%) [32]. Another probable cause of CMI is a primary cerebrospinal fluid disturbance (CSFD) that secondarily caused cerebellar tonsillar herniation. This latter occurrence was hypothesized in the first early descriptions of CMI [20,33]. Later, series found that this association was present in less than 10% of cases [34], making it a questionable etiology for CMI . As will be described later in this thesis, CMI can be acquired secondarily to many conditions, such as intracranial tumors [35] or intracranial hypotension [36-38].

Syrinx

Since CMIs were first described by Stephanus (1545), many theories have been proposed to explain their pathogenesis, which remains controversial today [39]. Table 2 shows a summary of the main theories that have been published regarding the pathogenesis of syrinx.

Mechanism	Author/yr
Primary inflammation leading to glial proliferation and degenerative changes [40,41]	Hallopeau 1870 Schultze 1882
Hydrodynamic theories and obstruction of 4th ventricle outlet [42]	Gardner 1958
A pressure effect via perivascular spaces on the spinal subarachnoid spaces [43]	Bali and Dayan 1972
Intracranial-intraspinal pressure dissociation [44]	Williams 1980
Persistence of the central canal [45]	Millhorat 1994
Systolic pressure causes fluids in the subarachnoid space to move into the spinal cord secondary to tonsillar ectopia [46]	Oldfield 1994
Lack of synchrony between pressure waves in the cerebrospinal fluid (CSF) and spinal cord tissue resulting in high pressure in the spinal cord ,causing the section near the obstruction area to be filled with extracellular fluid [47].	Greitz 2006
Decreased compliance of the spinal subarachnoid space leading to disturbed absorption of extracellular fluid and the accumulation of fluids in the cord [48]	Koyanagi 2010

Table 2: The main pathophysiological mechanisms of syrinx.

ASSESSMENT OF CHIARI I MALFORMATION

Subjective clinical assessment

The typical CMI symptom is an occipital headache that is short in duration and strain-related (e.g., occurs when coughing, laughing and exercising) [12,49]. This might be related to impaired cerebrospinal fluid (CSF) dynamics and crowding at the foramen magnum or pressure at the meninges [50,51]. Atypical types of headache, such as those with a long-duration or that are migraine-like, have been reported, and these symptoms can make further decisions regarding patient management difficult [52]. Other common presentations of CMI include ophthalmological manifestations, such as double or blurred vision [12,53]. Furthermore, CMI patients, especially in cases of associated syrinx, can present with medullary symptoms, such as a loss of sensation or limb weakness [12,49,54]. Finally, reports have described CMI patients who presented with unsteadiness and positional dizziness [12].

Other atypical presentations of CMI, such as swallowing difficulty or cognitive dysfunctions, been described in case reports and series. Some swallowing-associated neuroanatomical considerations related to CMI are discussed in the side bar. The explanation for these atypical

Anatomical considerations related to swallowing function

Swallowing is a very coordinated process that involves very organized connections between the central nervous, respiratory and gastrointestinal (GI) systems. Derangement or injury in any of these systems or their connections results in swallowing difficulties and aspiration of the bolus into the airway. Cranial nerves (V, VII, IX, X and XII) are involved in this coordinated process. The swallowing centre in the medulla oblongata processes signals conveyed by cranial nerves in response to a bolus in the pharynx to modulate the protective mechanisms that function to prevent food aspiration into the respiratory system or regurgitation into the mouth [6].

manifestations is complex and briefly described at the end of this section. Few prospective and systematic studies have explored this issue, and this makes it difficult to assign patients with unusual symptoms and a radiological finding of CMI for occipitocervical decompression (OCD). Further research aimed at investigating the association between CMI and atypical presentations as well as the effects of surgery are needed. Figure 2 summarizes the proposed origins of these symptoms and the relevant involved structures.

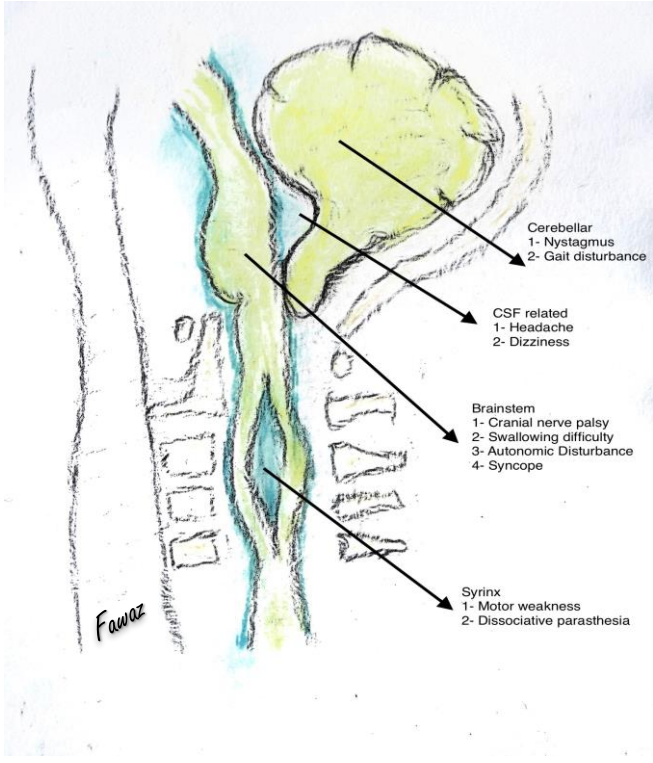


Figure 2: Illustration of Chiari I malformation showing the probable origin of some CMI related signs and symptoms.

CMI symptoms usually have a gradual onset. However, acute presentation has been reported in 1.2 to 3.2% of cases [55,56]. The clinical presentation of reported acute cases have involved medullary signs and even sudden death [56-59]. The risk factors that might help to predict these incidents remain unknown, and evidence is currently based solely on case reports and series.

This will be the focus of Study III, which investigates preoperative radiological findings on magnetic resonance imaging (MRI) of the brain and spinal cord that may help when assigning patients for early OCD.

Self-reported questionnaires

Self-reported questionnaires are frequently used to assess subjective symptoms and the general well-being of patients.

In this thesis, questionnaires were used to assess quality of life (QOL), swallowing function and neuropsychological (NP) functions in CMI patients. The following discussion will briefly focus on the use of questionnaires in these areas.

Validity and reliability

Before they are implemented in real practice, questionnaires are tested for two important concepts: validity (internal vs. external) and reliability (stability, homogeneity and equivalence). A questionnaire is valid when it measures what it intends to measure and its extent reflects the real concept being tested. Reliability reflects how reproducible the results of a questionnaire are with each new use [5].

Quality of life

The World Health Organization (WHO) defines QOL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Many aspects of an individual's environment can affect QOL. These include but are not limited to the socioeconomic, functional, health and vocational status of the individual [60].

Interest in medical inventions has in past decades focused mainly on finding the best medical and surgical cures for diseases. This has resulted in longer patient survival, even among those with severe diseases that had high mortality in the past. Researchers and clinical practitioners later became secondarily interested in how a certain disease might affect the daily life of an individual. This has allowed us to convey better information to patients about their problems and the expected impact of their condition on their daily activities. In addition, it allows us to assess the effects of an

intervention on a given disease, which improves how patients are assigned for multidisciplinary care covering both the medical and psychosocial aspects of the disease [5].

Quality of life in CMI

In contrast to many other conventional investigation tools, there is no gold standard for measuring QOL. However, in contrast to generic instruments, QOL assessment questionnaires can be made disease-specific by including questions that target different aspects of a medical condition. Previous investigations of QOL performed in CMI patients have included the use of different instruments and are summarized in table 3 [61-65]. As shown, The Chiari Symptom Profile (CSP) is the only CMI-specific QOL instrument used in the literature. However, it is rarely used to research outcomes in Chiari patients and should therefore be further assessed [65,66].

The only prospective study on QOL that has been performed in CMI was conducted by Parker et al., who used a generic and validated tool, the Euroqol-5 dimensional questionnaire (EQ-5D), and found that patient QOL significantly improved after surgery [67].

Study II of this thesis investigates QOL in CMI along with NP functions both before and after surgical decompression

Questionnaire	Characteristics
Short form (SF-12)	• Less precise than the detailed SF-36. • Assesses physical and mental health status.
Euroqol-5 dimensional (EQ-5D)	• See methods section
The World Health Organization WHOQOL-BREF	• Developed by the WHO. • A concise form of the original WHOQOL-100 that contains 26 questions. • Assesses four domains: physical health, psychological health, social functioning and environment
Sickness impact profile (SIP)	• One of the most widely used generic instruments • Very long and detailed • Comprised of 136 items (divided into 12 categories) describing daily living activities (ADL).
Chiari Symptom Profile (CSP)	• Recently developed, has strong content validity • Scarcely used to research Chiari outcomes, therefore needs to be further assessed
Chicago Chiari Outcome Scale (CCOS)	• Assesses pain symptoms, non-pain symptoms, functionality, and complications • Designed for retrospective chart review • Some CCOS sub-scores, particularly those for functionality, have poor interrater reliability.

Table 3: An overview of assessment tools that have been used to assess quality of life in Chiari I malformation.

Self-reported swallowing function

Some questionnaires are helpful because they complement instrumental assessments of swallowing and allow dysphagia to be quantified, leading to easier comparisons and statistical analyses. Many validated tools are available that differ in the question they answer as well as their aims (e.g., "swallowing QOL and assessment if dysphagia present"). Table 4 shows some of the swallowing assessment questionnaires that are commonly used in the literature[68-71].

