THE PATHOPHYSIOLOGY OF CHIARI MALFORMATION TYPE I
WITH RESPECT TO STATIC AND PULSATILE INTRACRANIAL PRESSURE

RADEK FRIČ

A doctoral thesis

Faculty of Medicine, University of Oslo
Department of Neurosurgery, Oslo University Hospital - Rikshospitalet
Oslo, Norway
2017
## CONTENTS

Abbreviations ................................................................. 7
Summary ................................................................. 8
List of original publications ............................................... 9

1. **Introduction** .......................................................... 10
   1.1 Background ......................................................... 10
   1.2 History ................................................................. 13
   1.3 Etiology of CMI ...................................................... 16
   1.4 Epidemiology of CMI ............................................. 17
   1.5 Natural history of CMI ............................................ 18
   1.6 Clinical symptoms of CMI ...................................... 19
   1.7 Radiological findings in CMI ................................. 20
      1.7.1 Syringomyelia and its pathophysiology ............... 21
      1.7.2 Skeletal anomalies at the CCJ ......................... 24
      1.7.3 CMI and hydrocephalus ................................... 25
      1.7.4 Scoliosis in CMI ............................................. 26
   1.8 Indication for treatment of CMI ............................... 26
   1.9 State-of-the-art in the treatment of CMI ................... 27
      1.9.1 Conservative treatment .................................... 27
      1.9.2 Surgical treatment ........................................ 28
   1.10 Outcome after treatment for CMI ............................ 32
   1.11 Intracranial compliance in CMI ............................. 32
   1.12 Static and pulsatile ICP in CMI ............................... 35
   1.13 Idiopathic intracranial hypertension (IIH) .......... 38

2. **Aims of the thesis** ................................................... 40

3. **Patients material and methods** ................................. 41
   3.1 Ethical considerations ............................................ 41
   3.2 Simultaneous measurements of static and pulsatile pressure within intracranial and intraspinal compartments (Paper I) ........................................ 41
      3.2.1 Patients ......................................................... 41
      3.2.2 Data acquisition ............................................. 42
      3.2.3 Radiological assessment ................................. 42
      3.2.4 Definition of tentative abnormal pulsatile and static pressure .......... 43
      3.2.5 Statistical analysis ......................................... 43
3.3 CSF pressure gradient across the CCJ derived from phase-contrast MRI (Paper II) .... 43
  3.3.1 Patients .............................................................................................................. 43
  3.3.2 Data acquisition ............................................................................................... 44
  3.3.3 Radiological assessment ................................................................................... 44
  3.3.4 Definition of tentative abnormal pulsatile and static pressure ......................... 44
  3.3.5 Statistical analysis ............................................................................................ 44
3.4 Perioperative changes in ICP following FMD (Paper III) ........................................ 44
  3.4.1 Patients .............................................................................................................. 44
  3.4.2 Data acquisition ............................................................................................... 45
  3.4.3 Definition of tentative abnormal pulsatile and static pressure ......................... 45
  3.4.4 Statistical analysis ............................................................................................ 45
3.5 A comparison of clinical, radiological, and ICP findings in CMI and IIH (Paper IV) .. 46
  3.5.1 Patients .............................................................................................................. 46
  3.5.2 Data acquisition ............................................................................................... 46
  3.5.3 Radiological assessment ................................................................................... 46
  3.5.4 Definition of tentative abnormal pulsatile and static pressure ......................... 47
  3.5.5 Statistical analysis ............................................................................................ 47
3.6 Cardiovascular comorbidity in CMI and IIH (Paper V) ........................................... 47
  3.6.1 Patients .............................................................................................................. 47
  3.6.2 Data acquisition ............................................................................................... 47
  3.6.3 Prevalence of cardiovascular disease and diabetes versus pulsatile ICP .......... 48
  3.6.4 Statistical analysis ............................................................................................ 48

4. Results ....................................................................................................................... 49
  4.1 Simultaneous measurements of static and pulsatile pressure within intracranial and
  intraspinal compartments (Paper I) ............................................................................ 49
    4.1.1 Patients .............................................................................................................. 49
    4.1.2 Radiological findings ....................................................................................... 49
    4.1.3 Clinical symptoms versus radiological findings .............................................. 49
    4.1.4 Pressure recordings ........................................................................................ 49
    4.1.5 Clinical symptoms versus pressure parameters ............................................ 50
    4.1.6 Radiological findings versus pressure parameters ......................................... 50
  4.2 CSF pressure gradient across the CCJ derived from phase-contrast MRI (Paper II) .... 50
    4.2.1 Patients ........................................................................................................... 50
    4.2.2 Comparison of MRI-dP and CSF flow velocities in patients with CMI and healthy
    subjects .................................................................................................................... 50
‘It’s better to be roughly right than precisely wrong’.

*(John Maynard Keynes 1883-1946)*
ACKNOWLEDGEMENTS

The studies included in this thesis were carried out at the Department of Neurosurgery, Oslo University Hospital – Rikshospitalet. I would like to express my sincere gratitude and respect to all patients, whose patience and cooperation were crucial for the successful accomplishment of the studies.

I am most indebted to the principal supervisor of this thesis, Professor Per Kristian Eide. During my years at Rikshospitalet, he has been the source of great inspiration and influence to me, both as a clinical scientist and as a neurosurgeon. I feel privileged to have been introduced by him to the exciting area of hydrocephalus research, and I owe him so much for all his ideas, support, help, and excellent tutorship with many fruitful discussions, but also for all his patience and endurance during the realization of this project.

My collaborators Erika Kristina Lindstrøm, Geir Ringstad, Kent-Andre Mardal, and Are Hugo Pripp have been of great help and provided me with crucial expertise during the conduction and publishing of the studies. I also thank Sissel Reinlie for her support of my research project, and Matthew Spreadbury for struggling with all my long sentences when editing some of my manuscripts.

Being in principle a man of the journey rather than of the goal, I have during my career enjoyed and benefited greatly from meeting and working with so many outstanding colleagues who have inspired me with their work as well as their attitude. Just to mention some of them, Petr Suchomel and Pavel Buchvald must be credited for introducing me to the real life of a neurosurgeon during my early years in Liberec. Later in Oslo, I have been lucky to work with Bernt Due-Tønnessen and Arild Egge, who have helped me to achieve my dream of becoming a pediatric neurosurgeon. With them and another good colleague, Jarle Sundseth, I can share all joys and sorrows we encounter during our working days. My dear senior colleague, a true role model of a dedicated neurosurgeon, and friend Milo Stanišić deserves many thanks for all the support and good advice I have received from him.

I do sincerely thank my parents and my whole family for all their support and encouragement.

There is always a woman beside the man, or women in my own case. My greatest thanks and gratitude I owe to my beloved life companion, Michaela, for her incredible patience and tolerance, and to our two wonderful princesses, Madeleine and Stella, for being my greatest motivation and providing me with true meaning of life.

Oslo, May 2017

Radek Frič
ABBREVIATIONS
AH = arterial hypertension
AP = angina pectoris
AQP4 = aquaporin-4
BMI = body mass index
CCJ = craniocervical junction
CDH = chronic daily headache
CFD = computational fluid dynamics
CMI = Chiari malformation type 1
CSF = cerebrospinal fluid
CT = computed tomography
DM = diabetes mellitus
FM = foramen magnum
FMD = foramen magnum decompression
HUNT3 = Nord-Trøndelag Health Study 3
ICE = intracranial elastance
ICC = intracranial compliance
ICP = intracranial pressure
ICV = total intracranial volume
IIH = idiopathic intracranial hypertension
iNPH = idiopathic normal pressure hydrocephalus
MI = myocardial infarction
MRI = magnetic resonance imaging
MRI-dP = pressure gradient derived from phase-contrast MRI
MWA = mean ICP wave amplitude
MWRT = mean wave rise time
MWRTC = mean wave rise time coefficient
ncHC = non-communicating hydrocephalus
PCF = posterior cranial fossa
PCFV = posterior cranial fossa volume
REF = reference group
VV = ventricular CSF volume
SUMMARY

Chiari malformation Type I (CMI) is a condition of still poorly understood etiology and pathophysiology. This limits the choice of optimal therapeutic strategies, particularly in cases refractory to standard treatment, which is the surgical decompression of the foramen magnum (FMD). One of the unexplored issues in CMI is the role of intracranial compliance (ICC), as addressed in this thesis.

Changes in ICC may be indicated by the pulsatile intracranial pressure (ICP). Therefore, we invasively measured both pulsatile and static pressure simultaneously from the brain and the lumbar CSF compartment (Paper I). The pulsatile ICP was elevated in 69% of 26 patients with symptomatic CMI; the intracranial-lumbar pulsatile pressure gradient was abnormal in 71% and significantly higher in patients with syringomyelia. The pulsatile ICP correlated significantly positively with the pulsatile pressure gradient; a similar correlation was not found for static ICP, which in addition was not clearly abnormal in any of the patients.

We also aimed to explore how the findings from invasive ICP measurements in patients with symptomatic CMI correlated with the patterns of CSF flow derived non-invasively from phase-contrast MRI, specifically the pressure gradient (MRI-dP). Using a mathematical analysis (Paper II), we found that MRI-dP, CSF flow velocities, as well as the occurrence of bidirectional flow did not differ significantly between patients with CMI (n=5) and healthy controls (n=4). However, we found a significant association between MRI-dP and pulsatile ICP measured invasively in patients with symptomatic CMI.

We wondered how elevated pulsatile ICP in patients with symptomatic CMI changed following FMD. Data from perioperative ICP measurements in 11 patients (Paper III) showed no significant decrease of preoperatively elevated pulsatile and/or static ICP during the first 3 days after FMD. This finding points to a more fundamental underlying change in ICC, rather than only the one caused by ‘decoupling’ of intracranial from spinal CSF compartments.

In order to further explore such a hypothesis, we focused on similarities observed in CMI and idiopathic intracranial hypertension (IIH) and compared the symptoms, intracranial volumes, and ICP scores from patients with either CMI (n=66) or IIH (n=41) (Paper IV). Pulsatile ICP was elevated in both cohorts compared to the reference group, while static ICP was higher in the IIH cohort. The ventricular, posterior cranial fossa, and total intracranial volumes were similar in both cohorts. The extent of tonsillar ectopy – although significantly different between the CMI and IIH cohorts - was more significant in both cohorts compared to the reference group. Finally, by estimating the prevalence of cardiovascular risk factors from 48 patients with CMI and 52 patients with IIH older than 20 years (paper V), we wanted to explore the potential impact of these factors on changes in vascular compliance. Compared to data from the general population, we found an increased prevalence of diabetes mellitus (DM) in male CMI and female IIH cases, and of arterial hypertension (AH) in female IIH cases.

Taken together, our findings challenge current theories of CMI as a disease caused by a distorted anatomy of the PCF and the FM, where syringomyelia and disturbed CSF circulation are the secondary events. Instead, and while being well aware of the still insufficient evidence, we suggest that the primary pathological events may be the reduced ICC, due to cranial constriction, structural changes of brain parenchyma as well as of the vascular wall, and changes of paravascular flow, leading secondarily to tonsillar ectopy and findings typical of CMI. Due to different treatment strategies, the clinical identification of this subset of patients with CMI appears crucial. Based on current knowledge, our own findings, and the pathophysiological considerations, we advocate the use of the term ‘Chiari syndrome’ rather than ‘malformation’.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to by their Roman numerals (Papers I-V):


1. INTRODUCTION

The topic of this thesis is the pathophysiological mechanism behind Chiari malformation type 1 (CMI), with particular emphasis on indices of intracranial compliance (ICC) and the potential implications for clinical practice. Before defining the aims of the thesis, a comprehensive introduction will be given in order to review current knowledge about the condition and to introduce the terms discussed in this thesis.

1.1 Background

The term Chiari malformation refers to a condition anatomically characterized by pathological ectopy or descent of the cerebellar tonsils into the foramen magnum (FM), causing compression of the brain stem (medulla oblongata) and the cranial nerves. This anatomical situation results in obstruction of cerebrospinal fluid (CSF) pathways, syringomyelia, and occasionally hydrocephalus. As the condition may have different causes, the rather general term Chiari malformation must be further specified and several types need to be distinguished:

**Type I** (CMI) is the most common form of supposedly congenital Chiari malformation, which typically manifests in older children and young adults, usually without any other associated anomalies. Up to 50% of patients have syringomyelia. An acquired form of CMI may develop in patients with hereditary disorders of connective tissue (such as achondroplasia, Ehlers-Danlos, or Marfan syndrome) as a result of craniocervical instability with basilar invagination. Finally, CMI has been reported to occur secondary in patients with lumbo-peritoneal shunts, where it may be present in up to 70% of cases [1], but is considered potentially reversible if the shunt is removed [2].

Hence, CMI is considered a mesodermal disease, i.e. a disease where the neural tissue is not primarily affected. Other types of malformations, in contrast, are in principle of neuroectodermal origin:

**Type II** is characterized by dislocation of the cerebellar vermis, the fourth ventricle, and the brainstem under the level of the FM; the cerebellar tonsils may lie under the level of the FM or may be rudimentary in some cases. Type II typically accompanies lumbosacral myelomeningocele. Low-lying torcular herophili, tectal beaking, hydrocephalus, and clival hypoplasia are the classical anatomical features of this type.
**Type III** is the most serious form of cerebellar ectopy found in small infants. Most of the cerebellum and brain stem are dislocated under the FM. Affected children do not survive if the malformation is untreated, and even if treated, the prognosis is far worse than for Types I and II. This type of Chiari malformation is often associated with suboccipital encephalomeningocele or high cervical myelomingingocele.

**Type IV** is characterized by a hypoplastic cerebellum without herniation of the content of the posterior cranial fossa (PCF) into the FM and – importantly and according to Chiari’s own original description from 1895 – is associated with occipital encephalomeningocele with supratentorial contents [3].

Furthermore, two additional types of Chiari malformation have recently been suggested:

**Type 0** has been proposed as a description of cases with isolated syringomyelia where all other potential causes are excluded, and where obstruction of CSF flow through the FM is suspected despite no obvious tonsillar ectopy [4-6]. As there are no established specific diagnostic criteria, this diagnosis becomes first justified when syringomyelia resolves after performed foramen magnum decompression (FMD), which sheds doubt on the concept of Chiari malformation Type 0 as an independent diagnostic entity.

**Type 1.5** is supposed to be characterized by tonsillar herniation as in CMI, with the addition of the elongated brainstem and the fourth ventricle. It is speculated that this malformation may represent an advanced and often progressive form of CMI [7, 8].

In clinical practice, Types I and II are most commonly encountered. In principal, they should be easily distinguishable, as Type II almost exclusively accompanies lumbosacral myelomingingocele, and since the radiological features of the two types are different (Tab. 1; Fig. 1).