Questionnaires	Characteristics
The M.D. Anderson Dysphagia Inventory (MDADI)	• Developed to assess dysphagia and QOL in individuals with head and neck cancer. • Assessment of four domains, including global, emotional, functional, and physical subscales of a patient's response to swallowing • Has high reliability and internal consistency
Swallowing QOL (SWAL-QOL)	• Long (44 items) • Has high internal consistency and short-term reproducibility
Eating Assessment Tool (EAT-10)	• A tool validated in the Swedish population in 2016 • Good internal consistency and reliability
EORTC QLQ-OG25	• See methods section
Watson dysphagia score (WDS)	• See methods section
Sydney Swallow Questionnaire	• Assesses swallowing and severity • Validated in Sweden in 2014

Table 4: The most commonly used questionnaires in the literature to assess swallowing function.

Objective clinical assessment

Neurological examination

In CMI patients, a detailed bedside examination will complement the patient's history and helps when forming a comprehensive assessment before making a final diagnosis. It is also valuable for choosing further investigational tools if necessary. The cranial nerve problems most frequently encountered in CMI are diplopia and nystagmus (especially downbeat nystagmus), which are characteristic of craniocervical junction abnormalities [72,73]. Cerebellar signs, such as truncal ataxia, have been reported in 40% of CMI cases [74]. These occur in addition to long tract manifestations, such as paresthesia or motor disturbances in the upper or lower limbs [12,49]. Because it is a central lesion, syrinx frequently affects the spinothalamic tracts and causes a dissociative paresthesia [75], which results in the loss of pain and temperature sensation without the loss of fine touch and proprioception [76].

Neuropsychological assessment

These are not routinely performed in CMI but were used in Study II of this thesis. The rational for testing NP function in CMI is based on previous reports of cognitive dysfunction in CMI patients, as will be described later in the discussion section of this thesis. Two possible explanations for this association are the stress related to being diagnosed with CMI and the prospect of undergoing surgical decompression, both which can affect a patient's performance on NP testing. Klein et al. proposed, based on their study of two cases of CMI with NP sequelae, that environmental and psychological rather than neurological factors should be considered when evaluating cognitive and affective functioning in CMI [77]. Furthermore,

Mechtler et al. suggested that an incidental finding can place the patient at an increased risk of developing a vast array of psychological issues and may make their symptoms more exaggerated [78]. Other explanations that have been proposed include the notion that CMI symptoms might trigger anxiety and other psychiatric symptoms, especially CMI-associated sleep apnea and deprivation, both of which can increase stress in the patient and cause anxiety [79].

Organic causes of NP problems in CMI could originate from the cerebellar injury that is associated with CMI. Such injuries were suggested as a cause by previous reports of "Cerebellar affective syndrome", which was first described by Schmahmann. This syndrome manifests as problems with executive functions and emotions in patients with cerebellar lesions [80]. Radiological studies have demonstrated that the cerebellum is involved in cognitive functioning [81]. This notion is supported by diffusion tensor imaging (DTI) studies that have shown that before treatment, the connectivity between the brainstem and cerebellum via the middle cerebellar peduncle is impaired in CMI patients [82,83].

Radiological investigations

Swallowing assessment using videoflouroscopy (VFS)

Videofluoroscopic examination of swallowing is considered the gold standard tool for examining swallowing dysfunction. It allows an objective assessment of swallowing, the results of which can be quantified and compared to normal data. In addition, the results can be always reproduced as a baseline to test the efficacy of a certain treatment for swallowing function [84-86].

VFS provides a very detailed assessment of dysphagia. While it is not part of routine assessments of CMI, it was used in Study I of this thesis. VFS can be used to track a bolus as it moved through the upper gastrointestinal system until it reaches the stomach. In addition, bolus aspiration into the respiratory tract can be easily observed and graded using different systems, such as Penetration-Aspiration Scale (PAS) scoring (see Discussion). Potential side effects include exposure to radiation, patient discomfort and allergic reactions, though these are very rare. More invasive measures, such as fiber optic endoscopic evaluation of swallowing and manometry, can also be used to complement VFS if necessary [87].

Computed Tomography (CT) scan

A CT scan is often the first imaging modality applied in patients with Chiari-related complaints. It may also be performed when magnetic resonance imaging (MRI) is contraindicated. It is useful for delineating any associated osseous abnormalities, such as basilar invagination, assimilation or scoliosis. In addition, it can reveal associated CSFD, tonsillar ectopia or syrinx [88,89].

MRI scan

1. T1/T2 sequences: This is the modality of choice and is usually used along the upper cervical cord area to show cerebellar tonsillar ectopia ≥ 5 mm below McRae's line (a line drawn from the tip of the basion to the tip of the opisthion). It is helpful for excluding other differential diagnoses of patient complaints, such as intracranial masses, intracranial hypotension or hydrocephalus. These sequences can also be used to delineate any associated syrinx and provide extensive information about its

characteristics. CMI patients have been found to have larger diameter and more rostrally extended syrinx than are observed in other causes of syrinx [90]. In addition, the size of a syrinx is associated with the severity of CMI symptoms and can be used to determine the pace of progression [91].

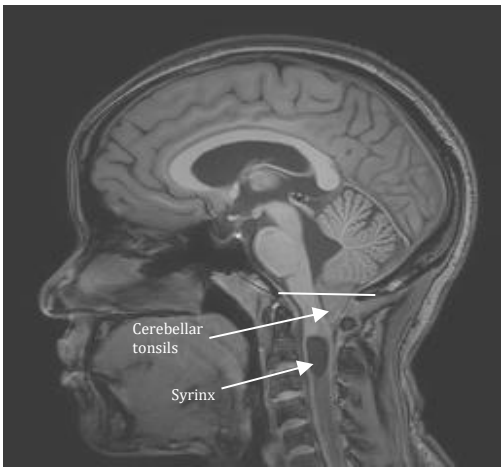


Figure 3: T1 sagittal MRI image of a 36 years old Chiari I malformation patient showing cerebellar tonsillar ectopia below McRae's line (white line).

2. CSF flow sequences: Many reports have described these sequences and their application in CMI patients [92-94]. They show CSF flow in relation to the cardiac cycle and usually demonstrate slight movement of CSF within the cerebellar tonsils. In a healthy individual, there is a down-flow of CSF (white signal) during systole and an up-flow of CSF (black CSF) during diastole [95]. Flow velocity is slower in cerebellar tonsillar herniation in CMI patients than in normal controls, and when an affected patient is tested after surgical decompression, flow should improve and show normal readings [96].

3. DTI: This procedure is used to investigate the integrity of white matter tracts in the brain and cerebellum. While DTI is rarely used in CMI, studies have shown that symptomatic CMI patients exhibit microstructural tissue alterations, which are mostly evident in the middle cerebellar peduncle [82,83].

DIFFERENTIAL DIAGNOSIS

Pseudotumor cerebri (PTC)

This condition, also called idiopathic intracranial hypertension, is defined by the modified Dandy criteria as a syndrome manifesting as increased intracranial pressure (ICP) with normal CSF composition in the absence of ventricular dilatation or any space-occupying lesion on radiological examination of the brain [97]. PTC is more common in obese females and clinically presents as headache and other signs and symptoms associated with increased ICP [98,99].

It can be difficult to differentiate a diagnosis between CMI and PTC. They have a very similar clinical presentation and are more common in females [12,100]. However, PTC is highly associated with obesity [101]. In the literature, researchers have found that a radiological finding of cerebellar tonsillar ectopia similar to that of CMI is observed in in 2-5% of PTC cases [102,103]. One study, a series by Banik et al., reported that this number was even higher (24%) [101]. Hence, PTC patients may be consequently be misdiagnosed as CMI and offered unnecessary OCD, and this could explain why some patients never improve after OCD. Some such cases have been

reported, and while they exhibited a rise in ICP after OCD, they were all improved following CSF diversion procedures [104].

In Study IV of this thesis, we investigated preoperative factors that help to predict the risk to develop high ICP and hydrocephalus after OCD.

Space occupying lesions

Posterior fossa lesions can displace the cerebellar tonsils caudally towards the foramen magnum due to high ICP, resulting in secondary CMI [35].

Intracranial hypotension

This condition results from low CSF pressure and can develop iatrogenically after lumboperitoneal shunts or lumbar punctures. It is associated with peculiar features on MRI, and these, in addition to the presence of cerebellar tonsillar herniation, aid in its diagnosis. These peculiar features include sagging brain, meningeal enhancement and enlarged venous sinuses [36-38], as shown in figure 4.

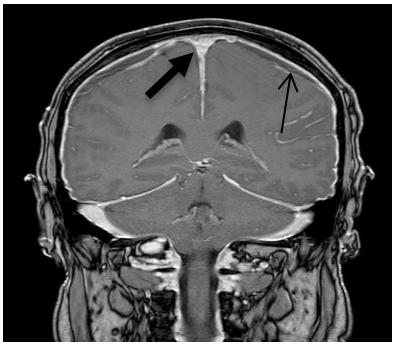


Figure 4: T1 coronal MRI showing the characterstic features of intracranial hypotension; sagging brain, meningeal enhancement (thin arrow) and enlarged venous sinuses (Thick arrow).

Basilar invagination

This is one of the most common anomalies of the craniocervical junction. It is associated with CMI, which is found in approximately 12-13% of cases with basilar invagination [12,105]. This association has been reported to be even higher, as in Goel, who reported a series of 190 basilar invagination patients, 53% of whom had associated CMI [106]. Its characteristic feature is an inward and upward displacement of the caudal part of the occipital bone to a position in close proximity to the vertebral column. Failure to exclude basilar invagination before OCD in CMI might lead to unsatisfactory results and a risk of decompensation in affected patients.

NATURAL HISTORY OF CMI

The study of the natural history of CMI is challenging, and it has rarely been investigated. One of the obstacles is the tendency to offer surgery as an option in symptomatic patients with a radiological finding of a cerebellar tonsillar herniation ≥ 5 mm. This is observed even more often in patients with syrinx, which is considered an indication to operate by some authors. Hence, it becomes difficult to determine which patients should be assigned for conservative vs. surgical management [107-109]. It is worth mentioning that the cerebellar descent of the tonsils (observed as a radiological finding) has in some reports been found to undergo spontaneous resolution [110,111]. However, the radiological findings in CMI remain stable according to most reports [112,113]. The following discussion is focused on highlighting descriptions in the literature of the natural history of asymptomatic vs. symptomatic CMI.