In this thesis, CMI (i.e. Type I) is being discussed exclusively.
**Tab. 1** Different clinical and radiological features in Chiari malformation Types I and II

<table>
<thead>
<tr>
<th>Findings</th>
<th>Chiari I</th>
<th>Chiari II</th>
</tr>
</thead>
<tbody>
<tr>
<td>structures dislocated caudally</td>
<td>tonsils</td>
<td>caudal vermis, medulla oblongata, 4th ventricle</td>
</tr>
<tr>
<td>dysraphism (myelomeningocele)</td>
<td>occasionally</td>
<td>seldom missing</td>
</tr>
<tr>
<td>hydrocephalus (ventriculomegaly)</td>
<td>unusual</td>
<td>seldom missing</td>
</tr>
<tr>
<td>medullar ‘kink’</td>
<td>missing</td>
<td>present in more than half of the cases</td>
</tr>
<tr>
<td>course of upper cervical roots</td>
<td>normal</td>
<td>usually cranially</td>
</tr>
<tr>
<td>usual age at onset of symptoms</td>
<td>young adults</td>
<td>infants / small children</td>
</tr>
<tr>
<td>most usual symptoms</td>
<td>headache, dizziness, neck pain</td>
<td>symptoms of progressive hydrocephalus and/or syringomyelia, respiratory distress, stridor, dysphony, dysphagy</td>
</tr>
</tbody>
</table>

**Fig. 1** Radiological appearance of typical Chiari malformation Type I (left) and II (right). Courtesy of the Dept. of Radiology, Oslo University Hospital – Rikshospitalet.
1.2 History

The term Chiari malformation refers to the name of Hans Chiari, an Austrian pathologist (Fig. 2). He was born on September 4, 1851 in Vienna, where his father, Johann Baptist Chiari (1817–1854), was a prominent gynecologist who is credited for describing prolactinomas. Chiari’s younger brother Ottokar Chiari (1853-1918) later became a well-known rhinolaryngologist.

Following the completion of his medical studies in Vienna (1875), Hans Chiari assisted the renowned pathologist Karl Rokitansky (1804–1878) and his successor Richard Ladislaus Heschl (1824–1881), before he was habilitated in pathological anatomy in 1878. Four years later, he was appointed to the German University in Prague, a city which at the time was part of the Austrian-Hungarian Empire, and where Chiari was also superintendent of the pathological-anatomical museum. He was the first to describe the features of choriocarcinoma in 1877, and in 1899, he and the British internist George Budd (1808–1882) provided a clinical and pathological explanation of hepatic vein thrombosis (Budd–Chiari syndrome). Additionally, he published on the autodigestive capacity of the pancreas and described connections (‘Chiari’s network’) between the Thebesian (valve of the coronary sinus) and the Eustachian (valve of the inferior vena cava) valves [9]. Chiari was also the first to relate arteriosclerosis of the carotid bifurcation to cerebral embolism.

Fig. 2 Hans Chiari (1851-1916)
Chiari’s contribution to the knowledge of pathology of the nervous system was also extensive. He described malformations of the brainstem and the cerebellum, reported on pituitary adenomas and, in 1883, probably on the first case of traumatic pneumocephaly published before the era of rentgenology.

Already in 1888, Chiari made the observation that the intramedullary syrinx usually communicated with the central canal of the spinal cord. Three years later, in 1891, he published his legendary work on hindbrain herniation [10, 11]. In this work, he described the case of a 17-year-old woman who died of typhoid fever and in whom he found hydrocephalus. Despite the fact that she reportedly had had ‘no symptoms referable to the cerebellum or the medulla’, Chiari found in her also a ‘peg-like elongation of tonsils and medial divisions of the inferior lobes of the cerebellum into cone-shaped projections, which accompany the medulla oblongata into the spinal canal’. This original description refers to what Chiari himself described as ‘Type I malformation’, where the cerebellum itself appeared normal in most cases, but softening or sclerosis was found in some instances. The fourth ventricle was normal or slightly elongated; the medulla appeared flattened. Chiari was not sure whether these changes caused symptoms or not, but he was prone to believe that they might result in bulbar symptoms. He described Type II changes in a 6-month-old child with paraplegia and a paralyzed bladder, who had succumbed to pneumonia. In this child, the pons descended into the spinal canal over 6 mm, and the medulla extended to the level of the third cervical vertebra. The baby had hydrocephalus and ‘a cylindrical hole 6 mm in width, filled with clear serum’ in the dorsal side of the spinal cord extending from the first to the seventh segment. A second cavity, a ‘hydromyelic’, was found a few segments below. There was also diastematomyelia, myelomeningocele, and displacement of the conus to the level of the sacrum. Chiari reported on only one example of Type III malformation, with absence of part of the tentorium cerebelli and herniation of the cerebellum and the fourth ventricle into the cervical canal, as well as an associated hydromyelic cavity communicating with the fourth ventricle. In 1896, Chiari added 63 cases of congenital hydrocephalus, of which 14 children or adults had a Type I malformation, and seven had a Type II; mainly neonates a few days old with various types of spinal dysraphism. He had noticed that the severity of the hydrocephalus did not relate to the extent of the malformation, and he postulated that defective growth of the skull led to raised local pressure, presumably forcing down the hindbrain. He thought that there was a graded increase, ranging from descent of cerebellar tissue within the fourth ventricle to descent with the ventricle, but dorsal to it. No new cases of Type III malformation were added to the one case described in 1891, but two cases
of the new Type IV were described, with hypoplasia of the cerebellum that Chiari believed had been caused by hydrocephalus [12] (Fig. 3).

**Fig. 3** The title page of Chiari’s original publication from 1896 (left) and his drawing showing cone-shaped elongations of both tonsils and both inferior cerebellar lobi (right) [12]

In 1906, Chiari moved to Strasbourg where he was appointed professor of pathological anatomy. There he died suddenly after a throat infection on May 6, 1916, aged 64.

Several other names must be mentioned in association with what we today call Chiari malformation [13]. The phenomenon of ectopy of the cerebellar tonsils was probably first described by the Dutch physician and anatomist Nicholas Tulp (1593-1674) in his Observationes Medicae, later, in 1829, also by the French anatomist and pathologist Jean Cruveilhier (1791-1874), in 1881 by the German pathologist Theodor Langhans (1839-1915), who hypothesized that the ectopy may result in the development of syringomyelia [14], and finally, in 1883, by the Scottish surgeon and anatomist John Cleland (1835-1925), who described an infant with spina bifida and hydrocephalus with the cerebellar nodulus displaced into the elongated fourth ventricle, separating the cerebellar lobes (i.e. Type II malformation) [15]. In 1894, the German pathologist Julius Arnold (1835–1915) described - in a neonate who died shortly after birth - a malformation where the fourth ventricle and the cerebellum herniated
through the FM while sparing the medulla [16]. The child had spinal dysraphism, but without hydrocephalus, and Chiari believed that it was an example of his Type II malformation, despite the absence of enlarged ventricles.

In 1907, two of Dr. Arnold's students coined the eponym of ‘Arnold–Chiari malformation’ in honour of the two scientists [17], and this term is still commonly used in the medical literature. However, although Hans Chiari himself gave credit to both Cleland and Arnold, the attachment of Arnold’s name is probably appropriate only in the case of Type II malformations, since his writings were mainly about the dysraphism, and consideration of the hindbrain descent was a small and peripheral issue in his work [18, 19]. Due to the considerably greater contribution of Hans Chiari, the condition is now most often referred to only as ‘Chiari malformation’, which is also the case in this thesis.

Finally, Russell and Donald [20] described in 1935 10 additional pathological specimens of Chiari malformations.

1.3 Etiology of CMI

Unlike Types II–IV of Chiari malformation, which are closely associated with embryological defects of the neural tube and therefore regarded as neuroectodermal anomalies, the origin of CMI is still uncertain. At this point, the most accepted opinion seems to be that CMI is a disorder of mesodermal origin, in which tonsillar ectopy may be secondary, attributable to underdevelopment of the occipital bone and 'overcrowding' of the normally developed cerebellum within a developmentally small posterior cranial fossa (PCF) [21, 22], due to a primary defect of the occipital somites originating from the paraaxial mesoderm [23]. Currently available analyses of genetic data seem to support the hypothesis that variants in genes involved in development of the paraaxial mesoderm may determine the size of the PCF [24-26], although studies further identifying potential genetic defects leading to the development of CMI remain to be performed.

Another etiological consideration is the original one of Hans Chiari who assumed the malformation to be a result of hydrocephalus [10-12], and the controversial opinion of Goel [27, 28], that CMI is the consequence of atlanto-axial instability, as described below (Chapter 1.7.2).
The complexity of etiological considerations was illustrated by Milhorat et al. [29], who found significantly reduced size and volume of the PCF only in patients with ‘classical’ CMI, Chiari malformation Type II, or CMI associated with craniosynostosis; in patients with CMI associated with occipito-atlanto-axial instability, tethered cord, intracranial mass lesions, and in patients with CMI following lumbo-peritoneal shunts, size and volume of the PCF were normal. In all these latter cases, the CMI may thus probably be described as ‘secondary’. Accordingly, the size and area of the foramen magnum were significantly smaller in patients with classical (i.e. ‘primary’) CMI and CMI associated with craniosynostosis, but significantly larger in patients with Chiari malformation Type II and CMI associated with tethered cord. Therefore, the authors suggested the causal mechanisms behind CMI shown in Fig. 4. Williams [22, 30] proposed a unifying hypothesis in which CMI was caused by a combination of reduced PCFV and intraspinal hypotension, along with venous insufficiency causing hydrocephalus.

**Fig. 4** Different mechanisms possibly causing CMI, as suggested by Milhorat et al. [29]

- cranial constriction (overcrowding)
- cranial settling
- spinal cord tethering
- intracranial hypertension
- intraspinal hypotension (spontaneous of following lumbo-peritoneal shunt)

At this point, the question arises whether CMI really is a malformation or rather a syndrome in which tonsillar ectopy is related to one of the different mechanisms mentioned above. This provocative question reflects our still limited understanding of the etiology and pathophysiology of CMI and will be further discussed later in this thesis.

1.4 Epidemiology of CMI

Although a known entity for more than a hundred years, the diagnosis of CMI has been revolutionized after the advent of magnetic resonance imaging (MRI) that reveals not only cases previously hidden behind other neurological diagnoses, but also many asymptomatic cases. Out of 22,591 patients who underwent MRI of the head and cervical spine, Meadows et al. [31] found tonsillar ectopy extending more than 5 mm (average 11.4±4.9 mm) below the FM in 175
(0.8%) cases, of which 25 (14%) were found to be clinically asymptomatic. Similarly, Vernooij et al. [32] found an incidental CMI in 18 out of 2,000 subjects (0.9%). A higher prevalence has been reported from pediatric series by Strahle et al. [33], who found 509 cases of CMI among 14,116 children (<18 years) undergoing MRI (i.e. 3.6%), 32% of whom were considered symptomatic, whereas Aitken et al. [34] reported only 51 (1%) cases of CMI among 5,248 children/young adults under 20 years of age, of which 63% were symptomatic.

1.5 Natural history of CMI

In fact, the natural history of CMI is poorly understood, as most patients come to the attention of a neurosurgeon first when presenting with symptoms. On the other hand, an increasing incidence of asymptomatic/oligosymptomatic cases as revealed by MRI performed for unrelated reasons has allowed for the use of a conservative strategy and hence the observation of the natural history of CMI over time. Available data indicate that CMI in most cases does not significantly progress either clinically or radiologically, although cases with acute onset of symptoms have also been described [35-38]. Novegno et al. [39] followed up on 22 children with CMI (11 discovered incidentally) for 5.9 years on average. Only five patients (22.7%) experienced worsening of symptoms and only three required surgery during the follow-up. Tonsillar ectopy remained stable in 16 patients, whereas a mild reduction was observed in four and complete resolution in one patient, respectively. In another report from the same group, only two out of 16 initially asymptomatic cases required intervention during follow-up (mean 5.8 years), both due to hydrocephalus. Benglis et al. [40] reported on 124 initially conservatively treated cases, 43 of which (35%) were asymptomatic and only 14 of which (11.3%) were patients with symptoms attributed to CMI, five of them requiring surgery. Only seven out of 124 patients presented with syrinx, without any progression during a relatively short follow-up (mean 2.83 years). In the study by Strahle et al [41], 147 children were followed up clinically (mean 4.6 years) and by MRI (mean 3.8 years). Only nine of them (6.1%) exhibited new symptoms attributed to CMI during the follow-up period. In total, only 14 patients (9.5%) received surgical treatment, while other patients remained asymptomatic or only minimally symptomatic. With a focus on radiological dynamics, Whitson et al. [42] prospectively followed 52 children for whom surgery was not initially recommended. Interestingly, they found that initial tonsillar descent, as assessed on MRI, remained stable in 50%, increased in 12% and reduced in 38% of cases; a complete resolution was seen in 12% of patients. Only three children (5.7%) ultimately underwent surgery during the follow-up period of up to 7 years.
Lately, Pomeraniec et al. [43] showed that the vast majority (92.9%) of their patients with CMI (n=70) managed conservatively did not experience any clinical (mean follow-up 66.3 months) or radiological (44.8 months) progression, and that even 41.7% of those presenting with symptoms improved. In this cohort, only 4.3% of patients developed new or progressive syringomyelia.

Also in our own practice, we have encountered mainly pediatric CMI cases with somewhat dynamic radiological findings. A later appearance of CMI after previously normal MRI occurs infrequently in children with subclinical forms of hydrocephalus, but we have also seen cases of spontaneous resolution of initially diagnosed CMI (Fig. 5), as occasionally reported in the literature [44].

**Fig. 5** Spontaneous resolution of incidentally diagnosed CMI in a 5-year-old boy. The initially observed significant tonsillar ectopy below the level of the FM (the white line) has become moderate, as seen on serial MRI scans, 20 months later. Courtesy of the Dept. of Radiology, Oslo University Hospital – Rikshospitalet.

### 1.6 Clinical symptoms of CMI

A plethora of symptoms has been described in association with CMI. Looked at systematically, the symptoms typically attributable to CMI may be either (a) those presumably attributable to altered intracranial pressure (ICP) (i.e. headache other than migraine or tension headache, dizziness, nausea, vomiting, visual disturbances/phenomena, fatigue, cognitive deficits), (b) those caused by the local compression/tension of lower cranial nerves (i.e. tinnitus, dysphagia, dysarthria, dysphonia, palpitation), and/or (c) those originating from the
compression of long neural tracts, either due to compression of the medulla oblongata at the level of the FM or due to syringomyelia. According to the study by Milhorat et al. [21], headache was experienced by 81% of 346 patients and was typically accentuated by physical exertion, Valsalva maneuver, and sudden postural changes; 78% of patients had subjective visual and 74% otoneurological disturbances including dizziness, both aggravated by the same factors as headache. However, besides some typical clinical features of CMI, patients may present with many other symptoms far less specific for the condition, which often leads to diagnostic confusion and delay.

1.7 Radiological findings in CMI

MRI is the superior radiological modality in the diagnosis of CMI. Significant ectopy of the cerebellar tonsils, typically with a peg-like shape, at least 5 mm under the level of the FM (i.e. the McRae’s or FM line between the basion and the opisthion) is considered conditional for diagnosis along with obliteration of the CSF space at the level of the FM. However, this definition may be too restrictive as shown in a study by Milhorat et al. [21], where 9% of patients with tonsillar ectopy of less than 5 mm had symptoms typical of CMI, and 53% of these patients also had syringomyelia.

The role of a developmentally small PCF in CMI has been widely debated in the literature and often referred to as ‘overcrowding’ of normally developed neural structures in an underdeveloped PCF. This has been documented by several studies [21, 29, 45-50] (Tab. 2 in the Discussion), even in children [51], at least in those with syringomyelia [52]. However, as emphasized by Roller et al. [53], age, race, sex, and body mass index each have a significant effect on the posterior cranial fossa volume (PCFV) as well as on the total intracranial volume (ICV). The latter authors could not find any statistically significant differences in PCFV, ICV, or the ratio between these volumes when comparing patients with CMI and a control group after controlling for patient demographics.

Other relevant radiological findings commonly associated with CMI are syringomyelia, skeletal anomalies at the CCJ, hydrocephalus, and in some cases also scoliosis.
1.7.1 Syringomyelia and its pathophysiology

Syringomyelia is a pathological intramedullary cavity occurring secondary to either an intramedullary tumour, spinal cord tethering, or CSF flow obstruction [54], the latter being the case in syringomyelia associated with CMI. Syringomyelia may be present in up to 50% of patients with CMI.

After the first attempt to treat syringomyelia was made by Johann Conrad Brunner (1653-1727) as early as in 1700 [55], many theories on the etiology and pathophysiology of syringomyelia have been brought forward, including the dysraphic, neoplastic, inflammatory, ischemic, hematomyelic, secretory, and transudation hypotheses [54]. In the modern era and following suggestions by Gull in 1862 and later Lichtenstein in 1937 [56] that syrinx resulted from hydrocephalus and obstruction of the foramina of Luschka and Magendie, the hydrodynamic (or ‘water-hammer’) hypothesis of Gardner and Angel was introduced [57, 58].

As the central canal of the spinal cord in humans normally occludes progressively with age, Gardner believed that an abnormally patent central canal due to a dysraphic defect combined with an obstruction of the foramina of Luschka and Magendie and at least intermittent pre- or postnatal hydrocephalus created ‘hydromyelia’. This hypothesis probably resonated well with Chiari’s own speculations that even the malformation itself with tonsillar ectopy was a result of prenatal hydrocephalus as mentioned in his classical works [11, 12]. Based on his own hypothesis, Gardner introduced an operation in which foramen magnum decompression (FMD) with duraplasty as described below (Chapter 1.9.2.1) was complemented by plugging of the obex (i.e. the cranial orifice of the central canal into the fourth ventricle) with a piece of muscle [57], a method that gained much popularity among neurosurgeons for a long time. However, from today’s perspective it is not clear whether the effect of this operation as reported in many cases was due to plugging of the obex or simply due to the FMD itself. Moreover, if Gardner’s hypothesis was correct, the most appropriate and effective treatment of syringomyelia would be a simple ventricular shunting, which, however, is not in agreement with experience from clinical practice. Finally, both obstruction of the foramina of Luschka and Magendie in the fourth ventricle as well as direct communication of the ventricle with the syrinx could be confirmed radiologically or intraoperatively in only a minority of patients with syringomyelia [59, 60].

Well aware of the drawbacks of Gardner’s hypothesis, Williams adapted it and proposed his own pressure dissociation hypothesis by simultaneously measuring the intracranial and intraspinal pressure in patients with CMI, particularly under maneuvers that led to elevation of
intracranial pressure, such as coughing and Valsalva [61, 62]. He thus observed an increase in intracranial pressure, which persisted even after the lumbar CSF pressure had normalized, suggesting a ball-valve mechanism by which the CSF passed the area of obstruction at the CCJ, but could not flow back. Applying Gardner’s original hypothesis at this point, Williams believed that the intracranial pressure in such situations normalized with CSF flow through the obex into the central canal, thus causing syringomyelia. In Williams’ hypothesis, hydrocephalus was no longer conditional for the development of syringomyelia, but a patent central canal and its communication with the fourth ventricle still was a premise that, however, could not be consistently demonstrated in all cases, particularly not in adult patients. The main difference between the hydrodynamic and the pressure dissociation hypothesis was that in the former the CSF outflow from the fourth ventricle should be blocked and the driving force was an arterial-derived pulse pressure wave expanding the syrinx from the inside, while in the latter the CSF flow was supposed to be obstructed at the level of the FM and a more prolonged venous pressure wave in case of, for example, coughing first squeezed the spinal cord from the outside and then expanded it from the inside.

As Oldfield et al. [63] could not find any communication between the fourth ventricle and the syrinx on intraoperative ultrasound or during dynamic MRI studies, they proposed a pathophysiological mechanism not requiring a patent communication between the fourth ventricle and the syrinx as formulated in Gardner’s and William’s hypotheses. Instead, a piston-like movement of the ectopic cerebellar tonsils induced by brief systolic pressure pulses was proposed to create and accentuate the pulsatile wave of CSF pressure in the upper cervical subarachnoid space, which in turn was transmitted to the wall of the spinal cord and to the syrinx [64], compressing the spinal cord with each heartbeat. At this point, this theory became closely linked to the transmedullary hypothesis previously proposed by Ball and Dayan [65] who demonstrated an accumulation of water-soluble contrast medium in syrinx after intrathecal injection through the transparenchymal flow along perivascular (Virchow-Robin) spaces. This hypothesis, however, supposes a sufficient positive gradient between the intraspinal subarachnoid space and the syrinx, while direct pressure measurements show the opposite [66]. Oldfield’s piston hypothesis became therefore accepted as a mechanism for the progression of a pre-existing syrinx, but not as a mechanism for its formation.

Klekamp [54] introduced another pathophysiological concept suggesting syringomyelia as a state of chronic interstitial edema of the spinal cord resulting from an accumulation of extracellular fluid. In search for understanding of the complex pathogenesis of both formation
and progression of syringomyelia in CMI, Greitz [67] suggested the *intramedullary pulse pressure hypothesis*, in which spinal cord distension was proposed as the major mechanism for syrinx formation (Fig. 6). Although seemingly in contradiction to the cord compression mechanism described by Oldfield’s group [64], there were some links between both concepts, as distension of an organ is generally accompanied by a secondary increase in its water content in order to compensate for the vacuum phenomenon with large negative pressures in distended tissues and cavities. Medullary edema and syringomyelia are thus logical consequences of cord distension [67]. Greitz also suggested a mechanism by which the pressure may be higher in the syrinx than in subarachnoid CSF that explained why syrinx fluid may originate from the microcirculation of the spinal cord [68] (Fig. 7).

**Fig. 6** Development of syringomyelia associated with Chiari I malformation as illustrated by Greitz [67]. The increased intracranial pulse pressure and downward motion of the cerebellar tonsils increases the systolic pressure transmission to the distal CSF spaces. (a) Pre-systolic phase of the cervical spinal canal. (b) When the spinal canal is wide, the systolic CSF flow jet at the foramen magnum (black arrow with tail) causes a Venturi effect or a suction effect on the spinal cord, which distends the cord and the central canal just below the obstructing cerebellar tonsils (white arrows). (c) When the subarachnoid space is narrowed, e.g. by the cervical intumescence, the pressure differences between the cord and the CSF are rapidly levelled out in the high-pressure region above the subarachnoid impediment. However, at the intumescence of the cervical cord, the Venturi effect or the suction effects of the systolic CSF flow jet are unrestricted. Therefore, syringomyelia often develops at this level. (d) When a bulging disc is present, syringomyelia develops just below that level. Permission to reuse obtained through Copyright Clearance Center’s RightsLink® (License No. 4035860949085).
Fig. 7 (a) Greitz’s [67] drawing demonstrating pressure differences in the spinal microcirculation, in the spinal cord and CSF spaces. Pressure decreases from the upper part of the drawing towards its lower part. A vertical vessel indicates a large pressure decrease, whereas a horizontal vessel indicates no pressure decrease. Arteriolar constriction causes a large pressure drop from the artery (red) to the capillary system (transparent red/blue level). Pressure is determined by and is always higher in the capillaries than in the spinal cord. The vascular pressure is transmitted to the cord, causing an outflow constriction of the veins and a pressure drop from the spinal cord to the CSF spaces (vascular waterfall phenomenon). The fluid exchange is much larger in the microcirculation of the spinal cord (black arrows) than between the CSF and the spinal cord (green arrows). (b) The fluid flow from the capillaries via the extracellular fluid (ECF) to the cyst is marked with black arrows. The cyst compresses the spinal microcirculation (dark blue circle) and decreases spinal blood flow. It also increases the vascular resistance on the venous side and increases the vascular pressure in the spinal cord. Permission to reuse obtained through Copyright Clearance Center’s RightsLink® (License Nr. 4035860949085).

1.7.2 Skeletal anomalies at the CCJ

An association of CMI with bone anomalies at the CCJ has been noticed. Milhorat et al. [21] found a retroflexed odontoid process in 26% and basilar invagination (i.e. the tip of the odontoid process of the second cervical vertebra, C2, at least 2.5 mm above the Chamberlain’s line drawn
between the hard palate and the opisthion) in 12% of 364 patients with CMI. Similarly, Klekamp [69] found basilar invagination in 46 (14.2%) out of his 323 patients operated on for CMI; the ventral compression of neural structures by the odontoid was present in only 31 of these patients.

According to a somewhat extreme and controversial opinion proposed by Goel [28], the primary initiator of the entire process resulting in CMI and syringomyelia is the atlanto-axial instability/dislocation, with or without basilar invagination. Goel claims that remodelling of the entire musculoskeletal system and neural structures of the CCJ and the rest of the spine is the body’s ‘natural attempt to sustain the instability and avoid or minimize the compromise of critical neural structures, even at the cost of self-destructive processes such as syringomyelia and morphological alterations in the form of basilar invagination and CMI’. He therefore calls CMI ‘Nature's air-bag phenomenon’ by which ‘the tonsils migrate into the spinal canal and are designed and positioned to prevent pinching of critical neural structures between bones. Syringomyelia is formed in an effort to neutralize cranial and spinal pressure and to support the bulk of Chiari malformation’ [27].

Milhorat et al. [70] reported an association between CMI and hereditary disorders of connective tissue such as Ehlers-Danlos syndrome that can present with occipito-atlanto-axial hypermobility and cranial settling. The authors identified such an association in 12.7% of patients with CMI in their cohort counting 2,813 individuals, and suggested that hypermobility of the occipito-atlantal and atlanto-axial joints contributed to retro-odontoid pannus formation and symptoms attributable to basilar impression.

1.7.3 CMI and hydrocephalus

Although Hans Chiari in his original work had already considered hydrocephalus to be the actual underlying cause of the malformation [10, 11], and while at least intermittent pre- or postnatal hydrocephalus was one of the crucial factors also in Gardner’s hypothesis of development of syringomyelia [58], the role of hydrocephalus in the etiology and pathophysiology of CMI is poorly reflected in the literature. Hydrocephalus in CMI is considered to be a rather secondary phenomenon (a ‘complication’), due to obstruction of the fourth ventricle’s outlets (i.e. the foramina of Luschka and Magendie) and/or due to obstruction of CSF flow through the FM by ectopic tonsils, although a more complex theory has also been proposed [22, 30] as mentioned above (Chapter 1.3). An overt hydrocephalus in the traditional
meaning, i.e. defined as ventriculomegaly evaluated by morphometric measures, is reported to be present only in about 7-10% of patients with CMI [21, 71]. However, ventriculomegaly is not a mandatory finding for the evidence of disturbed CSF circulation [72, 73], which therefore may be an underestimated issue in CMI. This particular aspect will be specifically addressed in this thesis.

1.7.4 Scoliosis in CMI

Scoliosis is a well-known and commonly encountered issue in children with myelomeningocele, tethered cord, and Chiari malformation Type II, where the progressive tethering of the spinal cord is considered to be the cause of scoliosis. In CMI, however, the pathophysiology of scoliosis is more difficult to explain. Although scoliosis is less common in CMI, it is still reported to be present in some degree in about 20% of patients without and 60% of those with syringomyelia [74]. However, in a statistical analysis of a large pediatric population undergoing MRI, Strahle et al. [75] found that syringomyelia was independently associated with scoliosis, whereas CMI was not independently associated with scoliosis when controlling for age, sex, and syringomyelia in a multivariate analysis. Therefore, the authors stated that scoliosis should not necessarily be considered a symptom related to CMI in patients without syringomyelia.

1.8 Indication for treatment of CMI

Apart from conservative, i.e. observational strategy, there is no alternative to surgical treatment of CMI. Although subject to personal preferences, opinions, and experience, most authors seem to agree [76] on the following rules regarding indication criteria, based on the available knowledge of the natural history and outcomes in CMI:

- asymptomatic/oligosymptomatic patients with radiologically evident CMI (i.e. tonsillar ectopy of at least 5 mm), when encountered incidentally, should not be offered surgery, even if syringomyelia is present. The latter finding, however, may justify treatment in pediatric CMI cases, particularly if radiological progression is documented on serial MRI. CMI should also be treated in patients with scoliosis in whom syringomyelia is present.

- patients with non-specific or atypical symptoms, not clearly attributable to CMI, may be considered for surgery if the severity of the symptoms seriously compromises their quality of
life and if all other potential causes are excluded by thorough neurological and radiological examination. This applies particularly to atypical headache, dizziness, and neck pain.

- patients with MRI findings and a clinical history typical of CMI, with symptoms considerably affecting their quality of life, are generally good candidates for surgery, as favourable outcomes of surgery have been reported by most authors [77-87].

1.9 State-of-the-art in the treatment of CMI

CMI is undoubtedly a ‘surgical’ condition, as decompressive surgery is the most straightforward solution in symptomatic cases. However, it is most challenging for a neurosurgeon in clinical practice to select for surgery only those candidates in whom CMI is a primary cause of their symptoms. CMI is to a great extent a radiological diagnosis, based on typical MRI findings. Although computed tomography (CT) could also reveal CMI, it is reasonable to believe that CMI remained undiscovered in many patients in the pre-MRI era. Given the increasing availability of MRI in Western countries during last few decades, today’s problem is rather that of an ‘overdiagnosis’ of CMI in cases where even a significant tonsillar ectopy is revealed incidentally when investigating patients with unrelated conditions or symptoms. A proper clinical investigation and a critical review of MRI findings must therefore always precede the surgeon’s decision regarding surgical treatment. In particular, a patient with newly diagnosed CMI on MRI should be seen by a neurologist, in order to provide thorough differential diagnostic considerations and to exclude alternative causes of the symptoms. This applies particularly to headache and neck pain, the symptoms dominating in patients with CMI but also non-specifically presenting in many other clinical conditions.

In a newly diagnosed CMI patient, the clinician’s options comprise several strategies:

1.9.1 Conservative treatment

The rationale for observational strategy is based on data from the studies mentioned above (Chapter 1.5) showing that patients with asymptomatic or barely symptomatic CMI rarely progress clinically or radiologically. For the latter reason, it is also not necessary to repeat radiological studies in an asymptomatic patient.
1.9.2 Surgical treatment

1.9.2.1 Foramen magnum decompression (FMD)

FMD is considered the tentative and most straightforward surgical method of treating CMI. The rationale for FMD is based on the assumption that restoration of CSF pathways at the CCJ will lead to alleviation of symptoms. Some neurosurgeons describe the procedure as reconstruction of the cisterna magna, which indeed is the crucial goal of surgery. The term occipito-cervical decompression is also broadly used, although somewhat inaccurate, as it gives an impression of a more extensive surgery than what is actually necessary.

The first documented attempt at surgical decompression of hindbrain herniation was probably undertaken by the Dutch surgeon Cornelis Joachimus van Houweninge Graftdijk who in 1930 operated on a patient with myelomeningocele, hindbrain herniation, and rapid head growth. He removed a part of the occipital bone and posterior elements of the first two vertebrae. Although the patient died more than three months after surgery, the case was published in his thesis entitled ‘Over Hydrocephalus’ from 1932 (Fig. 8) [88].