Asymptomatic cases of tonsillar herniation > 5 mm

As previously described, a radiological finding of cerebellar tonsillar descent can be incidentally found. Table 5 shows the natural history of asymptomatic CMI as reported in the literature.

Author	No. cases	Follow up
Atikan et al [9]	19 (37%)	Four of 19 cases developed symptoms over a 4-year period.
Meadows et al [10]	25 (14%)	Only one patient had headache attributed as secondary to migraines. No follow up was performed in this study.
Bindal et al [114]	5 cases	All remained asymptomatic after 2 year follow up
Nishizawa et al [115]	9 cases	After approximately 11 years of follow up, 8 remained asymptomatic One patient developed neurological symptoms at 7 years after the first visit and subsequently underwent surgery.
A Santoro et al [116]		Reported one patient who remained asymptomatic after 5 years of follow up.
Novegno et al [112]	11 cases	Seven (63.6%) patients showed no changes in follow up clinical examinations. The remaining 4 (36.4%) experienced the onset of clinical symptoms between 3 and 5 years after the first diagnosis.
Benglis et al [108]	43 cases	One of 43 patients developed symptoms not typically attributed to CMI over the course of the follow up period.

Table 5: Reports of the natural history of asymptomatic Chiari I malformation.

Symptomatic cases of tonsillar herniation > 5 mm

Chavez et al. proposed that presenting symptoms are important indicators of improvement and should be used to select cases for a conservative approach [117]. A younger age at presentation has been found to be a positive prognostic indicator for successful conservative management, and this finding was later supported by a comparison between pediatric and adult cases [118]. However, many case reports and series have described acute deterioration and sudden death in patients with CMI [119-123]. It is currently difficult to predict the risk of acute deterioration based on preoperative patient factors. However, 50% of reported emergency cases were found to have an associated syrinx [55].

Follow up studies have shown that when a CMI patient presents without a syrinx, it is rare to develop a syrinx in the future [108,109]. However, the factors that predict syrinx development have rarely been investigated.

In conclusion, patients with no symptoms or symptoms not attributable to CMI can safely be observed. The risk of an acute deterioration will be the focus in Study III of this thesis.

MANAGEMENT OF CMI

Surgical management of CMI is the treatment of choice in symptomatic cases. Since its first description by Hans Chiari, many operative techniques have been advocated and compared with regard for their postoperative outcomes and complications. The first study to describe the use of OCD for CMI was published in 1938 by McConnell and Parker [124].

Choosing which technique will be best in each case is not an easy task, and one should first address whether the CMI is primary or secondary, as previously described. For example, a CMI that is a secondary etiology of cerebellar tonsillar descent may not require OCD. It is therefore necessary to rule out any underlying intracranial hyper/hypotension, tumors, craniosynostosis, etc. Part of a basic evaluation involves examining the craniocervical area for any instability (e.g., basilar invagination, which could render OCD a dangerous choice without stabilization and fixation).

Today, the most widely discussed procedures are posterior fossa decompression with duroplasty (PFDD) and posterior fossa decompression without duroplasty (PFD) [125]. In addition, other techniques have been performed, including decompression plus resection of the tonsils [126,127], CSF diversion procedures [128,129], section of filum terminale [130-132] and stabilization/fusion surgeries [133,134]. Strahle et al. reported that both CMI and craniosynostosis were observed in 8% of 383 consecutive patients with craniosynostosis. Almost 50% of these patients had an isolated lamboid synostosis. Additionally, of 7 patients who underwent only craniosynostosis repair, 6 showed a decrease in tonsillar ectopia, 5 had improved CSF flow, and in 2, a syrinx was resolved [135].

In table 6, I present the five systematic reviews and meta-analysis that discussed this topic. In most reported studies, PFDD was superior to PFD

in terms of clinical improvement, syrinx resolution and reducing the risk of re-operation. However, the risk of postoperative complications was lower and operation times and hospital stays (days) were shorter in PFD than in PFDD. This is not surprising because in PFD, it is not necessary to open the dura and expose the subarachnoid spaces containing CSF [125,136-139].

Some authors have investigated the impact of MRI flow studies and intraoperative ultrasound (US) in this condition [92,140]. For example, Yeh et al. performed intraoperative US in 130 pediatric patients with CMI, of whom 40 achieved satisfactory US results and therefore underwent only bony decompression. No complications were noted in these 40 patients, whereas complications occurred in 12 of 85 patients who underwent duroplasty, and these patients experienced more postoperative symptoms. Hence, the authors proposed that intraoperative US could be a valuable tool for choosing an appropriate surgical technique [141].

Section of filum terminale is a controversial treatment option. Royo-Salvador proposed that underlying occult tethered cord syndrome is associated with CMI. They reported performing section of filum terminale in a small series of CMI patients, and they reported that this group achieved clinical improvement [130]. However, larger and controlled studies with longer-term follow up are rare and needed to explore this issue.

Posterior occipitocervical fixation in CMI can be justified, when feasible, as a necessary approach in select patients, such as those with confirmed instabilities at the craniocervical junction [142,143]. Goel took this further in his published series of 65 CMI patients. He speculated that the primary incident underlying CMI is an instability at the C1-2 area regardless of whether the patient had an associated basilar invagination and that,

therefore, all CMI patients should be primarily managed with posterior fixation of C1-2 using lateral mass screws [144,145]. This approach was later criticized because in Goel's series, the morbidity rate in patients who underwent posterior fixation was higher than the mortality rate in reports of only OCD (1.5% vs. 0.9%, respectively). In addition, the risk of injury to the vertebral artery was higher than that observed for conventional CMI procedures. Stabilization procedures are also known to restrict the range of movement at the craniocervical junction. However, it has been suggested that in CMI cases in which stabilization is needed, it is more biomechanically reasonable to perform occipitocervical fixation than atlantoaxial stabilization alone [146,147].

Author		PFDD	PFD
Durham et al	Reoperation	2.1%	12.6%
	Clinical improvement	78.6%	64.6 %
	Syrinx improvement	87%	56.3%
	CSF complications	18.5%	1.8%
	Wound infections	3.7%	0.9%
	Bleeding risk	0.7%	0%
Forander et al	Reoperation	2%	11%
	No clinical improvement	23%	22%
	No syrinx improvement	22%	26%
	CSF complications	7%	0%
Zhao et al	Reoperation	9%	10%
	Clinical improvement	82.2%	73.6%
	Syrinx improvement	83%	77%
	Worsening of symptoms	3%	7%
	Surgical complications	20%	4%
	Recurrence of symptoms	7%	10%
Xu et al	Mean operative time (min)	179	105
	Clinical improvement	↑↑	↑
	CSF complications	↑↑	↑
	complications	=	=
	Wound infections	=	=
Lu et al	Hospital stay	↑↑	↑
	Blood loss	=	=
	Reoperation	3.5%	2%
	complications	15.6%	11%
	CSF complications	↑↑	↑
	Infection	↑↑	↑
	Syrinx resolution	73%	60%
	Clinical improvement	88%	72%

Table 6: Systematic reviews and meta-analysis on the comparison of surgical outcomes between posterior fossa decompression with (PFDD) or without duroplasty (PFD).

SURGICAL COMPLICATIONS

- Pseudomeningocele: a “collection of cerebrospinal fluid under the skin at the surgery area” after surgery: the most common surgical complication in CMI patients [148-152]. Many theories have been discussed previously regarding why some patients develop this complication. For example, different types of grafts are used to close the dura, and they achieve very different results [153-155]. Some authors have proposed that postoperative exertion by the patient increases the risk of this condition [156]. While small fluid collections can be managed conservatively, large ones that cause symptoms must be treated accordingly with temporary lumbar drainage or by repairing the defect [157,158].
- CSF disturbance: while this may be associated with a radiological finding of ventriculomegaly, it can also take many other forms, such as CSF leakage, failure to improve after decompression or the recurrence of symptoms [149,150,159]. Perioperative factors hypothesized to increase the risk of this complication include opening the arachnoid and subarachnoid or the development of a blood clot that negatively affects CSF circulation [160]. These cases may also reflect a misdiagnosis of CMI in a patient who actually has PTC. Patients respond well to shunting procedures, in which the complication risk is lower than that observed in OCD. (See differential diagnosis).
- Other complications are aseptic meningitis, wound infections, cerebellar ptosis (rare), haemorrhage and mortality (1%) [125,136].

AIMS

AIMS

To prospectively evaluate the occurrence of pre- and postoperative swallowing difficulties in adult patients with Chiari I malformation (CMI) and to determine whether surgical treatment can help such patients (Paper I).

To prospectively investigate the effect of CMI and decompressive surgery on neuropsychological performance and quality of life (Paper II).

To retrospectively describe the acute deterioration of CMI and evaluate the need for urgent surgical decompression in adult patients and its relation to preoperative radiological findings on magnetic resonance imaging of the brain (Paper III).

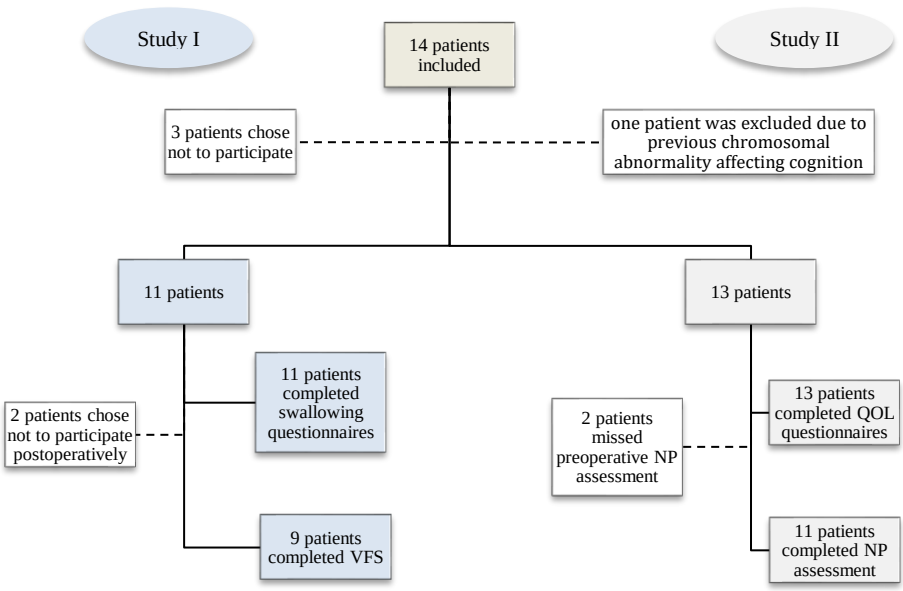
To retrospectively examine the need for cerebrospinal fluid diversion after occipitocervical decompression and its relation to preoperative characteristics, such as age, gender, pre-existing syrinx, obesity, and the extent of tonsillar herniation (Paper IV).

PATIENTS AND METHODS

PATIENTS AND METHODS

PATIENTS

In Studies I and II, we prospectively included all adult patients with Chiari I malformation (CMI) who were seen between Sep 2015 to October 2017, underwent magnetic resonance imaging (MRI) of the brain showing cerebellar tonsillar herniation > 5 mm, and were subsequently referred to Sahlgrenska University Hospital (covering all of western Sweden, population: 1.87 million inhabitants). Table 7 and the flowchart below summarize the inclusion and exclusion criteria applied in these studies.



Flowchart 1: A summary of the number of included patients and drop-outs in studies I & I

	Study I	Study II
Inclusion criteria	1. Adult patients > 18 years old 2. Radiological diagnosis of CMI as a "tonsillar herniation > 5 mm into the foramen magnum" 3. Patients who were assigned for surgical management of CMI	
Exclusion criteria	1. Pediatrics patients < 18 years old 2. Other Chiari malformations other than type I 3. Patients who were unable to participate and perform the tests due to, for example, severe cognitive dysfunction	
	1. Patients who were previously diagnosed with swallowing difficulties attributed to focal gastroenterological causes 2. Patients who were operated on in the upper gastrointestinal system 3. Pregnant and breastfeeding women (Study I, B-Hcg was offered before inclusion in the study)	1. Patients who were previously diagnosed with neurocognitive dysfunctions

Table 7: Inclusion and exclusion criteria in studies I & II.

In Studies III and IV, we retrospectively included patients who were referred to Sahlgrenska University Hospital from all parts of western Sweden during two overlapping 10-year periods (2003-2013 in Study IV and 2006-2016 in Study III). Table 8 shows the inclusion/exclusion criteria and the number of patients included in each study.

	Study III	Study IV
Identification of patients	• We searched our operation database for code ABE50, which indicates "occipitocervical decompression" • The identified patients were then assessed using our clinical system (Melior) to confirm a diagnosis of CMI with the ICD code.	
Inclusion criteria	1. Adult patients > 18 years old 2. Radiological diagnosis of CMI a "tonsillar herniation > 5 mm into the foramen magnum". 3. All patients underwent occipitocervical decompression	
Exclusion criteria	2. Pediatrics patients < 18 years old 3. Chiari malformations other than type I.	
		Patients who were previously diagnosed with cerebrospinal fluid (CSF) disturbances or who underwent any CSF diversion procedure before CMI presentation (Study IV)
No. of patients identified	65	52
No. of patients excluded	None	One patient "was previously operated on for a "ventriculoperitoneal shunt" due to normal pressure hydrocephalus"
Total patients included	65 patients	51 patients

Table 8: Inclusion and exclusion criteria in studies III & IV.

Definitions:

Acute deterioration (III)

CMI patients who presented with worsening CMI-related symptoms or a life-threatening condition that necessitated urgent surgical decompression within 24 hours of admission.

Postoperative cerebrospinal fluid disturbance (IV)

Any patient who was postoperatively found to have either enlarged ventricles on computed tomography (CT) of the brain (Evan's index > 0.3) or a rise in intracranial pressure (ICP) as documented by an ICP-monitoring device and who required either temporary or permanent CSF diversion.

ETHICAL CONSIDERATIONS

Studies I and II were approved by the regional ethics board of the University of Gothenburg (Diary no. 865-14) and carried out according to the principles of the Declaration of Helsinki.

In Studies III and IV, the regional ethics board was consulted. Because only unidentified retrospective register data were used, no ethical approval was needed.

Patient risks in the prospective Study I and Study II:

The management and indication of surgery are not changed. However, participation implies that the symptoms and the effect of surgery becomes more carefully investigated. Videofluoroscopy (VFS) is a safe investigative technique, but some complications can occur. For instance, allergic reactions or anaphylaxis can affect people who are allergic to the contrast material. In addition, patients may experience discomfort while swallowing the contrast liquid or notice a change in stool color that could last for 1-3 days after the study. The radiation dose is considered low and has a mean entrance skin dose of 1.65±0.85 mGy (n=8). We offered a B-Hcg pregnancy test to all female patients before inclusion in Study I.

While neuropsychological (NP) tests and questionnaires might be stressful for some individuals, they have no major risks.

Before inclusion, patients were given a consent form to sign if they wanted to participate in either or both of the studies.

METHODS

Subjective assessment (I & II)

The preoperative assessment involves comprehensive history taking, a physical examination and introducing the patient to the planned surgery along with an explanation of the risks, potential complications and benefits of doing surgery. During the visit, a case report form (CRF) is filled out by the neurosurgeon (See appendix).

All included patients were required to fill out a written questionnaire at home that subjectively assessed swallowing (Study I) using the Watson Dysphagia Score (WDS) [161,162] and EORTC QLQ-OG25 [163] and/or quality of life (QOL, Study II) using a life satisfaction questionnaire (LiSAT-11) [164], the EQ-5D-5L [165] and the Hospital Anxiety and Depression Scale (HAD) [166] as shown in table 9. Patients were required to return the form to us no later than 3 months before the planned surgical decompression.

Study	Questionnaire	Aims	Scales and domains
I	WDS	Dysphagia scale	Nine ingestible items are assessed (liquids to solids).
	EORTC-QLQ25	QOL measure in patients with dysphagia (upper gastrointestinal cancer).	Six scales: dysphagia, eating restrictions, reflux, odynophagia, pain and anxiety; and ten single items.
II	EQ-5D-5L	QOL	1. The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. 2. The EQ visual analogue scale (EQ VAS) records the respondent's self-rated health on a vertical, visual analogue scale.
	LiSAT-11	QOL	The LiSat-11 includes one item regarding satisfaction with life as a whole and ten items regarding satisfaction with different domains of life.
	HAD	Depression and anxiety scale	Includes 7 items for depression and 7 items for anxiety.

Table 9: Patient-reported questionnaires in studies I & II.

Objective clinical assessment

Neuropsychological assessment (II)

All included patients underwent NP assessment 3 months before their planned surgery and 3 months after surgery. The assessment started with an interview and an introduction to the NP assessment. The assessment took approximately 20-30 minutes and included the tools described in table 10. Each patient's performance was compared to the normal values for the specific test. Results that were 1.5 or more standard deviations from the mean or that fell below the 5th percentile for healthy individuals were considered to indicate impairment.

Test	Assessed tasks
The Brief Visuospatial Memory Test-revised (BVMT-R)	A test of visual learning and retention
Rey Auditory Verbal Learning Test (RAVLT)	Measures verbal learning and retention
Grooved pegboard	Tests manual dexterity in placing 25 pegs into randomly positioned slots
Coding from the Wechsler Adult Intelligence Scale	A paper-and-pencil task that measures psycho-motor speed
The Swedish Stroop test	Consists of two subtasks - the first measures colour naming speed and the second, response selection and inhibition (aspects of executive functioning).

Table 10: Neuropsychological (NP) test in study II.

Radiological assessment

Videofluoroscopic (VFS) examination of swallowing (I)

All patients who chose to be part of the swallowing assessment were referred to our radiology unit and placed under the care of a gastroenterological radiologist 3 months before their planned surgery. They were assessed by VFS according to a unified protocol for all CMI patients as shown in the diagram below.

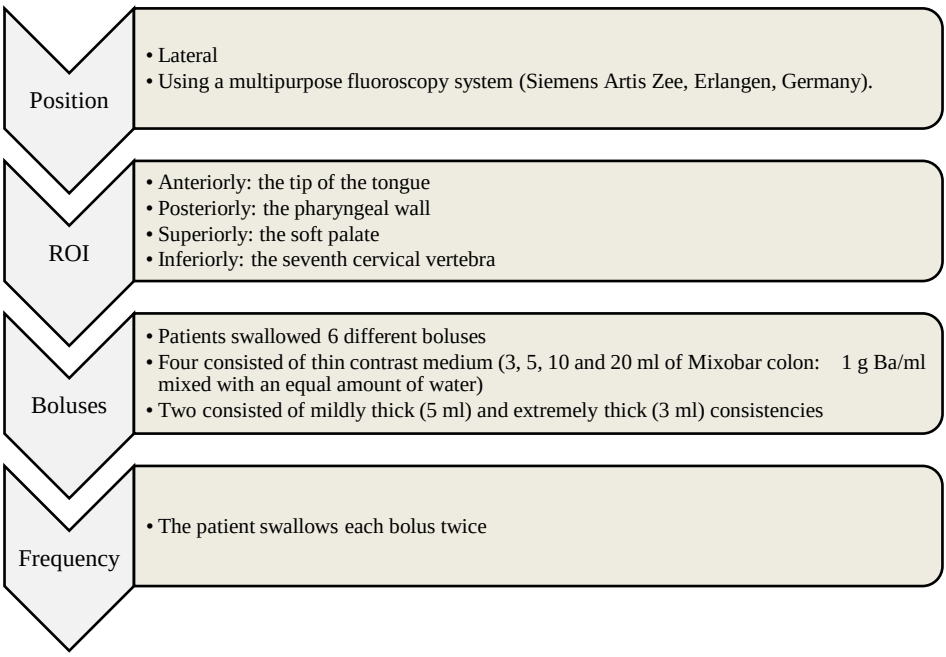


Diagram 1: Unified protocol of videoflouroscopy in study I to assess swallowing function in Chiari I malformation.(ROI= Region of interest).