Fig. 8 Left, a picture of Cornelis Joachimus Van Houweninge Graftdijk (1888–1956) who performed the first documented attempt at surgical decompression in a patient with hindbrain herniation. Right, a title page of his thesis in which he reported on the case. Reprinted from Mortazavi et al. [88] with permission obtained through Copyright Clearance Center’s RightsLink® (License Nr. 4035870290741).
Better known is the work of Penfield and Coburn, from 1938 [89], who performed a rather exploratory suboccipital craniectomy in a patient who turned out to have Chiari Type II malformation. McConnell and Parker [90] reported in the same year on posterior fossa decompression performed in five patients with CMI, two of them with successful outcomes. After the Second World War, Bucy and Lichtenstein, in 1945 [91], and Chorobski and Stepień, in 1948 [92], published their case reports on decompressive surgery in patients with CMI. In 1950, Gardner and Goodall [93] suggested surgical treatment of syringomyelia by decompressing the hindbrain and sealing off the hypothetical communication between the syrinx and the fourth ventricle (as briefly mentioned in Chapter 1.7.1). They performed this operation in 17 patients, out of whom 13 experienced improvement, three worsening of the condition, and one patient died. After these initial reports, FMD has become widely accepted as the tentative treatment for CMI.

Several variations of FMD in terms of the extent of the surgery have been described in the literature [94]. First, the suboccipital craniectomy may either be limited to just allowing anatomical restoration of the cisterna magna [82, 95-102], or may be performed more extensively [79, 103, 104], even uncovering the whole PCF [105, 106]. Most authors routinely perform laminectomy of the first cervical vertebra (C1) and in some cases also of C2. The latter step is problematic, as the spinous process of C2 is an important point of attachment to muscles contributing to functional stability of the CCJ. In our own practice, we prefer resection of the ectopic cerebellar tonsils in rare cases when their position should require laminectomy of C2. Second, some authors believe that bone decompression alone, sometimes even performed endoscopically [107, 108], provides a sufficient effect of surgery [109-111], while others advocate open durotomy without closure [97, 99] or duraplasty with patch-augmentation, which is a tentative method [83, 101, 104, 112, 113] associated with a lower risk of reoperation [114] and better results in some studies [115, 116] including two meta-analyses [117, 118]. In two other separate meta-analyses on this issue, however, patients with duraplasty had a significantly lower reoperation rate than those without, while rates of clinical and radiological improvements were similar [119, 120], although these findings only represent a class IIb/B evidence [121]. Another option is to incise only the external layer of the dura (i.e. its delamination), leaving the internal layer intact [86, 122-131], a method particularly effective in patients without syringomyelia. Third, some authors strongly recommend to leave the arachnoid intact to avoid both scarring and postoperative CSF leakage [79, 95, 99, 106, 132], while others routinely perform subarachnoid dissection of the tonsils and the foramen of Magendie [96, 133]. Finally,
resection or at least coagulation with shrinkage of both tonsils has been advocated by some authors in order to achieve optimal decompression [83, 102, 134-138], although the majority of surgeons do it only selectively and/or tailor the extent of surgery by using peroperative transdural ultrasonography [86, 98, 109, 125, 139-141].

In case of associated syringomyelia, some authors combine FMD with syringo-subarachnoid shunting [142], although it is well documented that in most cases syringomyelia will resolve even with FMD alone [64, 96, 100, 104, 106, 113, 116, 126, 133, 137, 143].

Based on all these data and our own experience, a standard method of performing FMD as practiced by the author of this thesis is as follows: With the patient in a park-bench position with the right side up and the head in a Mayfield clamp, the FM is approached by midline dissection between nuchal musculature and opened by a C1 laminectomy and a tailored suboccipital craniectomy that typically does not extend more than 1.5 cm above the level of the opisthion. The dura is opened in a Y-shaped type of incision and microsurgical subarachnoid dissection of the cerebellar tonsils is conducted. An inspection into the caudal part of the fourth ventricle allows reassurance that the foramen of Magendie and the central canal are not blocked by arachnoidal adhesions, in which case they are re-opened. The dura mater is then closed with a watertight closure using a triangle-shaped, artificial dura graft (Neuro-Patch®; Aesculap, B.Braun, Melsungen, Germany), which size is tailored to each individual patient, usually not exceeding 2.5 (width) × 3.5 × 3.5 cm (Fig. 9). The dural suture is then secured by fibrin sealant (Tisseel; Baxter Healthcare Corporation, Westlake Village, CA, USA) before closing the wound in anatomical layers.

**Fig. 9** Some of the crucial steps in performing FMD as practiced by the author: left, an exposure of the cerebellar tonsils (white asterisks) after durotomy; centre, an inspection into the fourth ventricle and the orifice of the central canal at the obex (black asterisk); right, duraplasty with artificial dura graft.
1.9.2.2 CSF diversional procedures

There is some controversy regarding the management of hydrocephalus associated with CMI. The common opinion among neurosurgeons is that by performing FMD, particularly with an inspection into the fourth ventricle in order to verify the patency of CSF outlets, the CSF flow will normalize and the hydrocephalus will resolve [144]. However, clinical experience warrants some caution when hydrocephalus is present in a patient with CMI. The safe method in such case is diversion of CSF by implantation of a ventricular shunt before FMD. As shunts pose a certain risk of related complications, several authors have recommended endoscopic third ventriculostomy as an alternative option with good results [145-148].

1.9.2.3 Craniocervical stabilization procedures

As mentioned above, Goel [27, 28] considered CMI to be primarily related to atlanto-axial instability and suggested that the surgical treatment should be directed toward atlanto-axial stabilization and segmental arthrodesis; he considered FMD not necessary and actually harmful in CMI. This strategy, however, has been widely criticized [149, 150], and it has been argued that occipito-cervical (i.e. not only atlanto-axial) stabilization is probably justified in a very small subset of complex CMI cases in which instability of the CCJ clearly contributes to compression of neural structures and related symptoms.

Menezes [151] also reported on 298 patients with CMI and associated CCJ anomalies (basilar invagination/impression) in whom he performed ventral decompression using the transoral or transpalatopharyngeal approach combined with FMD and complemented with occipito-cervical stabilization. In contrast to these somewhat extreme attitudes, Klekamp [69] stated that patients with CMI without basilar invagination or with invagination but without ventral compression can be managed by FMD alone, and that the majority of patients with ventral compression can be treated by posterior decompression (i.e. FMD) plus realignment and stabilization, reserving anterior decompression only for patients with profound, symptomatic compression of the brainstem.

1.9.2.4 Section of the filum terminale

Although somewhat controversial and still under debate, it is important to note the theory of occult tethered cord syndrome (‘tight filum terminale’) and the resulting traction of the spinal cord as a common etiology for syringomyelia, idiopathic scoliosis, and CMI [152]. Based on this theory, section of the filum terminale was proposed as a surgical alternative in these conditions and favourable results from a small CMI cohort were reported by Royo-Salvador et al. [153]. According to Milhorat et al. [154], the association of CMI with tethered cord
syndrome appears to be a unique clinical entity that is distinguished from generic CMI on the basis of an enlargement of the FM and normal PCFV (as mentioned in Chapter 1.3). There is, however, still no convincing evidence for such an association, and the current opinion is that the section of the filum terminale may be beneficial only in a small selected subgroup of patients with CMI [155].

1.10 Outcome after treatment for CMI

The overall long-term outcome after treatment of patients with CMI is considered favourable according to most authors. However, Greenberg et al. [156] pointed out a wide variation and inconsistency in the methods used to evaluate clinical outcomes in CMI in 74 publications dealing with the topic, thereby complicating efforts to analyse results across studies. Three different approaches could be found: a ‘gestalt’ impression of overall symptomatic improvement (45 articles), postoperative changes in specific signs or symptoms (20 articles), and results of various standardized assessment scales (22 articles), in which 11 general function measures were used, compared with six disease-specific tools, and only three papers using scales actually validated in patients with CMI. Moreover, only seven articles incorporated patient-response instruments when reporting outcomes and only 22 articles explicitly assessed quality of life. Own efforts have been made to obtain reliable tools for the evaluation of outcomes in pediatric CMI populations, such as the Chicago Chiari Outcome Scale [157] or the Chiari Health Index for Pediatrics [158].

1.11 Intracranial compliance in CMI

The limited space inside the skull is occupied by the brain, the CSF, and the blood volume present in intracranial vessels. All three parts are very dynamic: The volume of the brain may change with the varying intracerebral (intra/extracellular) water content, and the volumes of CSF and blood relentlessly change during each cardiac cycle.

The physiological ability to maintain the ICP within physiologically normal thresholds even with increasing volumes of intracranial contents is crucial. The intracranial pressure-volume reserve capacity is defined by the intracranial elastance (ICE), which may mathematically be expressed as the ratio between the changes in volume and pressure (dP/dV). Accordingly, ICE increases when even a minor change in volume leads to an inadequate increase in ICP.
Intracranial compliance (ICC), which is the mathematical inversion of ICE, becomes reduced in such a situation (Fig. 10).

**Fig. 10** A schematic figure showing an exponential relation between intracranial pressure and volume as first proposed by Marmarou et al. [169]. While the pressure-volume curve itself refers to static ICP, the pulsatile pressure is represented by the mean pressure amplitude (MWA, i.e. dP) of a single-pulse pressure wave (red frames) induced by the cardiac beat. As ICC refers to dV/dP, it is obvious that a reduction in ICC is reflected by an increase in MWA.

Measurements of ICE or ICC as indices of intracranial pressure-volume reserve capacity have been challenging in clinical setting, particularly because the diagnostic artificial increase of the intracranial volume in order to evaluate the response in ICP may be problematic in patients already suffering from intracranial hypertension. Several different approaches have been used to retrieve information about ICE/ICC: 1) invasive assessment of pressure-based pulsatility by either (a) infusion test techniques using short and small volume changes [159], or (b) an analysis of the ICP waveform (i.e. the pulsatile ICP) from ICP measurements [160-163], as described in detail in the next chapter (1.12), and 2) non-invasive derivation of indices of flow-based pulsatility from either (c) transcranial dopplerometry (TCD) [164] or lately (d) phase-contrast MRI [165]. However, as these methods assess different aspects of ICE/ICC, their results cannot always be considered equivalent [166].
In reality, ICE and ICC depend significantly on the elasticity of intracranial structures including the brain, vasculature, the dura, and the skull. ICE/ICC are naturally limited and may become challenged in different pathological conditions affecting the brain. Physiological thresholds for ICE are not well defined, while ICC has been referred to as reduced at <0.5 ml/mmHg [167, 168], i.e. when less than 0.5 ml of added volume causes a pressure increase of 1 mmHg. For this practical reason, in the following, we will also refer to ICC rather than to ICE.

Importantly, ICC represents only a part of the compliance provided by the entire space given by the sum of volumes of the cranial cavity and the spinal canal. Some evidence suggests that the spinal canal contributes to the compliance of the whole ‘system’ to a larger degree than the cranial cavity, accounting for approximately two thirds of it [170]. This particular fact may become very important in CMI, characterized in a typical case by ‘decoupling’ of the intracranial from the intraspinal CSF compartment due to ectopy of the cerebellar tonsils into the FM that then becomes obstructed. A traditional opinion is that ICC in CMI therefore becomes reduced and improves by FMD [171]. However, the evidence for such a mechanism is still scarce, although it has been nicely modelled with methods of computational fluid dynamics (CFD) [172].

The other components of the overall ICC are the brain tissue compliance (considered small) and the compliance of intracranial vessels. Stiffening of the arterial wall (e.g. due to atherosclerosis) may cause a reduction of vascular compliance, which itself may affect the cerebral pulsatility even without any significant changes in ICP. In contrast, the wall of the cerebral veins is highly compliant, and with normal anatomy of CSF pathways at the FM, the retrograde flow of venous blood into the CNS may be easily compensated. However, if the venous volume increases in the presence of obstruction at the level of the FM as in CMI, it will, according to the hypothesis proposed by Williams [22], cause a greater response in ICP than if CSF pathways were unobstructed (Fig. 11).
Fig. 11 Graph suggesting the relationship between intracranial or intraspinal CSF pressure and venous volume, with and without CMI. Due to craniospinal pressure dissociation in CMI, the pressure response to the influx of venous volume in one of the compartments may be enhanced by the obstruction at the level of the FM. Redrawn and cited from Williams [22].

1.12 Static and pulsatile ICP in CMI

As mentioned above, an indirect assessment of ICC, i.e. intracranial pulsatility, is theoretically possible by analysing the pulsatile ICP measured invasively.

The measurement and monitoring of ICP is an important part of the treatment and surveillance of patients with neurosurgical conditions. Most technological methods compute the mean ICP during short time windows of 5–15 seconds, which provides information about the static component of ICP, i.e. the simple pressure difference between the intracranial compartment and the atmospheric reference pressure. The pulsatile component, i.e. the single ICP wave as created by the cardiac beat, is thus not taken into account, which limits the value of ICP monitoring since pulsatile ICP indicates the state of ICC more reliably than static ICP [173]. It is known that pulsatile ICP increases with reduced ICC and that there is a linear relationship between static and pulsatile ICP, as far as the mean ICP is below 60 mmHg [174, 175]. Above this threshold, pulsatile ICP shows a steeper linear increase, while static ICP remains constant.

Information about the single ICP wave is difficult to retrieve from the ICP signal in a clinically useful way. Some authors have utilized spectral analysis with fast Fourier
transformation [160, 161, 176-179]. However, this method did not include a reliable algorithm for identification of the single ICP wave, and the resulting information depended very much on the quality of the ICP signal, which is affected by sudden variations in blood pressure and heart rate. Eide therefore presented a method for quantitative analysis of mean ICP levels by counting the number of ICP elevations during a standardized period of recording time [180-182]. As this methods still did not include an analysis of a single ICP wave, the same author later developed an algorithm for identifying a single ICP wave during 6-second time windows, with selection criteria assuring that only pressure waves induced by cardiac beat were processed into further analysis [183] (Fig. 12). The quality of the ICP recordings was determined as the percentage of 6-second time windows accepted for analysis, while other windows were rejected because of artefacts in the ICP signal. For such selected single ICP waves, the following parameters were calculated using dedicated software (Sensometrics Software, dPCom AS, Oslo, Norway): for the static ICP (a) the mean ICP (averaged ICP over the 6-s time window); for the pulsatile pressure (b) the mean ICP wave amplitude (MWA; averaged ICP pulse amplitude [dP] over the 6-s time window); (c) the mean ICP wave rise time (MWRT; averaged pulse rise time (dT) over the 6-s time window); and (d) the mean ICP wave rise time coefficient (MWRTC; averaged pulse rise time coefficient [dP/dT] over the 6-s time window).
The pulsatile ICP is tentatively considered elevated when the average mean ICP wave amplitude (MWA) is higher than 4 mmHg, combined with a MWA higher than 5 mmHg in more than 10% of the recording time [184]. With respect to ICC, observations from ventricular infusion testing [173] support the concept of reduced ICC (<0.5 ml/mmHg) when the MWA is higher than 4 mmHg.

The static intracranial pressure is defined as elevated when the mean ICP is higher than 15 mmHg. These thresholds are also respected in our studies presented in Papers I-V.
Pulsatile ICP as represented by the MWA has proved to be a better predictor of the state of ICC than static ICP in conditions such as intracranial bleeds [163], idiopathic normal pressure hydrocephalus [184], subarachnoid hemorrhage [185], idiopathic intracranial hypertension [186], as well as in children with treatment-responsive communicating or non-communicating hydrocephalus [187]. In fact, ICC may be reduced even despite normal static ICP [163, 184]. It is also important to remember that contrary to pulsatile ICP, the mean ICP as a parameter of static ICP is generally more prone to significant baseline pressure errors [188, 189], a fact that further questions its reliability in clinical practice.

Pulsatile ICP has still not been studied specifically in CMI, and neither has the pulsatile pressure gradient between the intracranial and the intraspinal CSF compartments. The latter is of crucial importance for our understanding of the pathophysiology of CMI, and particularly of syringomyelia, as mentioned above (Chapter 1.7.1). So far, only static ICP, not so well reflecting ICC, has been studied in this setting [61, 190].

However, pulsatile ICP does not simply reflect ICC, but is also dependent on vascular compliance as well as on the cerebral pressure-volume reserve capacity.

It is obvious that an assessment of the pulsatile ICP should optimally be performed non-invasively. However, this is very difficult to achieve in a clinically useful and reliable way. Experimental evidence of the correlation between invasively measured (static) ICP and the elastance index derived from MRI has been provided [165], allowing for MRI-based differentiation between normal or elevated ICP, as also demonstrated in patients with CMI [46, 191, 192] (Chapter 5.6.2 in the Discussion). Patterns of CSF flow at the CCJ and the upper cervical spine [193-199] have been investigated using phase-contrast MRI, and also studied by means of CFD in simulation studies [172, 197, 200-203], but no previous study has investigated the association between the CSF flow pressure gradient derived from phase-contrast MRI (MRI-dP) and pulsatile ICP measured invasively in patients with symptomatic CMI.

1.13 Idiopathic intracranial hypertension (IIH)

IIH is addressed in part of this thesis and must therefore be introduced by a few words. There has been a certain confusion regarding the nomenclature of this condition characterized by modified Dandy criteria [204-206], i.e. clinical signs of elevated ICP (particularly papilledema and transient visual obscurations, yet no neurological deficits except abducens nerve palsy), no radiological evidence of structural abnormalities in brain parenchyma or hydrocephalus, and an
elevated lumbar puncture opening pressure (>250 mm CSF in adults and >280 mm CSF in sedated and obese children). The terms ‘pseudotumor cerebri’, ‘benign intracranial hypertension’, and ‘idiopathic intracranial hypertension’ have widely been used in the medical literature. Furthermore, the issue of diagnostic errors resulting in overdiagnosis of IIH has recently been discussed [207]. The recently proposed classification [205] distinguishes between primary and secondary pseudotumor cerebri syndrome, where IIH is a subset of the former, having no underlying cause attributable to the finding of elevated ICP. This is also the definition of IIH as presented in patients included in studies referred to in this thesis.

The majority of IIH patients are obese young women [208-210], although children as well as older and non-obese adults of either sex can also be affected, particularly those who recently experienced weight gain [211]. The estimated incidence of IIH is about one to three new cases per 100,000 cases per year [209, 210, 212].

The specific radiological findings associated with IIH, although not conditional for the diagnosis [205], may be empty sella (turcica), flattening of the posterior aspect of the ocular globe, distension of the perioptic subarachnoid space with or without a tortuous course of the optic nerve, and stenosis/occlusion of the transverse venous sinus.

The treatment options include weight reduction, repeated lumbar tapping, and carbonic anhydrase inhibitors such as acetazolamide [212]. Although most patients with IIH exhibit a relatively benign, self-limiting course and never require any surgical treatment [204], surgical intervention must be considered in refractory cases. CSF diversion (shunt) has usually a good effect on symptoms [213], but optic nerve sheath fenestration has also been occasionally performed in ultimate cases threatened by vision loss [214].

Like CMI, IIH is a condition of unknown etiology and not fully understood pathophysiology [215, 216]. As overweight and female sex are clearly the most prominent characteristics of the patient population with IIH, any proposed pathophysiological theory must ultimately account for the dominating prevalence of IIH among young women [204].
2. AIMS OF THE THESIS

Despite seemingly well-established diagnostics and treatment for CMI, many questions regarding the etiology and pathophysiology of the condition remain unanswered. The main aim of this thesis was to explore the role of pulsatile ICP in patients with symptomatic CMI. Improved understanding of the pathophysiology may be beneficial for the choice of optimal treatment strategies, particularly in cases not responsive to standard treatment (FMD). For this purpose, the following questions will be addressed:

1) To which extent do patients with CMI present with elevated pulsatile ICP and how significant is the pulsatile pressure gradient between the intracranial and intraspinal CSF compartments? How do the pressure parameters relate to clinical and radiological findings? In case of abnormally elevated ICP parameters, particularly pulsatile ICP, in patients with symptomatic CMI, do these simply normalize after successful FMD, which is the tentative treatment for CMI? If not, does this suggest a more fundamental underlying change in ICC?

2) In order to determine a non-invasive measure for the assessment of pulsatile ICP and ICC in CMI, is there any significant association between pulsatile ICP as measured invasively and parameters that could be derived non-invasively from radiological CSF flow studies such as phase-contrast MRI?

3) Is CMI indeed primarily a ‘malformation’, i.e. a congenital condition that becomes symptomatic in some patients, or is it rather an anatomical epiphenomenon secondary to the state of chronically elevated pulsatile ICP/reduced ICC due to a more fundamental underlying pathology such as idiopathic intracranial hypertension (IIH)? Taken even further, could CMI and IIH in theory be two different consequences of the state of chronically reduced ICC where tonsillar ectopy and/or syringomyelia as seen in CMI are only secondary events?
3. Patients Material and Methods

All patients included in the studies presented in Papers I-V were investigated and treated at
the Department of Neurosurgery, Oslo University Hospital – Rikshospitalet, during the period
spanning from 2002 to 2015 as specified below. Only the study referred to in Paper I was
performed prospectively, all other studies were retrospective. The studies presented in Papers
III and IV included data also from some pediatric patients, while all other studies only contain
adult patient data.

As mentioned in the Introduction (Chapter 1.12), Professor Per Kristian Eide introduced a
new method for analysing ICP signal, with a particular focus on pulsatile ICP [183]. Patients
with CMI analysed in the studies presented here were identified in the department’s database
of diagnostic ICP measurements among patients with various conditions related to disturbed
CSF circulation. Radek Frič has been involved in the treatment of virtually all newly identified
patients with CMI after he joined the department’s faculty in 2005. From that time on,
diagnostic ICP measurements have become part of the preoperative work-up in nearly all
patients with symptomatic CMI treated at our department.

3.1 Ethical considerations

All studies were approved by the Oslo University Hospital, as specified in the attached
documents. Only the study presented in Paper I was performed prospectively. Here, patients were
offered participation; only those who agreed and gave their written informed consent were
enrolled. In this case, we therefore obtained approval from the Regional Committee for Medical
and Health Research Ethics (REK) of the Health Region South-East, Norway. For all
retrospective studies described in Papers II-V, the REK was informed in writing and had no
objections to the studies.

3.2 Simultaneous measurements of static and pulsatile pressure within intracranial and
intraspinal compartments (Paper I)

3.2.1 Patients

During the study period between May 2011 and December 2013, all newly diagnosed
patients with CMI referred for treatment were consecutively offered participation in this
prospective study.
3.2.2 Data acquisition

As described in detail in Paper I, all patients received the ICP sensor implanted under local anaesthesia through a cranial burr hole and 1-2 cm into the frontal brain parenchyma. In the same session, an intrathecal catheter was placed through a lumbar spinal puncture. Both the ICP sensor and the spinal catheter were calibrated in a standard manner and connected to the transducer. The simultaneous monitoring of intracranial and lumbar pressure continued overnight, typically lasting 16-24 hours (Fig. 13). Dedicated software was used for analysis of ICP recordings, as described in detail in Chapter 1.12 and Paper I.

Fig. 13 An example of simultaneous measurements of intracranial (above) and lumbar CSF (below) pressure. The blue/bright green curves show the static ICP/lumbar CSF pressure, while the pulsatile ICP/lumbar CSF pressure is represented by the dark green curves. Note the independence of pulsatile pressure from changes in static pressure due to postural changes, sleep, etc.

3.2.3 Radiological assessment

The extent of caudal ectopy of the cerebellar tonsils under the level of the foramen magnum was defined by the distance (in mm) of the caudal tonsillar tip on a line perpendicular to the line between the basion and the opisthion (i.e. the foramen magnum or McRae’s line) on sagittal MR images. Measurements of ventricular CSF volume (VV), total intracranial volume (ICV), as well as the volume of the posterior cranial fossa (PCFV) were performed from patients’ MRI scans using iPlan® volumetry software (Brainlab, Feldkirchen, Germany) with manually adjusted automatic delineation. From these, we calculated the ratio between VV and ICV (VV index) and between PCFV and ICV (PCFV index).
3.2.4 Definition of tentative abnormal pulsatile and static pressure

We tentatively defined abnormal pulsatile ICP as the average mean ICP wave amplitude (MWA) >4 mmHg, combined with a MWA ≥5 mmHg in more than 10% of the recording time. An average MWA of 4-5 mmHg was considered borderline. Abnormal static ICP was defined as mean ICP >15 mmHg and borderline as mean ICP of 10-15 mmHg. We did not define thresholds for abnormal static and pulsatile pressure in the lumbar compartment, i.e. the lumbar pressure (LP).

We tentatively defined abnormal pulsatile pressure gradients as MWA_{ICP} − MWA_{LP} ≥2 mmHg, based on the previous finding that the lumbar CSF pulse pressure amplitudes are about 2 mmHg below the intracranial pulse pressure amplitudes, a fact that reflects differences in compliance between the lumbar CSF and intracranial compartments [217]. We did not define thresholds for abnormal static pressure gradients.

3.2.5 Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS™) software (version 20.0 for Windows; SPSS, Chicago, IL, USA). The correlation between MWA and pulsatile pressure gradient (MWA_{ICP} - MWA_{LP}), and the correlation between mean ICP and the static pressure gradient (mean ICP − mean LP) were expressed by Pearson correlation coefficient values (R). Statistical significance was accepted at the 0.05 level.

3.3 CSF pressure gradient across the CCJ derived from phase-contrast MRI (Paper II)

3.3.1 Patients

From the department’s database of diagnostic ICP measurements, we retrospectively identified those performed in patients diagnosed with CMI during the period from 2002 to 2015. From these patients, we selected those in whom quantitative 3-Tesla phase-contrast MRI measurements of CSF flow at the CCJ were performed as part of a diagnostic work-up and could be used for further analysis.

As a control, we performed phase-contrast 3-Tesla MRI scans in four healthy volunteers, without any history of neurological complaints.
3.3.2 Data acquisition

The method of pixel transformation and aliasing filter, CSF velocity and pressure gradient computations from the phase-contrast MRI, as well as an assessment of the synchronous bidirectional flow and a comparison of the CSF flow in the anterior versus the posterior subarachnoid space is described in detail in Paper II. The method of measurement and analysis of ICP in patients with CMI was the same as described in Paper I.

3.3.3 Radiological assessment

The MRI acquisition protocol is described in detail in Paper II, where we also calculated VV, ICV, and PCFV following the same method as in Paper I. In addition, we determined the degree of ‘crowding’ at the level of the foramen magnum by manual measurement of the area of free CSF space in an axial MRI section through the foramen magnum using the planimetric tool of the radiological picture archiving and communication system (PACS) (IDS7®, Sectra AB, Linkoping, Sweden). For the phase-contrast MRI, the CSF space was manually delineated with a region-of-interest (ROI) using nordicICE® (NordicNeuroLab AS, Bergen, Norway).

3.3.4 Definition of tentative abnormal pulsatile and static pressure

Thresholds for abnormally elevated pulsatile and static ICP were the same as mentioned in Chapter 3.2.4.

3.3.5 Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS™) software (version 22.0 for Windows; IBM Corporation, Armonk, NY, USA). Statistical significance of differences between groups was accepted at the 0.05 level.

3.4 Perioperative changes in ICP following FMD (Paper III)

3.4.1 Patients

This retrospective study included all patients with CMI who underwent FMD with perioperative ICP monitoring during the period from 2006 to 2014. We excluded the patients who had been operated on with either FMD or cerebrospinal fluid (CSF) diversional procedures
previously. It is important to stress that the included patients were those with moderately elevated or borderline ICP parameters on preoperative measurements. The reason for perioperative monitoring of ICP was the clinical concern whether or not elevated ICP parameters would normalize after FMD. Patients with severely pathological ICP parameters on preoperative ICP measurements are usually treated primarily by CSF diversion at our institution.

3.4.2 Data acquisition
The patients’ clinical records, radiological images, and intracranial pressure scores were reviewed retrospectively. FMD including duraplasty was performed by the same surgeon (Frič) in all patients using a standard approach as described in the Introduction (Chapter 1.9.2.1).

Some of the patients underwent diagnostic overnight ICP measurements a few weeks before FMD; in those patients, we placed a new intracranial pressure sensor in the same session immediately after FMD, through a cranial burr hole in front of the coronal suture and 1–2 cm into the brain parenchyma. In the patients undergoing FMD immediately after completed diagnostic overnight ICP measurements, we simply kept the ICP sensor in place for perioperative monitoring. The ICP recordings were analysed as described in Chapter 1.12.

3.4.3 Definition of tentative abnormal pulsatile and static pressure
Thresholds for abnormally elevated pulsatile and static ICP were the same as mentioned in chapter 3.2.4.

3.4.4 Statistical analysis
All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS™) software (version 22.0 for Windows; SPSS, Chicago, IL, USA). Differences between groups for repeated measures were analysed using linear mixed models with a random intercept. Statistical significance was accepted at the 0.05 level.
3.5 A comparison of clinical, radiological, and ICP findings in CMI and IIH (Paper IV)

3.5.1 Patients

For this study, we retrospectively identified patients diagnosed with either CMI or IIH from the department’s prospective database of diagnostic ICP measurements performed in patients with various conditions related to disturbed CSF circulation during the period from 2002 to 2014. We excluded all patients in whom ICP recordings had been performed after a previous attempt at surgical treatment. The CMI and IIH cohorts were compared with a reference (REF) group consisting of subjects who had undergone overnight diagnostic ICP measurements for suspected idiopathic normal-pressure hydrocephalus (iNPH) or chronic daily headache (CDH). The rationale for ICP measurements in this latter group was to rule out IIH without papilledema. None of the patients in the REF group had undergone relevant surgical treatment, and their ICP scores were considered to be within normal thresholds.

3.5.2 Data acquisition

From the patients’ electronic health records, we retrieved information regarding clinical symptoms or findings as noted at the outpatient clinic and/or at admission prior to the initial diagnostic ICP measurements. Treatment outcome was defined as a change in symptoms and/or findings at the latest follow-up (responders/non-responders). However, it must be stressed that neither details of clinical treatment nor evaluations of clinical outcomes were the primary focus of this particular study.

Diagnostic ICP measurements were performed in all patients in a standard manner as described in Papers I-III and in Chapter 1.12. For the purpose of this retrospective study, the ICP scores were reviewed.

3.5.3 Radiological assessment

We retrieved patients’ MRI scans as obtained at the time of initial investigation, i.e. prior to any treatment. As in Paper I, the position of the cerebellar tonsils caudal or cranial to the level of the FM was defined by the distance (in mm) to the caudal tonsillar tip on a line perpendicular to the foramen magnum line on midsagittal MRI. As patients with CMI or IIH do not usually have ventriculomegaly as defined by morphometric measures, we decided to measure relevant intracranial volumes to compare these cohorts. For this purpose and as in Papers I and II, we also used iPlan® volumetric software to measure VV, ICV, and PCFV.
3.5.4 Definition of tentative abnormal pulsatile and static pressure

Thresholds for abnormally elevated pulsatile and static ICP were the same as mentioned in chapter 3.2.4.