Analysis of VFS

All VFS analyses were performed by the same gastrointestinal radiologist (MA), who was blinded to the results of the self-report questionnaires and the outcomes after surgical decompression. Objective measurements were obtained as described by Leonard et al [85] and are summarized in table 11. Hmax, pharyngeal constriction ratio (PCR) and upper esophageal sphincter opening (UESo) values were considered abnormal if they were more than one standard deviation from the normal mean for the corresponding sex and age category [85,86].

Objective measure	Definition
Maximal hyoid displacement(H_{max})	The distance in cm from the anterior aspect of the hyoid bone in the "hold" position to its point of maximal anteriosuperior displacement during swallowing
The pharyngeal area (PA)	Determined in the "hold" position by calculating the area (cm^2) bordered by the soft palate, the posterior pharyngeal wall, the arytenoid cartilages, the epiglottis, the valleculae, and the base of the tongue.
The pharyngeal constriction ratio (PCR)	The ratio between the PA at maximal pharyngeal constriction while swallowing a 20-ml bolus and the PA in the "hold" position for a 3-ml bolus.
The opening of the upper esophageal sphincter (UES_o	Measured in the anterior-posterior plane at the narrowest point between C4 and C6 when the bolus induced maximal distention.
The duration of UES_o	Measured in seconds from the start of the opening of the pharyngoesophageal segment to the time of complete closure of the segment.

Table 11: Objective measurements of videoflouroscopy in study I.

To maximize the information gained from VFS, we included some categorical variables that are commonly used to assess swallowing dysfunction [167,168]. These are discussed in table 12 below. Problems with initiating swallowing, the premature loss of the bolus from the oral cavity and/or delayed onset of the pharyngeal swallowing phase were also subjectively estimated.

Penetration-Aspiration Scale (PAS)	The vallecular retention of contrast
Scales 1 – 8 1. No contrast enters the airway 2. Contrast enters the airway, remains above the vocal cord and is ejected. 3. Contrast enter the airways, remains above the vocal cord and is not ejected. 4. Contrast enters the airway, contacts the vocal cord and is ejected. 5. Contrast enters the airway, contacts the vocal cord and is not ejected. 6. Contrast enters the airway, passes below the vocal cord and is ejected. 7. Contrast enters the airway, passes below the vocal cord and is not ejected. 8. Contrast enters the airway, passes below the vocal cord and is not ejected and no effort is made to eject.	Grades 0 – 3 Grade 0: no residue. Grade 1: Residue occupied <10% of the width of the valleculae. Grade 2: Residue occupied between 10 and 50% of the width of the valleculae. Grade 3: Residue occupied >50% of the width of the valleculae.

Table 12: Categorical variables to assess swallowing function using videoflouroscopy.

A PAS score of 3 or higher was considered pathological because such scores are not observed when normal materials are swallowed in the relevant age group [169]. There is currently no consensus in the literature regarding the limits of normality for post-swallow pharyngeal fluid residue [170]. We calculated and compared the pre- and postoperative percentage of swallows with grade 2 or higher residue in the valleculae. Because there was also substantial variability in the timing and temporal measures of

healthy swallowing, we report only a subjective impression of deviations from normal that were related to problems with initiating swallowing or a delayed onset of the pharyngeal swallowing phase [171]..

MRI brain and cervical spine (Study III)

Preoperative MRI factors that indicate acute deterioration:

We assessed the following parameters on preoperative MRI:

1. Degree of tonsillar herniation (in mm) below McRae's line.
2. Size of the syrinx (in mm) measured on axial MRI images as the maximum anteroposterior diameter of the syrinx.
3. Length of the syrinx as viewed in sagittal MRI images and assessed as the number of vertebral segments traversed by the syrinx; and
4. Rostral extension of the syrinx in relation to the vertebral level.

Surgical outcomes and complications

Studies I-II

All subjective and objective assessments were repeated 3 months after surgical decompression. Postoperative complications were also recorded and reported if observed.

Study III

Clinical outcomes observed at a 3-month follow up visit were reported, and a postoperative MRI brain exam was performed. Changes in the syrinx were recorded as improved, unchanged or worsened.

Study IV

We assessed the following preoperative parameters and used statistical analyses to assess their significance as indicators of CSF disturbance after surgical decompression:

1. Age and gender
2. Body mass index (kg/m^2)
3. Degree of tonsillar herniation (mm) below McRae's line
4. Presence of a syrinx

Surgical management

All patients in this thesis (Studies I-IV) were operated on and underwent surgical decompression in line with a standard protocol that involves a sub-occipital craniectomy plus cervical vertebra (C1) laminectomy. The cervical vertebra (C2) laminectomy was performed only in patients with severe forms of cerebellar tonsillar herniation behind the C2 lamina. The dura was opened, and the arachnoid adhesions between the cerebellar tonsils and upper cervical cord and medulla oblongata were released. The dura was then closed using synthetic grafts or a periosteal and fascia graft obtained from a nearby occipital area. Sutures were placed in a watertight fashion to close the subcutaneous tissue and skin.

RESULTS

Results

SUBJECTIVE CLINICAL ASSESSMENT

The clinical presentations of the patients included in Studies I and II are summarized in diagram 2.

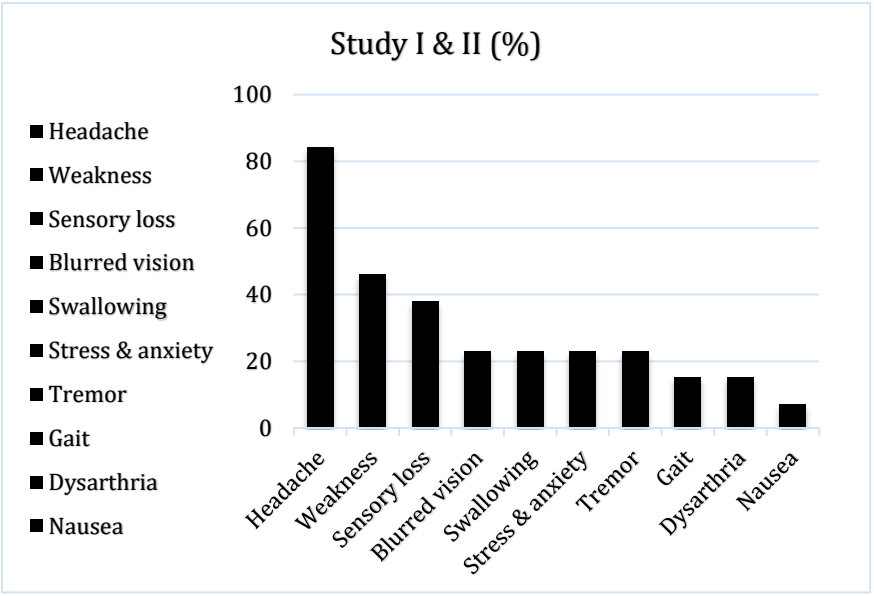


Diagram 2: The clinical presentation (percentage) of Chiari I malformation patients in studies I & II.

Swallowing (I):

Four patients (36%) with Chiari I malformation (CMI) presented with swallowing difficulty. All patients initially reported problems with swallowing liquids and later reported difficulty with swallowing solid foods. The frequency of experiencing problems with swallowing was reported as 1-2 per week in three of the patients and once monthly in one patient. The

duration of swallowing complaints ranged between 6 and 36 months with no temporal worsening of symptoms or associated pain. Two patients reported that the bolus temporarily stopped at the throat, while the other two reported that it stopped in the chest. Neither regurgitation nor vomiting was reported, and there were no problems with the subsequent passage of the bolus through the gastrointestinal system.

Dysphagia scores

Patients with no swallowing problems had a score of zero on both questionnaires. Table 13 shows the pre- and postoperative scores on both the Watson Dysphagia Scale (WDS) and QLQ-OG25 for the patients who reported swallowing difficulties. The mean WDS in these patients was 16, and their scores on the QLQ-OG25 were worse ("deviation > 1 SD") than the reference values (obtained from a population-based study) [172] in all but six domains (i.e., eating restrictions, pain and discomfort, dry mouth, trouble with saliva, coughing and trouble talking). Most scores improved after surgery, and the patients reported worsening in only one score (swallowing saliva).

	Reference value	Preop	Postop	Patients reporting the problem	I/U/W
Symptoms	Mean (SD)	Mean (SD)	Mean (SD)	N	N
Watson scale	-	16 (8)	6 (5)	4	4/0/0
Dysphagia	0.8 (5.5)	22 (15)	11 (9)	3	3/0/0
Eating restrictions	2.9 (9.9)	6 (7)	2 (4)	2	2/0/0
Reflux	6.7 (15.4)	25	25	1	0/1/0
Odynophagia	1.5 (8)	25	0	1	1/0/0
Pain and discomfort	7.6 (17)	25	0	1	1/0/0
Anxiety	-	33 (38)	12 (15)	3	3/0/0
Eating in front of others	1.3 (8.9)	33	0	1	1/0/0
Dry mouth	11.5 (23)	8 (16)	0	2	2/0/0
Trouble with taste	2.6 (12.5)	16 (33)	0	2	2/0/0
Trouble swallowing saliva	1.3 (9.2)	8 (16)	8 (16)	2	1/0/1
Choking when swallowing	3.7 (13.1)	66	0	1	1/0/0
Trouble with coughing	13.7 (23.6)	33	33	1	0/1/0
Trouble talking	2.2 (10.5)	0	0	0	0

Table 13: Self-administered questionnaires to assess swallowing function.