3.5.5 Statistical analysis

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS™) software (version 22.0 for Windows; SPSS, Chicago, IL, USA). Significance of differences in comparison between the two patient cohorts and the REF group were determined using one-way ANOVA with Bonferroni-corrected post hoc tests for continuous data and regression analysis for categorical data. The statistical significance of the differences between the cohorts was accepted at the 0.05 level.

3.6 Cardiovascular comorbidity in CMI and IIH (Paper V)

3.6.1 Patients

In this study, we retrospectively reviewed clinical data from the patients with CMI and IIH referred for treatment and managed at our department during the 12-year period from 2003 to 2014, with a particular focus on information about arterial hypertension (AH), angina pectoris (AP), myocardial infarction (MI), and diabetes mellitus (DM). All these patients underwent invasive measurements of ICP as part of their diagnostic work-up. We included only patients older than 20 years at the time of presentation.

The prevalence of AH, AP, MI, and DM in the general population was estimated from the Nord-Trøndelag Health Study 3 (HUNT3). In this population-based Norwegian public health study that has been running since 1984, the inhabitants of the county of Nord-Trøndelag, Norway, aged 20 years and older, were invited to participate in a general health survey that also included a questionnaire on cardiovascular diseases and DM. More than 50,000 individuals participated in the HUNT3 (2006–2008) survey.

3.6.2 Data acquisition

The history of cardiovascular disease (AH, AP, IM) and DM in patients with CMI and IIH was reported by the referring general practitioner or neurologist, and/or by the patient or his/her relatives at the time of admission to our department. The HUNT3 survey used a standardized
questionnaire where the occurrence of cardiovascular diseases and DM was self-reported by answering specific questions as described in detail in Paper V.

3.6.3 Prevalence of cardiovascular disease and diabetes versus pulsatile ICP

The patients with CMI and IIH included in the present study had undergone diagnostic overnight measurements and analysis of pulsatile ICP, as described in papers I-IV. We dichotomized patients according to thresholds for abnormal pulsatile ICP, i.e. mean MWA $>4$ mmHg on average during an overnight monitoring combined with a MWA $\geq 5$ mmHg during more than 10% of the recording time. The prevalence of cardiovascular disease and DM in patients with a MWA either below or above these thresholds was determined.

3.6.4 Statistical analysis

Statistical analyses were performed using the SPSS™ software version 22.0 (IBM Corporation, Armonk, NY, USA) and Stata version 13 (StataCorp LP, College Station, TX, USA). Descriptive statistics were mean (standard deviation) or number of patients (percentage). Differences between groups were assessed with Student’s t-tests or chi-squared tests for crosstabs if not otherwise stated. Odds ratios (OR) with 95% confidence intervals (95%CI) and p-values were calculated using logistic regression analysis. To take into account both the confounding and modifying effects of gender, a stratified analysis on gender was conducted. To adjust for any confounding effect by differences in age distribution between cases and controls, logistic regression with age as a continuous independent variable was also performed. Statistical significance was accepted at the 0.05 level.
4. RESULTS

4.1 Simultaneous measurements of static and pulsatile pressure within intracranial and intraspinal compartments (Paper I)

4.1.1 Patients
Between May 2011 and December 2013, 26 consecutive patients were prospectively enrolled in the study: 15 women and 11 men, median age 35 years (range 22–72 years).

4.1.2 Radiological findings
Syringomyelia was present in 12 out of 26 patients (46%). There was no significant association between the extent of tonsillar herniation and VV, ICV, or PCFV. Moreover, these volumes were not significantly different between patients with and without evidence of syringomyelia.

4.1.3 Clinical symptoms versus radiological findings
The only significant finding was the smaller PCFV in those five of the 26 patients with complains of nausea (200 ± 22 ml vs 176 ml ± 18 ml; p=0.03).

4.1.4 Pressure recordings
Pulsatile ICP (MWA) was elevated in 69.2% of patients: abnormal in 16 of 26 (61.5%) patients and borderline in another two of 26 (7.7%). However, static ICP (mean ICP) was not abnormal in any and borderline in only three out of 26 (11.5%) patients.

The comparison of pressure parameters from the cranial and lumbar compartments revealed a gradient for both pulsatile and static pressure. Only data from 24 of 26 patients could be analysed here, as the quality of signals from lumbar measurements was too poor in two patients. The median MWA gradient (hereafter ‘pulsatile pressure gradient’, MWA_{ICP} - MWA_{LP}) was 2.6 mmHg (range -0.04 to 6.9 mmHg) and it was abnormal (i.e. >2 mmHg) in 17 of 24 patients (71%). The median ICP gradient (hereafter ‘static pressure gradient’, mean ICP – mean LP) was -7.95 mmHg (range -27.7 to 3.5 mmHg). In other words, the static pressure tended to be higher in the lumbar compared to the intracranial compartment, while pulsatile pressure was typically higher intracranially. When comparing the pressure scores of overnight monitoring with differences (i.e. the gradient) between ICP and lumbar CSF pressure scores, we found a
highly significant positive correlation (p<0.001) between pulsatile pressure scores, but no significant correlation between static pressure scores.

4.1.5 Clinical symptoms versus pressure parameters
Neither pulsatile/static ICP parameters nor intracranial-lumbar pulsatile/static pressure gradients differed significantly between patients with or without symptoms/findings as specified and categorized in Paper I.

4.1.6 Radiological findings versus pressure parameters
The pulsatile pressure gradient between intracranial and lumbar compartments was significantly higher in those 12 of the 26 (46%) patients with syringomyelia than in those without (3.7 ± 2.0 mmHg vs 2.1 ± 1.3 mmHg; p=0.02), while the difference in static pressure gradients was not significantly different between the two patient groups. We found no significant statistical correlation between parameters of pulsatile/static pressure and extent of tonsillar ectopy, VV, ICV, and PCFV, or VV index and PCFV index, respectively.

4.2 CSF pressure gradient across the CCJ derived from phase-contrast MRI (Paper II)

4.2.1 Patients
Five patients (all female, median age 44 years) with CMI and four healthy subjects (one female and three male, median age 30 years) were included in the study.

4.2.2 Comparison of MRI-dP and CSF flow velocities in patients with CMI and healthy subjects
The phase-contrast MRI-derived CSF flow velocities at the level of the upper cervical spinal canal were comparable in patients with CMI and healthy subjects. We found no significant differences between the patients with CMI and healthy subjects regarding MRI-dP, CSF flow velocities, or CSF flow ratios between anterior versus posterior subarachnoid space. Bidirectional flow was observed in both patients with CMI as well as healthy subjects, more often in the former group; the difference was however not significant (p=0.19).
4.2.3 Invasive pulsatile ICP measurements and correlation with MRI-dP

The invasive ICP recording was performed in patients with CMI only. The pulsatile ICP (MWA) was elevated in four out of five patients, whilst static pressure (mean ICP) was normal in all cases. Both main parameters of pulsatile ICP (MWA, percentage of waves with a MWA ≥5 mmHg) correlated significantly with MRI-dP, while a similar correlation for the static ICP was not found (only for percentage of waves with mean ICP >15 mmHg, but not for mean ICP). Unlike pulsatile ICP, static ICP (mean ICP) did not correlate with the CSF flow and volume parameters derived from phase-contrast MRI.

4.2.4 Comparison of radiological findings

Patients with CMI differed significantly from healthy subjects by a significantly larger extent of caudal tonsillar ectopy (p=0.003), a smaller PCFV (p=0.049), a significantly bigger VV index (p=0.002) and smaller PCFV index (p=0.000), as well as a significantly smaller area of free CSF space at the level of the foramen magnum (p=0.000).

4.3 Perioperative changes of ICP following FMD (Paper III)

4.3.1 Patients

Eleven patients (nine adults and two children) with symptomatic CMI were included in the study (female/male ratio 9/2; median age 34, range 6–43 years). One patient was not available for the follow-up. In the rest of the group, all patients experienced improvement of their preoperative symptoms during a median follow-up period of 17.5 months (range 5–35 months). MRI conducted routinely several months after surgery showed sufficient decompression and restoration of CSF pathways at the level of the foramen magnum in all 10 patients. The syringomyelia was significantly reduced after FMD in one and unchanged in four out of five patients. Only two out of 10 (20%) patients available for a long-term follow-up required subsequent CSF diversion after FMD.

4.3.2 Pulsatile and static ICP after FMD

The preoperative diagnostic ICP measurements revealed normal average values of static ICP (mean ICP) and elevated pulsatile ICP (MWA) in all patients. During the first 3 days after surgery, parameters of both pulsatile and static ICP did not decrease. In fact, the percentage of mean ICP >15 mmHg increased during Days 2 and 3 after FMD. The MWA as well as the
percentage of MWA ≥5 mmHg remained unchanged compared with preoperative values. Mixed model analysis revealed no significant time-dependent differences in mean ICP (p = 0.90) or MWA (p = 0.85) during the observation period.

4.4 A comparison of clinical, radiological, and ICP findings in CMI and IIH (Paper IV)

4.4.1 Patients

Sixty-six patients with CMI (mean age 29.4 years, 95%CI 25.9-33.3) and 41 with IIH (mean age 27.1 years, 95%CI 22.6-31.4) were included in the study. The REF group consisted of 41 patients under 60 years of age (mean age 46.3 years, 95%CI 42.5-49.8) with suspected iNPH (30 patients) or CDH (11 patients), in whom elevated ICP was clinically suspected but not confirmed by ICP measurements. The two patient cohorts exhibited only slight differences in female predominance and body mass index (BMI).

4.4.2 Clinical symptoms and findings in the CMI and IIH cohorts

Of symptoms recorded in both groups, headache was the most dominant symptom with almost equal occurrence in the two groups (86.4 vs 85.4%), followed by nausea and/or vomiting, which affected approximately one third of the patients in each group. All of these symptoms were significantly more frequent than in the REF group. Dizziness and gait ataxia occurred significantly more often in patients with CMI, whereas visual symptoms/phenomena, diplopia and tinnitus were significantly more frequent in patients with IIH. Of symptoms specifically observed in only one of the patient cohorts, neck pain and sensory symptoms from the extremities dominated among patients with CMI, whereas papilledema was the most prominent finding specific to patients with IIH.

4.4.3 Tonsillar ectopy and cranial volume measures: MRI findings

The mean position of the cerebellar tonsils was 12.6 mm below the level of the foramen magnum in the CMI cohort and 1.7 mm above the foramen magnum in the IIH cohort. Notably, three out of 41 (7.3%) patients with IIH had tonsillar ectopy qualifying for a diagnosis of CMI (>5 mm). The position of the cerebellar tonsils was significantly lower in both the CMI and IIH cohorts than in the REF group. We found no differences in the cranial volume measurements (VV, ICV, PCFV, or the VV index as well as the PCFV index) between the CMI and IIH cohorts, while the VV and VV index were significantly higher in the REF group than in both
patient cohorts (as many REF patients presented with ventriculomegaly). Syringomyelia was observed in 48.4% of patients with CMI (data available for only 62 out of 66 patients); here, comparison with the IIH cohort and the REF group was not possible as only a few of the patients with IIH and the REF patients underwent spinal MRI examinations.

4.4.4 Pulsatile and static ICP scores in the CMI and IIH cohorts

The pulsatile ICP scores were comparable in the CMI and IIH cohorts and were significantly elevated in both cohorts as compared with the REF group. The static ICP (mean ICP) was significantly higher (p<0.001) in the IIH than in the CMI cohort and the REF group.

4.4.5 Association between ICP measures and MRI findings

There was a significant positive correlation between mean ICP and/or MWA (i.e. static and/or pulsatile ICP) and VV or VV index in the CMI cohort. In addition, there was a significant negative correlation between mean ICP and PCFV index, whereas this association was only close to significant for MWA. On the other hand, there was no significant correlation between the static or pulsatile ICP scores and ICV or PCFV, nor was there any significant association with the extent of tonsillar ectopy. No significant association between ICP parameters and MRI findings was observed in the IIH cohort. In the REF group, there was a significant positive correlation between the extent of tonsillar ectopy and MWA.

4.5 Cardiovascular comorbidity in CMI and IIH (Paper V)

4.5.1 Patients

Data from 48 CMI and 52 IIH cases, as well as from 42,461 controls participating in the HUNT3 survey were available. Specifically, the mean age in both patient cohorts was equal (48.7 years) and significantly lower than in the HUNT3 cohort. Both CMI and IIH cohorts were characterized by a significant female predominance.

4.5.2 CMI and IIH cohorts versus HUNT3

When CMI and IIH cohorts were taken together and compared to the HUNT3 cohort, the prevalence of DM was found to be slightly but significantly increased (p=0.048) in the patient cohorts, while the prevalence of AH was not significantly increased (p=0.19). The occurrence
of angina pectoris (AP) and myocardial infarction (MI) in the CMI and IIH cohorts was so low that it was not further studied.

Body mass index (BMI) was significantly different between groups (p<0.001). Gender- and age-adjusted analyses revealed a significantly increased BMI in both female and male patients with IIH (p<0.001 and p=0.018). Moreover, female CMI cases also had a higher BMI, with the difference approaching statistical significance (p=0.057).

4.5.3 Prevalence of AH and DM in patients with CMI and IIH

In a detailed analysis, the prevalence of AH was found to be significantly increased (p=0.015) in female IIH cases as compared to the general population. This was not the case in either male patients with IIH nor female/male CMI cases.

The prevalence of DM was significantly increased (p=0.045) in male CMI cases and highly significantly increased (p<0.0001) in female IIH cases, as compared to the general population.

4.5.4 Prevalence of AH and DM for different levels of pulsatile ICP

Comparing patients with MWA levels below/above the threshold for abnormality, the prevalence of AH was significantly increased (p=0.003) in IIH cases with an abnormal MWA (i.e. above the threshold), while the prevalence of DM was significantly increased (p<0.001) in IIH cases with a MWA below the threshold.
5. DISCUSSION

Inspired by our own clinical experience with patients with CMI, particularly with those not responding to standard treatment and exhibiting signs attributable to elevated ICP, we have in this thesis primarily aimed at exploring the role of the pulsatile ICP and pulsatile pressure gradient in the pathophysiology of CMI (Papers I and IV) and how these measures correlate with the pressure gradient derived non-invasively from the assessment of CSF flow by phase-contrast MRI (Paper II). Furthermore, we have investigated how the pulsatile and static ICP, whenever elevated, changed immediately following FMD (Paper III). As we hypothesized that the changes in pulsatile ICP seen in patients with CMI were of a more fundamental nature than just due to anatomical changes in PCF and FM, we have performed a systematic comparative study of clinical, radiological, and physiological features of patients with CMI and IIH (Paper IV). Given the findings indicating a close pathophysiological relationship between both conditions, we have also explored the prevalence of cardiovascular risk factors in patients with CMI and IIH (Paper V), in order to further support the hypothesis presented in this thesis.

In the studies included in this thesis, several important and up to now unanswered questions have been addressed. Our main motivation was to contribute to a better understanding of the still poorly explored pathophysiology and etiology of CMI, in order to improve treatment strategies, particularly in complex cases or those refractory to standard treatment.

5.1 Pulsatile ICP and ICC in CMI (Papers I and IV)

Paper I is the first and currently sole report exploring pulsatile ICP and the gradient in pulsatile pressure between the intracranial and spinal CSF compartments (i.e. above/below the site of supposed CSF blockage) in patients with CMI. The idea of simultaneous pressure measurements from both compartments is not new, but in studies of both Williams [61] and later Häckel et al. [190], the ‘cranio-spinal pressure dissociation’ was demonstrated in the same setting just by simple pressure measurements (intraventricular/intraparenchymal versus lumbar subarachnoid), without any attempt at assessment of pulsatile pressure.

It is important to keep in mind that ICC primarily refers to intracranial pressure-volume reserve capacity and is not equivalent to intracranial pulsatility as expressed by pulsatile ICP. As explained in the Introduction (chapter 1.12), however, pulsatile ICP has proved to be a reliable and far better indicator of ICC than static ICP.
Thus, we interpret our findings as indicative of reduced ICC (based on the fact that pulsatile ICP was pathologically elevated or borderline) in 69% of our 26 patients with CMI investigated prospectively (Paper I) and, correspondingly, in 74% of those 66 patients reviewed retrospectively (Paper IV). Furthermore, the cranio-spinal pulsatile pressure gradient was abnormal in 71% and significantly higher in patients with syringomyelia. Interestingly, Häckel et al. [190] also found a ‘pressure block’ (i.e. CSF flow obstruction) in eight out of nine patients with syringomyelia compared to three out of 16 of those without, but in their study only the static pressure was taken into account, while we could see such a difference only in the case of pulsatile pressure.

In our study, elevated pulsatile ICP correlated significantly with the pulsatile pressure gradient, while no similar correlation was found for static ICP (Fig. 3 in Paper I). To further underline the superior sensitivity of pulsatile compared to static ICP in detecting reduced ICC, it should be mentioned that in our prospective study (Paper I) static ICP was abnormal in none and borderline in only three out of 26 (11.5%) patients with CMI. In the retrospective review (Paper IV) of a larger group of patients with CMI, static ICP was abnormal in only five out of 66 (9.1%) and borderline in another 13 out of 66 (19.7%) of patients. These are dramatic differences, compared to the much higher percentage of patients with pathologically elevated pulsatile ICP as mentioned above.

For the sake of completeness, Poca et al. [218] also measured static ICP in 12 patients with CMI, although their study primarily investigated ICP changes after decompressive surgery. Static ICP in these patients were also measured at least 24 hours preoperatively; these values, however, are only reported as percentages of B-waves (Fig. 16) and therefore difficult to compare with other references. This is true as well for another study by Poca et al. [219] exploring posture-induced changes in ICP, among other conditions also in CMI, where only differences in ICP are reported but no absolute ICP values.

5.2 The role of pulsatile ICP in the pathophysiology and etiology of CMI

Our findings as mentioned above raise a crucial question: is pulsatile ICP elevated in such a significant proportion of patients with symptomatic CMI simply as a result of tonsillar ectopy and subsequent obliteration of CSF pathways in the FM?

Such a purely ‘anatomical’ theory might make sense considering that ‘decoupling’ of the intracranial and intraspinal CSF compartments would be expected to alter ICC [170]. However, two main arguments challenge this rather ‘mechanistic’ explanation:
First, we did not observe any association between values of the pulsatile ICP/cranio-spinal pulsatile pressure gradient and the real extent of caudal tonsillar ectopy in our data (Papers I and IV), as could be expected in such cases. In fact, many patients with severely elevated pulsatile ICP exhibited relatively modest tonsillar ectopy and vice versa. In addition, and in contrast to other similar studies [195, 196], we did not find any significant difference in CSF flow velocities at the CCJ, in the occurrence of bidirectional CSF flow, or in the pressure gradient derived non-invasively from phase-contrast MRI (MRI-dP) between patients with symptomatic CMI and healthy controls (Paper II), despite the evidence of a significant association between MRI-dP and invasively measured pulsatile ICP.

Second, neither static nor pulsatile ICP, when elevated in patients with CMI, seemed to normalize early after FMD (Paper III and [218]), which would be expected if compression of the CSF pathways at the level of the FM was the primary event. This observation is also supported by clinical experience from some of our patients with CMI who, despite no preoperative radiological signs of hydrocephalus, and even long time after successfully performed FMD, developed an acute/subacute hydrocephalus (Fig. 14a) or exhibited persistent clinical signs of elevated ICP (Fig. 14b). These events are difficult to explain from the traditional understanding of the pathophysiology of CMI, in which the issue of disturbed CSF circulation is probably underestimated: Only 7-10% of patients with CMI were reported to have an associated hydrocephalus (still commonly defined only as radiologically evident ventriculomegaly) [21, 71], which obviously contrasts with findings from our studies where ventricular CSF volume (VV) – typically very small in patients with CMI – did not correlate with either static and/or pulsatile ICP values (Papers I and IV), and where the pulsatile ICP was elevated in a significant proportion of cases. In fact, ventriculomegaly is not a mandatory finding for evidence of disturbed CSF circulation, as neither morphometric nor volumetric measurements of cerebral ventricles reflect the actual ICP [72, 73]. This fact has also been demonstrated in IIH (Paper IV and [186]) as well as in children with craniosynostosis [181].
Fig. 14 Two cases illustrating the issue of newly developed or persistently elevated ICP following FMD in patients with CMI

(a) A 36-year-old female patient with preoperatively normal static and pulsatile ICP. She developed an acute hydrocephalus (left) more than 2 weeks after successful FMD (right), requiring urgent CSF diversion by ventriculo-peritoneal shunting.

(b) A 31-year-old female patient with preoperatively moderately elevated pulsatile ICP. Operated on with FMD with ongoing perioperative ICP surveillance. She initially experienced a good clinical effect of the surgery, but started to suffer from headache and cognitive difficulties again approximately half a year later. Despite normal ventricle size (left) and a good radiological effect of FMD (right), new ICP measurements performed 18 months after surgery revealed still elevated pulsatile ICP, and a ventriculo-peritoneal shunt was therefore inserted.

Courtesy of the Dept. of Radiology, Oslo University Hospital – Rikshospitalet.
We therefore suggest another hypothesis for the mechanisms behind the finding of elevated pulsatile ICP in CMI, based on ‘physiological’ considerations. Here, we suspect that tonsillar ectopy (and subsequently syringomyelia) as seen in CMI – at least in a subset of patients – may be events that occur secondary to the state of chronically reduced ICC.

In our view, there may be several underlying mechanisms contributing to reduced ICC (Fig. 15). Obviously, some of these mechanisms relate to mesodermal changes (i.e. of the cranium) while others are of neuroectodermal origin (i.e. related to the brain).

**Fig. 15** A schematized proposal on mechanisms leading – probably in combination – to the development of CMI or IIH, presumably also allowing for an ‘overlap’ between these conditions (striped area).

5.2.1 Cranial constriction

The size and the volume of the PCF in CMI have been a subject of many studies (Tab. 2). The established opinion is that a developmentally small PCF is one of the characteristic features of CMI [21, 22]. However, confounding demographic factors such as age, sex, race, and BMI must be taken into account when assessing the significance of the PCFV, according to Roller et al. [53], who found no difference in PCFV (and ICV) when comparing adult patients with CMI to control subjects. In a family with documented occurrence of CMI in four generations, Tubbs et al. [220] could not find any difference in PCFV between those with CMI and age-matched controls, either.
Likewise, in our studies, we did not find any significant difference regarding PCFV in patients with CMI as compared to both patients with IIH and the reference group (Paper IV), and only a slight difference (p=0.049) in comparison to healthy controls (Paper II). In the latter case, however, the difference could be explained by comparison of very small groups where all patients were women while all but one of the healthy control subjects were men. Furthermore, PCFV did not correlate in any particular way with parameters of both static or pulsatile ICP (Papers I and IV).

**Tab. 2** Posterior cranial fossa volume (PCFV) in CMI as reported in the recent literature. Only studies specifically investigating PCFV are mentioned.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badie et al.[50]</td>
<td>20</td>
<td>adult</td>
<td>morphometry</td>
<td>ratio between PCF and supratentorial volumes smaller in CMI</td>
</tr>
<tr>
<td>Milhorat et al.[21]</td>
<td>50</td>
<td>adult</td>
<td>morphometry / volumetry (Cavalieri method)</td>
<td>PCFV and volume of CSF in PCF smaller in CMI</td>
</tr>
<tr>
<td>Sgouros et al.[52]</td>
<td>42</td>
<td>pediatric</td>
<td>volumetry (segmentation technique)</td>
<td>PCFV and PCFV index smaller only in children with syringomyelia</td>
</tr>
<tr>
<td>Trigylidas et al.[51]</td>
<td>61</td>
<td>pediatric</td>
<td>volumetry (Cavalieri method)</td>
<td>PCFV index smaller in CMI</td>
</tr>
<tr>
<td>Furtado et al.[48]</td>
<td>21</td>
<td>adult / pediatric</td>
<td>morphometry / volumetry (simple spheroidal formula)</td>
<td>AP diameter and width as well as PCFV and PCFV index smaller in CMI</td>
</tr>
<tr>
<td>Milhorat et al.[29]</td>
<td>388</td>
<td>adult</td>
<td>morphometry / volumetry (ImageJ, Cavalieri method)</td>
<td>size and volume of PCF and size/area of FM smaller in ‘classical’ CMI</td>
</tr>
<tr>
<td>Alperin et al. [46]</td>
<td>36</td>
<td>adult</td>
<td>morphometry / volumetry (automated atlas-based)</td>
<td>PCFV and PCFV index smaller in CMI</td>
</tr>
<tr>
<td>Roller et al. [53]</td>
<td>28</td>
<td>adult</td>
<td>morphometry / volumetry (manual segmentation)</td>
<td>no difference in PCFV and ICV (after controlling for demographics)</td>
</tr>
</tbody>
</table>

**5.2.2 Structural changes of brain parenchyma**

To our knowledge, there are no available studies focusing on structural changes of brain parenchyma specifically in CMI. However, given our findings indicating a close pathophysiological relation between CMI and IIH (Paper IV), one might speculate whether such changes may actually be present in CMI, as they recently were documented in IIH [221]: Here, histopathological alterations characterized by astrocyte hypertrophy, patchy astrogliosis (clustering of hypertrophic astrocytes), and a loss of distinct astrocyte domains were found in
patients with shunt-responsive IIH with abnormal pulsatile ICP. It has been suggested that the brain tissue expansion caused by astrogliosis may impair the intracranial pressure-volume reserve capacity, i.e. the ICC, and thus contribute to the pathophysiology of IIH by restricting the outflow of fluid from the cranium. Whether such a mechanism also applies in the case of CMI remains to be explored.

### 5.2.3 Stagnation of paravascular CSF transport

Findings from a histopathological study in patients with IIH mentioned above [221] provide additional significance. The described changes in brain parenchyma in patients with IIH were accompanied by significantly increased immunoreactivity to the water channel molecule aquaporin-4 (AQP4). The central pore of this transmembrane water channel protein allows the transport of water molecules across cell membranes. In the brain, AQP4 is expressed primarily in astroglia, particularly in membranes at the interface between the brain parenchyma and the blood or CSF, including astrocytic endfeet surrounding capillaries, the glia limitans and ependyma. The distribution of AQP4 predominantly at sites of fluid transport suggests a pivotal role of AQP4 in the transmembrane movement of fluid within the brain. As compared to rodents, in humans the polarization of AQP4 to astrocytic perivascular endfeet is less pronounced due to a higher expression of AQP4 in cell membranes towards neuropil [222]. This observation points to the important role of AQP4 in the human brain. It has been suggested that the hypertrophic astrocytes with their prominent vascular endfeet may reduce paravascular spaces, thus compromising the flow of both CSF and interstitial fluid as these drain along perivascular (Virchow-Robin) spaces. This paravascular pathway for transport of water and waste solutes has recently been denoted the glia-lymphatic (‘glymphatic’) pathway [223-225]. The resulting stagnation of fluids along arterioles and capillaries might alter pulsations, thus contributing to the altered intracranial pulsatility seen in patients with IIH. A potential role of disrupted paravascular flow in reduced ICC has also been suggested in patients with idiopathic normal pressure hydrocephalus (iNPH) [226].

Again, the extrapolation of this mechanism as documented in IIH to patients with CMI is still a speculation, although based on observed similarities between both conditions (Paper IV). So far, the expression of AQP4 has been investigated in an experimental model of syringomyelia in rats, without evidence of significant changes [227].
5.2.4 Structural changes of the vascular wall

In conditions characterized by disturbance of CSF circulation, such as iNPH and non-communicating hydrocephalus (nHC), the evidence of increased prevalence of cardiovascular disease has been provided [228, 229], suggesting a role of reduced vascular compliance in the pathophysiology of these forms of hydrocephalus, as the cerebrovascular system and CSF circulation are closely linked [230].

Since we demonstrated ICP parameters indicative of reduced ICC in a significant proportion of patients with CMI as well as IIH (Papers I and IV), we intended to assess the prevalence of selected cardiovascular risk factors and thus the potential significance of cardiovascular comorbidity also in patients with these two conditions. Our hypothesis was that changes in brain microvasculature induced by cardiovascular disease contribute in some way to the pathophysiology of both IIH and CMI, most probably via resulting changes in vascular compliance. An impact on cerebral microvasculature [231] and an association with reduced ICC [232] have been documented in diabetes mellitus (DM), but there is reason to believe that these effects also relate to arterial hypertension (AH) [233].

Indeed, despite the fact that patients with CMI and IIH typically present at a young age and that the prevalence of cardiovascular disease should therefore in principle be lower than in the general population, we found an increase in the prevalence of arterial hypertension (AH) in female IIH cases, and of diabetes mellitus (DM) in male CMI as well as female IIH cases, when comparing with data from the general population (Paper V).

An increased prevalence of AH and DM in typically overweight patients with IIH is perhaps not surprising, as obesity predisposes for both AH and DM. Giuseffi et al. [208] found also a significant association of AH with IIH, but not when controlling for obesity.

Importantly, the prevalence of AH was increased in those of our patients with IIH with pathologically elevated pulsatile ICP, an association previously observed also in patients with iNPH [228], despite an obviously significant difference in mean age in these two patient groups. The observation of reduced ICC as indicated by elevated pulsatile ICP in IIH (Paper IV and [186]) is traditionally believed to be associated with increased venous pressure secondary to obesity, seen in typical patients with IIH [208-210]. In this context, it needs to be mentioned that insufficient drainage of the central venous system was suggested as a main mechanism behind hydrocephalic conditions [22]. However, due to a demonstrated increase in perivascular AQP4 in IIH [221], the discussion returns back to the potential role of paravascular interstitial (glymphatic) cerebral microcirculation, as mentioned above (Chapter 5.2.3).
Interestingly, however, the prevalence of DM was significantly increased only in those patients with IIH with normal pulsatile ICP and in male patients with CMI. We do not have any obvious explanation for these particular findings, and further studies including larger cohorts of patients will be necessary to confirm and elucidate this association.

Taken together, our findings point to AH and DM as potential risk factors in the pathophysiology of CMI and IIH.