Neuropsychological function and quality of life (II)

Hospital Anxiety and Depression (HAD) scale

The pre- and postoperative results on the HAD are presented in table 14. Scores ranging from 0 to 7 are considered normal, whereas higher scores indicate mild to severe symptoms. The median value for anxiety among the CMI patients corresponded to the upper limit of this range. Four patients had anxiety scores > 8 both pre- and postoperatively, while depression scores remained within the normal range.

HAD variable	Preop results Median (IQR)	Postop results Median (IQR)	P value
Anxiety items,	7 (4-8)	7 (5-9)	.55
sum	2 (1-7)	2 (1-4)	.55
Depression items	9 (5-16)	10 (6-13)	.55
Sum total score			

Table 14: Comparison between preoperative and postoperative Hospital Anxiety and Depression scale (HAD) scores of CMI patients (n=11).

LiSat-11

There were no statistically significant differences between pre- and postoperative scores on the LiSat-11 in the CMI patients. We also investigated the proportions of satisfied/dissatisfied CMI patients and compared the results to those obtained in subjects in the normal Swedish population [164], as shown in table 15.

LiSat-11 domain	Norm (%)	Chiari (preop)%	P	Chiari (postop)%	P
	Satisfied	Satisfied		Satisfied	
Life	70	46	.001	62	ns
Vocation	54	23	<.001	23	<.001
Economy	39	39	ns	46	ns
Leisure	57	15	<.001	46	ns
Contacts	65	62	ns	54	ns
Sexual life	56	31	0.001	39	.016
ADL	95	77	<.001	85	.032
Family	81	85	ns	77	ns
Partner	82	70	ns	70	ns
Somatic health	77	0	<.001	23	<.001
Psychology	81	23	<.001	31	<.001

Table 15: Life satisfaction in CMI patients (N=13) before and after surgery, in comparison to data from a population-based study of normal Swedish subjects.
Abbreviations: ADL=activities of daily life, ns=non-significant

EQ-5D-5L

The results of both the EQ-5D-5L index and the EQ visual analog scale (VAS) were significantly improved following surgical decompression, as shown in table 16.

EQ-5D-5L variable	Preop results Median	Postop results Median	P	Improved/worsened/unchanged (number of cases)
EQ-5D index	0.69	0.76	.039	9/3/1
Health scale VAS	50	70	.008	10/2/1

Table 16: Comparison between pre- and postoperative EQ-5D-5L scores of CMI patients (N=13).

Acute deterioration (III)

We identified three patients (4.6%) who had acute deterioration of CMI and were therefore operated on within 24 hours. Neither trauma nor precipitating factors that could have aggravated the symptoms of CMI were reported in the patients with acute deterioration. None of the patients reported acute onset of symptoms, and all had already been diagnosed with CMI and were scheduled for surgery during the 6-month period prior to the acute deterioration.

NEUROPSYCHOLOGICAL (NP) ASSESSMENT

On average, the results of the tests performed in patients were within normal limits both before and after surgery. However, while their verbal learning, psychomotor speed, speed of color naming and ability to manage interference were significantly improved following surgery (with effect sizes of r=0.51, 0.53, 0.57, and 0.63, respectively; i.e., all > 0.5 and thus

large), the remaining NP variables were not significantly altered. The pre- and postoperative test results are presented in table 17.

NP variable	Preop results Median (IQR)	Postop results Median (IQR)	P
BVMT-R			
Sum of learning trials	21 (19-30)	26 (19-30)	.37
Delayed recall	11 (8-11)	11 (7-12)	.59
RAVLT			
Sum of learning trials	49 (40-55)	51 (47-63)	.02*
Delayed recall	12 (7-12)	13 (8-14)	.24
Grooved pegboard			
Dominant hand	54 (54-65)	55 (49-66)	.26
Non-dominant hand	61 (56-81)	55 (50-67)	.07
Coding	67 (52-82)	71 (60-84)	.01*
Stroop			
Color naming task	55 (49-71)	54 (46-63)	.01*
Interference task	104 (95-122)	95 (83-104)	.003*

Table 17: Neuropsychological (NP) test results of CMI patients, before and three months after occipitocervical decompression (n=11). Statistical differences are marked with asterisks.

Abbreviations: BVMT-R=Brief Visuospatial Memory Test-Revised, RAVLT=Rey Auditory Verbal Learning Test

RADIOLOGICAL ASSESSMENT

Videoflourscopic examination of swallowing (study I):

The pre-and postoperative mean Hmax and upper esophageal sphincter opening (UESo) values for each bolus size as well as the normative data for the 3-ml thin bolus obtained from reference 85 are shown in table 18. The mean values did not obviously deviate from the values reported in normal adult subjects. The mean pharyngeal constriction ratio (PCR) while

swallowing the 20-ml liquid bolus was 0.02±0.03 both pre- and postoperatively, which was similar to the normative data (for individuals younger than 65 years old: 0.03±.03 for females and 0.04±.03 for males [173]).

Of the four patients who complained of subjective dysphagia, one showed a Penetration-Aspiration Scale (PAS) score of 3-5 during 6 of 12 bolus swallows. Penetration (a PAS score of 4-5) was observed in five swallows in another patient. No penetration (= PAS 1) was observed in the other two symptomatic patients. One of these patients, however, had a lowered hyoid displacement (Hmax lower than one standard deviation from the sex-adjusted mean in normal subjects while swallowing a 3-ml bolus), and this patient also had a smaller than normal UES opening [85]. All four symptomatic patients showed signs that they were experiencing difficulty in initiating swallowing of the extremely thick bolus and/or a delayed onset of the pharyngeal swallowing phase. None of the patients had an elevated PCR. None of the asymptomatic patients had a PAS of 3 or higher. One patient showed a lower than normal range of hyoid displacement as well as a smaller UESo while swallowing a 3-ml liquid bolus. In this patient, a delayed onset of the pharyngeal swallowing phase was also noted. Another asymptomatic patient had a subnormal UESo, and yet another showed signs of difficulty in initiating the oral swallowing phase for the extremely thick bolus. Nine patients underwent both pre- and postoperative videoflouroscopy (VFS). The percentage of bolus swallows with vallecular residue of grade 2 or higher decreased from 18% preoperatively to 6% postoperatively. The mean duration of UES opening increased from 0.65 sec preoperatively to 0.74 sec postoperatively. Signs of difficulty initiating swallowing or a delayed onset of the pharyngeal phase remained unchanged in one patient and were diminished in the remaining patients.

	3 ml thin liquid	5 ml thin liquid	10 ml thin liquid	5 ml mildly thick	3 ml extremely thick
H_{max} baseline (mm)	13.5±3.6	15.5±3.7	15.8±3.6	13.1±4.2	12.0±6,5
H_{max} post-op (mm)	14.9±3.9	14.8±4.0	16.6±4.3	15.0±3.8	16.4±3.8
H_{max} normative data from ref 9 (mm)	18,6±6.0	-	-	-	-
UES_o baseline (mm)	4.5±1.8	6.3±1.9	8.0±1.7	6.8±1.3	6.1±2.0
UES_o post-op (mm)	5.3±1.6	6.4±2.3	7.8±2.1	6.9±2.0	6.5±1.6
UES_o normative data from ref 9 (mm)	5.1±1.5	-	-	-	-

Table 18: Pre- and postoperative mean values on VFS.
Abbreviations: UESo= esophageal sphincter opening, Hmax= Maximal hyoid displacement

Preoperative brain and cervical spinal MRI (III)

We investigated the degree of tonsillar herniation (mm), the size of the syrinx (mm) and the length of the syrinx in patients with acute deterioration of CMI (N=3) and non-acute CMI (N=62). As shown in table 19, the mean degree of tonsillar herniation was higher in the non-acute CMI patients than in the acute cases (12.4 mm and 9.3 mm, respectively). A syrinx was a finding in all three patients who presented with acute deterioration but in only 29 (46.7%) of the non-acute CMI patients. We evaluated the preoperative characteristics of the syrinx in all included CMI patients who had a syrinx (total, N=32) as follows: 1) the size of the syrinx (maximum AP diameter in mm), 2) the length of the syrinx (number of vertebrae traversed), and 3) the rostral extension of the syrinx in relation to vertebral level.

As shown in table 19, the mean value for the maximum diameter of the syrinx was higher in CMI patients with acute deterioration (11.0 mm) than in non-acute cases (8.2 mm). The mean length of the syrinx in patients with acute deterioration was twice (17.3 vertebrae) that observed in non-acute cases (7.8 vertebrae).

When we investigated the degree of rostral extension of the syrinx on a preoperative MRI of the brain we found that it was only a finding in CMI patients with acute deterioration compared to the finding of rostral extension only between C7 and C2 and never beyond the C1 level in non-acute cases who had syrinx (N=29).

Variables		Total	Acute cases	Non-Acute cases
Tonsillar herniation (mm)	Mean (SD) Median (min: max) N	12.3 (5.7) 11 (5:25) 65	9.3 (4.1) 10 (5:13) 3	12.4 (5.8) 11 (5:25) 62
Size of syrinx (mm)[1] (Maximum AP diameter)	Mean (SD) Median (min: max) N	8.5 (3.1) 8.5 (3:15) 32	11.0 (2.0) 11 (9:13) 3	8.2 (3.1) 8.5 (3:15) 29
Length of syrinx[2] (No. Of vertebrae)	Mean (SD) Median (min: max) N	8.7 (5.6) 8 (2:21) 32	17.3 (3.2) 16 (15:21) 3	7.8 (4.9) 7 (2:16) 29
Rostral extension of syrinx ≥ C1[3]	Yes	N= 3 (9.3%)	N= 3 (100%)	N= 0 (0.0%)
	No	N= 29 (90.6%)	N=0 (0.0%)	N=29 (100%)

Table 19: Comparison of preoperative MRI findings between acute cases of Chiari I malformation and non-acute cases of CMI.

SURGICAL OUTCOMES AND COMPLICATIONS

Studies I and II

One patient who was included in both studies presented with cerebrospinal fluid (CSF) collection at the surgical site 6 days after surgery. This was the only complication, and it was successfully managed with a temporary CSF diversion using a lumbar drain for 7 days. Preoperative swallowing problems were resolved at three months after surgery in all patients.

Study III

All the patients were followed up 3 months post-surgery, and they reported significant improvement with regard for preoperative symptoms. No reported perioperative or postoperative surgical complications and no mortality was reported in the three CMI patients who presented with acute deterioration. Preoperative syrinx significantly improved an all three affected patients after surgery.

Study IV

There were six patients who developed manifestations of cerebrospinal fluid disturbance (CSFD) (11.5%) out of a total of 51 included patients. Four of these patients eventually required a permanent CSF diversion procedure. Only one patient developed postoperative signs of infection with fever and high levels of C-reactive protein, and that patient was treated with antibiotics.

Five patients received a lumbar drain for three to seven days. Two of these patients were successfully treated with only lumbar drain and showed

no deterioration after close observation. In these two patients, repeat imaging demonstrated resolution of ventriculomegaly and their symptoms. Intracranial pressure (ICP) monitoring (n=2) was used when patients presented with signs of increased ICP, such as papilledema and no ventriculomegaly on a brain computed tomography (CT), the initial readings showed ICP above 30 mmHg. Both affected patients were shunted. The clinical presentation and radiological findings observed in the patients who developed postoperative CSFD are summarized in table 20.

	C/P	V.megaly	ICP monitor	Papilledema	LD	Shunt
1	H/A, CSF leak	Y	N	N	Y	N
2	H/A, CSF leak	N	Y	Y	Y	VP
3	H/A, fatigue	N	Y	Y	N	VP
4	H/A, blurred vision	Y	N	Y	Y	VP
5	H/A, CSF leak	Y	N	N	Y	LP
6	H/A	Y	N	N	Y	N

Table 20: Clinical presentation, and outcomes in CMI patients with CSF disturbance.
Abbreviations: H/A= headache, Y= Yes, N= No, VP= ventriculoperitoneal shunt, LD= lumbar drain

The mean time to presentation of CSFD following occipitocervical depression (OCD) was 7.0 days (range, 3 to 11 days). All patients were neurologically intact and had a Glasgow coma score of 15. All underwent urgent imaging on admission in the form of a brain CT.

All six cases with CSFD were females (100%) (p=0.22). The mean body mass index (BMI) of the CSFD patients was 32.3, whereas that of the non-CSFD group was 24.3 (p=0.0011). Age, degree of tonsillar herniation and syrinx were not significantly different between CSFD and non-CSFD patients. These findings are presented and summarized in table 21.

	Age	Gender M F	BMI	Syrinx Yes No	Tonsillar herniation
Total n=51	36(13.3) 33(20;67)	15(29%) 36(71%)	25(5.2) 24.6(16;48)	32(67%) 19(37%)	12.6(6.5) 11(4;28)
CSFD n=6	35(11.8) 35(22;51)	0(0%) 6(100%)	32.2(8.26) 30(24;48)	2(33%) 4(66%)	11.2(2) 11.5(8;14)
Non-CSFD n=45	36(13.6) 32(20;67)	15(33.3%) 30(66.7%)	24.3(4) 23(16;36)	30(66.7%) 15(33.3%)	12.8(6.8) 10(4;28)
p value	0.86	0.22	0.0011	0.26	0.58

Table 21: Significance and comparison of the preoperative risk factors between patients who developed cerebrospinal fluid disturbance after occipitocervical decompression and non-CSFD group.

Of the non-CSFD patients (n=45), five had temporary CSF discharge at three to four weeks after surgery with no signs of infection, increased ICP or enlarged ventricles. Because they exhibited epidural CSF collection, three of these patients underwent secondary duraplasty with excellent results. One patient had transient double vision that completely resolved one week after discharge. There was one postoperative death due to stroke three days after surgery.

DISCUSSION

DISCUSSION

Swallowing function

Study I is the first prospective study to investigate swallowing function in chiari I malformation (CMI) using both patient-reported questionnaires and videoflouroscopy (VFS). Swallowing difficulty was found in 4 out of 11 patients (36%), which was within the range previously described in the literature (4 to 47%) [54,174]. Dysphagia as the sole or main symptom of CMI has been reported in the literature [175,176] but in our patients, other symptoms dominated. In addition, all four of our patients initially had a problem swallowing liquids, and this is a striking feature of neurogenic dysphagia [177]. These patients had dysphagia scores that were worse in 7 out of 12 domains on the EORTC-QLQ25 than those observed in the normal population. Their preoperative scores on the WDS improved after surgical decompression (WDS=16 vs. 6, respectively).

The only previous study to report on CMI and radiological assessments of swallowing was reported by Yu et al., but only its abstract is available in English [178], They used a water swallowing test before and at 7 days after surgery and found that dysphagia significantly improved in 67.6% of the cases. In Study I, we found that there was some degree of deviation from normal VFS results in 7 out of 11 included patients, four of whom had reported swallowing problems before surgery. Significant bolus penetration into the laryngeal vestibule was observed in only two of the patients with swallowing difficulty. Preoperative swallowing symptoms improved in all patients after surgical decompression, and no patients reported swallowing problems at 3 months postoperative. These results are similar to the

excellent postoperative outcomes previously reported in CMI patients with swallowing difficulties [49,176,179].

It is not clear why some CMI patients exhibit variable degrees of swallowing dysfunctions. However, based on our previous discussion of the anatomy and physiology of swallowing in the introduction section, one can speculate that vascular ischemia, traction of the lower cranial nerves and compression of the brainstem and cerebellum are probable explanations [180,181]. With regard for swallowing difficulty that occurs secondary to brainstem injury, it has been reported that swallowing complaints always precede a more severe presentation of brainstem injury. Accordingly, physicians must be vigilant to avoid a late diagnosis of brainstem injury that could lead to a silent aspiration, which is a critical condition [181].

Animal and human studies have also shown that the cerebellum has functions in swallowing coordination [182-184]. Furthermore, reports have shown that swallowing difficulties are a presentation in patients with isolated cerebellar pathologies [185,186]. For example, Suzuki et al. used brain functional MRI and reported that certain areas of the cerebellum were activated upon swallowing [187].

Quality of life (QOL)

In Study II, scores on the EQ-5D-5L improved significantly after surgical decompression, but there was no difference between pre- and postoperative scores on the LiSAT-11. However, satisfaction with life, when measured using the LiSAT-11, was worse in six domains in preoperative patients than in the normal population (only four domains were worse in patients postoperatively). This discrepancy in the results between the EQ-5D-5L and LiSAT-11 can be explained by the fact that the EQ-5D is a

more symptoms-oriented tool and that it requires less time to show an effect than does the LiSAT-11, which assesses life as a whole and psychosocial characteristics. Accordingly, we believe that the lack of significant difference between preoperative and postoperative results on the LiSat-11 was possibly due to the small number of patients but was more likely caused by the short follow up period (three months).

Very little evidence related to QOL in CMI patients is available, and the best evidence currently available is based on only three studies. The Conquer Chiari report of 798 CMI patients showed that the patient mainly reported problems with daily life and with physical and recreational activities. They propose that the severity of CMI symptoms negatively affects QOL [188]. As mentioned in the introduction section of this thesis, the only prospective study on QOL in CMI was published by Parker et al., who found that QOL (measured using the EQ-5D) was significantly improved at one year after surgery, similar to our results at 3 months postoperative [67]. Furthermore, Mueller et al. used the Sickness Impact Profile to evaluate CMI and reported that QOL was improved in 75% of the cases. These results are in accordance with those obtained in our study, in which QOL was improved in 70% of the cases [189].

Neuropsychological (NP) function

Study II is, to the best of our knowledge, the first prospective study to show improvement in both NP functions and QOL in CMI patients.

Preoperative neurocognitive assessments of CMI patients have been previously reported in the literature. Kumar et al. used NP assessment tools and diffusion tensor imaging (DTI) to compare a CMI group to a matched control group. They found that CMI patients performed worse on NP assessments than did the controls [190].

The performance of most of our CMI patients was in the normal range on NP tests. The differences in findings might be explained by variation in NP tests as well as the patient selection process. For instance, we excluded a patient who had a chromosomal disorder and concomitant developmental delay to be sure that the NP performance and changes we reported were explained by CMI and surgical treatment. We also believe that a control group and a larger sample size may have helped to reduce the risk of confounders and bias. We therefore recommend that future studies use larger sample sizes and matched control groups.

Despite the fact that the preoperative results were relatively normal, we were surprised to find that verbal learning (RAVLT), psychomotor speed (Coding), the speed of color naming (Stroop color task) and the ability to manage interference (Stroop interference task) were significantly improved postoperatively and that the differences were large. Different versions of learning tasks (BVMT-R and RAVLT) were used both before and after surgery to minimize the effects of training and any differences in the level of difficulty between versions.

The effects of surgery on NP performance (i.e., with both pre- and postoperative assessment) has not been studied before. Allen et al. postoperatively tested 24 CMI patients and compared them to 24 age- and education-matched controls. The CMI group performed more poorly than the controls in response inhibition (Stroop interference), working memory computational speed (Ospan), and processing speed (automated digit symbol substitution task, a task almost identical to the Coding task used in this study). None of the NP tests except the Stroop interference test revealed any differences between the groups when depression and anxiety scores were statistically controlled as covariates [191].

Acute presentation of CMI

In Study III, we reported that we observed unusual acute deterioration in 4.6% of CMI patients. This is similar to the risk level previously reported in the literature [55,56] (see introduction). All patients with acute deterioration that were observed in this study had CMI-typical occipital headache in addition to at least one medullary symptom. None of the patients in this study reported any aggravating incidents prior to acute deterioration, although such symptoms were previously reported to occur in up to 41% of cases with acute CMI [55]. Patients with acute deterioration of CMI showed significant to complete resolution of preoperative symptoms. These results are similar to the postoperative outcomes observed in previous studies of CMI patients with acute deterioration, in whom the surviving patients were reported to have achieved significant improvement [55].

Syrinx and clinical presentation

CMI causes as many as 50% of cases of syrinx and is therefore by far its most common cause [14,192]. Syrinx has been proposed to be directly related to the severity of CMI symptoms [11,12]. For instance, the size of a syrinx was found to be directly related to the shortness of the duration and the rapidness of the progression of CMI symptoms [91] Syrinx is also known to be significantly associated with scoliosis in CMI patients [193]. Different pathophysiological mechanisms of syrinx were previously described in the introduction section of this thesis. In CMI patients, swallowing difficulty was found to be significantly associated with a high cervical and bulbar syrinx [174]. In our study (I), a syrinx was found in five patients, two of whom

reported swallowing difficulty. In Study II, we constructed a graphical representation to investigate QOL in subgroups (syrinx vs. non-syrinx) and, similar to previous studies, we found no discernible effect [67,189] In both Studies I and II, the small sample size did not allow such comparisons to be statistically tested, and this is therefore an area that should be investigated in future studies.

In Study III, syrinx was investigated as an indicator of acute deterioration in CMI patients. We found that patients with acute deterioration had the most extensive syrinxes of all included patients (i.e., they were larger, longer and more rostrally extended than those observed in non-acute CMI patients). An MRI finding of a syrinx extending rostrally beyond the C1 level was observed only in acute cases in this study, and of these, two (3%) had a finding of syringobulbia. It is worth mentioning a morphometric study by Tubbs et al., who tried to identify factors that could help predict the risk of syringobulbia in CMI patients. Those authors found that there were no peculiar characteristics on MRI that could distinguish between CMI patients with or without syringobulbia [194]. We accordingly believe that certain characteristics of preoperative CMI-associated syrinx could be helpful when assigning patients for early surgical decompression.

Postoperative cerebrospinal fluid (CSF) complications

Disturbance of CSF was observed in 11.5% of all included patients in Study IV. This is within the range that was previously described in the literature (6-25%). In this study, only females with a high body mass index (BMI) developed cerebrospinal fluid disturbance (CSFD) after surgery. Other tested preoperative factors (i.e., age, degree of tonsillar herniation

and syrinx) were not significantly associated with the risk of developing CSFD after CMI surgery.

Based on our findings, we suggest that pseuotumor cerebri (PTC) must be taken into consideration as a differential diagnosis in some patients. This would help to avoid unnecessary occipitocervical decompression (OCD) and better guide patient management. In addition, obesity can have detrimental effect on intracranial pressure (ICP) and therefore increase the risk of developing a CSFD [98,99]. This conclusion can be drawn from many animal and human studies that have shown a positive relationship between intra-abdominal pressure (IAP) and ICP [99,195-199]. Furthermore, reports has shown that ICP is decreased following bariatric surgery in patients with PTC and is associated with the further resolution of their symptoms [200,201].

STRENGTHS AND LIMITATIONS

STRENGTHS AND LIMITATIONS

Studies I & II

The main limitations of these studies are a small study sample size and a short follow up period of three months after surgery. We opted to choose this short follow up period based on our own experience and a previous study published by Magnus Tisell et al. who found that 91% of patients showed improvement at three months after surgery [49]. Because Chiari I malformation (CMI) is an uncommon diagnosis and it is difficult to prospectively follow a large number of patients, a multicenter study would be preferable. Another limitation of these prospective studies is the lack of a control group. It would be more feasible to include such a group in Study II but it would be difficult to do so in Study I due to the possible discomfort and invasiveness of the radiological assessment of swallowing. Both studies were exploratory, and we believe that the results should encourage future extensive studies. Nevertheless, these two studies were prospective studies of extensively examined patients, and both used both subjective and objective tools to evaluate the subjects. In addition, the patients were taken from a defined geographical area of Western Swe-

den, and they were demographically, clinically and radiologically similar to samples included in previous reports of CMI.

Studies III & IV

The main limitation of these studies was that they were retrospective and observational and the data used were not specifically designed to answer the specific research question. Moreover, the retrospective design meant that there was a lack of accurate information on many other risk factors (i.e., confounding factors that could have influenced the main outcome). However, the included patients were also consecutively enrolled from a defined geographical area in western Sweden, and the demographic data corresponded well to those reported in previous studies, indicating that they are representative. Accordingly, we believe that it is essential for prospective studies to address acute deterioration in CMI and the development of cerebrospinal fluid disturbance (CSFD) after surgery in CMI. Furthermore, all patients were operated on according to a standardized procedure, and this is likely to have minimized surgical variability.

CONCLUSION

CONCLUSION

- Dysphagia was reported in four of 11 (36%) consecutive adult patients with Chiari I malformation (CMI). Accordingly, it should not be ignored because it is potentially associated with CMI.
- Preoperative patient-reported dysphagia questionnaires and videoflouroscopy (VFS) confirmed that these patients had swallowing dysfunction.
- Postoperative outcomes were excellent in CMI with dysphagia. All patients were free from dysphagia after surgery, and the preoperative subjective and objective deviations from normal swallowing were decreased or had disappeared postoperatively.
- CMI patients had normal preoperative neuropsychological (NP) functioning. However, they had a poorer quality of life (QOL) before surgery than was reported by healthy individuals.
- After surgical decompression, there was a statistically significant improvement in four of the nine NP tasks tested after surgery. In addition, QOL showed improvement.

- Acute deterioration of CMI was reported in three (4.6%) of 65 consecutive adult patients with CMI who underwent occipitocervical decompression.
- CMI patients who presented with acute deterioration had more extensive syrinx features than were observed in non-acute cases.
- Cerebrospinal fluid diversion was needed in six (11%) of 51 consecutive adult CMI patients who underwent occipitocervical decompression.
- All patients with postoperative cerebrospinal fluid disturbance were female, and their body mass index mean was 32.3 (p=0.0011), which was higher than the mean of 24.3 observed in patients without this complication.
- We emphasize that it is important to consider pseudotumor cerebri (PTC) as a differential diagnosis in selected patients, especially obese females showing signs of high intracranial pressure (ICP).

FUTURE PROSPECTIVES

FUTURE PROSPECTIVES

- Atypical presentations of different diseases can be easily missed in initial patient assessments. In the case of Chiari I malformation (CMI), even when the majority of patients exhibit a CMI-typical occipital headache that worsens with exertion, our studies and previous reports have shown that there is a strong relationship between CMI and swallowing difficulties. This was confirmed in our studies, in which we used both subjective and objective assessments of swallowing. Swallowing function should routinely be evaluated in all CMI patients. In addition, aspects of swallowing function should be included in future prospective clinical protocols.
- CMI seems to have a significant impact on quality of life (QOL) in affected individuals. Many young and middle-aged patients significantly restrict their lives in relation to their symptoms and might be helped by surgical decompression. More long-term data are needed in this field to further establish the long-term benefits of surgical intervention.
- Brain and cervical spine magnetic resonance imaging (MRI) are excellent tools that can be used

to assign patients for early surgical decompression. The etiology of syrinx remains controversial and the characteristics of syrinx in relation to their pathophysiology and symptomatology is an area that should be considered in future studies.

- In obese patients, especially females, with cerebellar tonsillar ectopia, one should consider the possibility of pseudotumor cerebri (PTC) as a differential diagnosis and accordingly examine the patient for signs of high intracranial pressure (ICP).
- Future studies on swallowing, cognition, acute presentation and cerebrospinal fluid disturbance after surgery in CMI should use a multicenter prospective design. This will help to include as many patients as possible so that the clinical presentation and outcomes of this condition can be better defined.

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APPENDIX

Case Report Form (CRF)

General information

Patient ID	
Gender	○ Female ○ Male
Age	
BMI	
Past medical history	○ HTN ○ DM ○ Swallowing disorder ○ Cognitive disorder ○ Other
Past surgical history	○ GI surgeries ○ CSF diversion ○ Other
Family History	○ Yes ○ No
B-Hcg	○ Yes ○ No

Localization of headache	○ Occipital ○ Others, specify
Headache aggravators	○ Laughing ○ Coughing ○ Movement ○ Positional ○ Others
Duration of headache	○ Long (hours) ○ Short (min-sec)
Vision	○ Diplopia ○ Nystagmus ○ Blurred vision
Other symptoms	○ Dysarthria ○ Gait disturbance ○ Swallowing disorder ○ Cognitive disorder ○ Nausea/vomiting ○ Tremor ○ Other, specify
Weakness	○ Rt upper limb ○ Rt lower limb ○ Lt upper limb ○ Lt lower limb
Sensory loss	○ Rt upper limb ○ Rt lower limb ○ Lt upper limb ○ Lt lower limb
Duration of symptoms (months)	○ Yes ○ No

Clinical data

Social aspects

Marital status	○ Married/sambo ○ Divorced ○ Widowed ○ Single
Occupation	○ Works ○ Study ○ Unemployed ○ Retired ○ Other
Sick leave	○ Yes, days…. ○ No

Radiology

Syrinx	○ Yes ○ No
Hydrocephalus	○ Yes ○ No
Scoliosis	○ Yes ○ No
Other malformations	○ Yes ○ No
Tonsillar herniation	○ …….. mm