5.3 CMI and IIH: two different manifestations of the same underlying pathology? (Papers III, IV, and V)

As discussed above, the clinical, radiological, and ICP observations of persistently elevated pulsatile ICP even after successfully performed FMD (Paper III) suggest a more fundamental underlying change in ICC in patients with CMI than what can be attributed to tonsillar ectopy alone. Particularly, we often noticed similarities between CMI and IIH. By systematically comparing the clinical, radiological, and ICP data from our cohorts of patients with CMI and IIH (Paper IV) as well as by investigating the prevalence of cardiovascular risk factors in both conditions (Paper V), we aimed to explore to which extent these two conditions may share some common pathophysiological mechanisms or even possibly have a common etiological background. The idea might seem inappropriate, as CMI and IIH are traditionally considered to be two different conditions, and most clinicians would not see any possible link between them. However, an increasing body of evidence has suggested such a relation [234-239].

Specifically, the incidence of significant tonsillar ectopy (>5 mm under the level of the FM line) visible on MRI, which normally is about 0.8-0.9% among the general population [31, 32], has been found to be as high as 2.7% [239], 10.3% [240], and even up to 20.9% [241] in patients with IIH. In the latter study, where the incidence of significant tonsillar ectopy in controls was 2.3%, the IIH group also exhibited a significantly lower position of the cerebellar tonsils than age-matched controls. In our own study (Paper IV), we found ectopy of >5 mm in three of our 41 patients with IIH (7.3%). Moreover, the mean position of the cerebellar tonsils in the IIH cohort was also significantly lower than in our reference group (1.7 vs 5.6 mm above the FM line, p<0.01, Fig. 3 in Paper IV).

The increasing reflection of similarities between CMI and IIH in the literature [234] is mostly based on case reports [236-239, 242, 243], but also on larger case series. Bejjani et al. [244] successfully treated their six patients with CMI after failed FMD with CSF diversion and
speculated that initially misdiagnosed IIH could be one of the possible explanations. Fagan et al. [235] analysed 36 out of 192 (18.8%) patients with CMI undergoing FMD who did not show any clinical improvement. In 15 of these patients (i.e. 7.8% of the whole cohort), the authors diagnosed the ‘Chiari pseudotumor cerebri syndrome’, which they defined as the recurrence of Chiari-like symptoms after performed FMD, an absence of ventriculomegaly, elevated CSF pressure on lumbar puncture, and transient resolution of symptoms after lumbar CSF drainage. Notably, a very similar frequency (8.7%) of clinical and/or radiological signs of increased ICP (although not directly measured) after FMD was also reported by Zakaria et al. [245] who – in accordance with our own opinion – also suggested that these were all manifestations of fundamental underlying changes in CSF flow dynamics.

Most importantly, Paper IV provided evidence of very similarly elevated pulsatile ICP (indicative of reduced ICC) in both patient cohorts, without any significant difference in terms of pulsatile ICP parameters whatsoever, but both with a significantly elevated pulsatile ICP compared to the reference group (Table 4 and Fig. 4 in Paper IV). The fact that static ICP was significantly elevated only in the IIH cohort was not surprising, since in a previous similar study in patients with IIH, mean ICP was abnormal in 50% of patients [186], while it was abnormal in none (Paper I) or only 9.1% (Paper IV) of our patients with CMI, respectively. The discrepancy between CMI and IIH cohorts in terms of static ICP probably reflects the fact that patients with IIH often present with more dramatic symptoms of more sudden onset.

Elevated pulsatile ICP in patients with CMI and IIH was also reflected by a very similar frequency of headache, nausea/vomiting, as well as fatigue and cognitive difficulties in both cohorts, which are all symptoms that are in principle attributable to reduced ICC.

In search for a common pathophysiology behind CMI and IIH, Bejjani [234] suggested a mechanism of ‘craniocephalic disproportion’, in which disproportion between the skull and brain can lead to CMI (due to a small skull or PCF) and/or IIH (due to an ‘engorged’ brain) that in addition will occasionally lead to tonsillar ectopy. Our own findings do not fully support such a theory, particularly because we did not observe any differences in ICV or PCFV between the two patient cohorts. However, as schematized in Fig. 15, we agree that CMI and IIH may be two different manifestations of the same underlying pathology, which is probably the sum of the pathophysiological mechanisms discussed in Chapters 5.2.1 – 5.2.4. The proportional contribution of these mechanisms may differ in CMI and IIH, and it is still possible that cranial constriction is the crucial and dominant mechanism behind CMI. Finally, there also seem to be
a clinical and radiological ‘overlap’, i.e. a subset of patients in whom findings attributable to both CMI and IIH may be identified.

5.4 Is elevated pulsatile ICP really an issue in patients with CMI?

The vast majority of neurosurgeons do not conduct routine preoperative ICP measurements in their patients with CMI, and consider FMD as described in the Introduction (Chapter 1.9.2.1) the tentative treatment for symptomatic CMI cases. Indeed, even if we apply our own findings to all patients with CMI and assume that at least two thirds of all cases present with elevated pulsatile ICP and at least one tenth of them with elevated static ICP (papers I and IV), we cannot neglect the fact that most authors still report very good clinical results after FMD in the majority of patients [77, 78, 80, 82, 131, 246-250].

However, in cases with significantly elevated ICP, the concern arises how ICP will change after FMD. The common assumption among neurosurgeons is that even in cases of pathologically elevated ICP and/or development of radiologically evident hydrocephalus in CMI, the restoration of the CSF pathways at the CCJ provided by FMD will automatically - sooner or later - lead to the normalization of CSF circulation and the resolution of ICP elevation. Indeed, Williams [62] reported on two patients with cough headache due to CMI in whom the resolution of cranio-spinal pressure dissociation was documented by repeated pressure measurements 17 days and 1 week after FMD, respectively. The effect of FMD on CSF flow velocities and CSF pressure has also been simulated by computational fluid dynamics [251].

From our own clinical experience, we learned that patients with CMI with severely elevated static and/or pulsatile ICP should be offered a CSF diversional procedure (i.e. the ventriculo-peritoneal shunt) instead of or at least prior to FMD, in order to avoid complications resulting from persistently elevated ICP after FMD. To identify this subset of patients, we started in 2006 to routinely measure ICP in all newly diagnosed patients with CMI referred to FMD, as part of their preoperative work-up at the Dept. of Neurosurgery, Oslo University Hospital – Rikshospitalet.

The issue was at that time addressed only by Poca et al. [218] who demonstrated an increase of ICP immediately (1-7 days) after FMD, presented as percentage of Lundberg’s B-waves (which are defined as rhythmic ICP oscillations with sharp peaks occurring once every 1–2
minutes, in which the mean ICP rises in a crescendo manner from a variable baseline to a level 20–30 mmHg higher, and then falls abruptly) (Fig. 16).

**Fig. 16** ICP expressed as percentage of B-waves as measured by Poca et al. [218] before and after posterior fossa reconstruction (PFR, i.e. the authors’ variant of FMD), showing a significant increase after surgery in both early (1-3 days) and late (4–7 days) postoperative period (reprinted with permission obtained through Copyright Clearance Center’s Rightslink® (License Nr. 4035881221769).

In our own patient material, we could retrospectively identify 11 patients in whom we preoperatively measured elevated pulsatile ICP, but nevertheless decided for treatment with primary FMD and to avoid shunting, as the pressure parameters were not severely elevated (in which case they would primarily be offered shunting at our institution). For postoperative surveillance, however, we measured ICP the first few days after FMD, and the results are presented in Paper III. Here, we found also an increase in static ICP (presented as the percentage of mean ICP >15 mmHg) during Days 2 and 3 after FMD, while pulsatile ICP (MWA as well as the percentage of MWA ≥5 mmHg) remained unchanged compared to preoperative values, i.e. still elevated. This observation was similar to that reported by Poca et al. [218], despite an important difference in surgical technique compared to our study: These authors performed a
large decompression of PCF (‘PCF reconstruction’) with preservation of the arachnoid membrane, while we conducted a decompression limited to the foramen magnum, but including subarachnoid dissection of the cerebellar tonsils as described in the Introduction (Chapter 1.9.2.1). In the light of similar observations from both studies, we may therefore speculate that surgical technique and extent of decompressive surgery in CMI have probably little to say in terms of the effect on ICP immediately after surgery.

What may be an explanation for the phenomenon of persistent elevation of ICP following FMD? Postoperative CT scans of patients presented in the study of Poca et al. showed a small increase in the size of supratentorial ventricles in six out of 12 patients and effacement of the quadrigeminal cistern associated with a reduced size of the fourth ventricle in nine out of 12 patients [218]. The authors therefore believed that a transitory swelling of neural structures in the PCF secondary to reperfusion after FMD might explain the lack of normalization of ICP immediately after FMD.

We did not make a similar observation in our patients, although all of them had a routine CT control scan on the first day after FMD. Instead, and as discussed above (Chapter 5.3), we speculate that ICP observations after FMD actually reflect a more fundamental underlying change in ICC in patients with CMI. Although data on ICP changes following FMD are very scarce, there is reason to believe that many of the reported ‘complications’ after FMD are in fact events that are secondary to persistently elevated pulsatile and/or even static ICP, although not always recognized as such. This pertains particularly to the postoperative aggravation of headache, dizziness, nausea (all quite consistently encountered early after FMD), occasionally also the development of hydrocephalus, hygroma (i.e. the external hydrocephalus), submuscular CSF collection in the wound after FMD (often referred to as pseudomyelomeningocele), or even CSF leakage from the wound.

There are no available data regarding the expected time of ‘normalization’ of CSF circulation and the pulsatile ICP following restoration of CSF pathways by FMD. Among published reports on postoperative events supposedly related to persistently disturbed CSF circulation following FMD, Marshman et al. [252] mentioned two cases of acute hydrocephalus associated with infratentorial subdural hygromas occurring on Days 5 and 6 after FMD. Other published cases of subdural hygromas [253-255] and external hydrocephalus (i.e. subdural fluid collection and ventricular dilatation) [256, 257] all presented between one and two weeks after FMD. Generally, at least according to our clinical experience, only a minority of typical patients
with CMI recover significantly from their symptoms earlier than a few months after FMD, despite satisfactory postoperative results as seen on MRI.

5.5 Chiari malformation or syndrome?

Our findings and the pathophysiological considerations presented here obviously challenge a traditional understanding of the pathophysiological mechanisms behind CMI. In fact, the denotation of ectopic cerebellar tonsils, with or without syringomyelia, as ‘malformation’ might appear inappropriate and misleading, for the following reasons:

First, a malformation is usually defined as a structural defect due to abnormal embryonal or fetal development*. In other words, the definition includes the premise that it is a congenital condition with a more or less well-definable cause from an embryological point of view. However, specific hereditary factors relevant for CMI have been scarcely explored [24, 258], and definitive evidence of the genetic background of CMI is still lacking. In our present material, we have observed only one case of CMI in close relatives (siblings). Although cases of familial aggregation of CMI have been reported in the literature [21, 44, 220, 258-275], these appear rather occasional, considering the assumed prevalence of CMI in the general population of almost 1%, as revealed by MRI [31, 32]. To further illustrate this point, Professor Michel Zerah (Hôpital Necker, Paris) reported that during more than 22 years of practicing in antenatal clinics and while seeing two to three pregnant women every week, he observed only three (!) cases of (syndromic) CMI, and none of these was associated with syringomyelia. Furthermore, he operated on only five (!) cases of CMI with syringomyelia in children under the age of 1 year, out of 841 CMI cases (382 with syringomyelia) that he was involved in during his career as a pediatric neurosurgeon (personal/email communication, 16th EANS Congress, Athens, September 2016).

*Malformation: failure of proper or normal development; more specifically, a primary structural defect that results from a localized error of morphogenesis. Most malformations are considered to be a defect of a morphogenetic or developmental field that responds as a coordinated unit to embryonic interaction. Farlex Partner Medical Dictionary (2012). Retrieved from http://medical-dictionary.thefreedictionary.com/malformation.
Second, it seems that radiological findings typical of CMI, i.e. tonsillar ectopy with/without syringomyelia, may develop secondary to several different, mostly mutually independent, pathophysiological mechanisms, as listed by Milhorat et al. [29] (Fig. 4 in Chapter 1.3). This is not characteristic of malformations, which usually have one definable cause.

Many of these mechanisms (cranial constriction, idiopathic intracranial hypertension, hydrocephalus, craniosynostosis, or intracranial mass lesions) may be associated with elevated pulsatile ICP (Fig. 17). Indeed, that was what we found in a significant proportion of our unselected sample of patients with CMI, in whom, however, none of these mechanisms could be detected, except for a potential association with IIH in some patients, as discussed elsewhere (Chapter 5.3 and Paper IV).

**Fig. 17** Application of Milhorat’s list of possible pathophysiological mechanisms [29] behind tonsillar ectopy to a definition of Chiari syndrome. The red frame marks the mechanisms in which we suggest a significant role of reduced ICC. *Cranial constriction/overcrowding supposes an evidence of reduced PCFV.

One might ask whether it is justified to distinguish between primary and secondary CMI as proposed in Fig. 17. Such a division respects the original suggestion of Milhorat et al. [21, 29] who believed that evidence of an abnormally small PCF points to cranial constriction as the most likely cause of CMI, and denoted such cases as ‘classical’ (here, the primary). In cases of normal size/volume of the PCF, however, these authors meant that evidence of alternative mechanisms was required in order to explain the cause of tonsillar ectopy [29], which then may be described as secondary. In our view, as it has been presented here, we consider all CMI cases to occur secondary to other pathological events, including cranial constriction.

When limiting the discussion to the issue of pulsatile ICP as explored in our studies, the traditional model of tonsillar ectopy as a primary cause of both syringomyelia and disturbed CSF circulation/hydrocephalus is challenged by a new view, in which factors leading to reduced
ICC (discussed in Chapters 5.2.1 – 5.2.4) result subsequently in downward ectopy of the cerebellar tonsils into the FM, which in turn leads to the development of syringomyelia in some cases (Fig. 15).

Taken together, all these considerations support the opinion that a definition of significant caudal ectopy of the cerebellar tonsils as a malformation (i.e. CMI) needs to be revised. We propose that ectopy combined with evidence of one or more of the mechanisms listed in Figs. 4 and 17 shall be defined as Chiari syndrome** rather than malformation. Hopefully, this paradigm shift will force clinicians to focus more consciously on identifying the underlying cause of radiological findings seen in an individual patient presenting with CMI.

**Syndrome (originating from the Greek word σύνδρομον, meaning ‘running together’ or ‘concurrence’) is defined as ‘a group of signs and symptoms that occur together and characterize a particular abnormality or condition’ (retrieved from https://www.merriam-webster.com/dictionary/syndrome).

5.6 Clinical implications

It is important to stress that evaluations of different treatment strategies and/or of clinical outcomes after treatment for CMI are beyond the scope of this thesis. However, having explored the role of pulsatile ICP in the pathophysiology of CMI, the findings from our studies and the considerations presented here have an obvious potential impact on clinical management of patients with CMI.

5.6.1 Might specific symptoms indicate changes in ICP parameters? (Papers I and IV)

In our prospective study (Paper I), no obvious correlation between symptoms indicating altered intracranial pulsatility/reduced ICC (described as category A: headache, nausea, dizziness, visual disturbances, fatigue, cognitive deficits) and the pulsatile and/or static ICP parameters could be detected. On the other hand, our comparative study in patients with CMI and IIH (Paper IV) showed that headache was the dominating symptom in almost identical proportions of patients with CMI as well as IIH (86.4 vs 85.4%). This appears to be an interesting correlation, given that 74% of patients with CMI and 85% of patients with IIH in this study showed elevated pulsatile ICP. Other symptoms presumably attributable to reduced
ICC (nausea and/or vomiting, fatigue, cognitive deficits) also occurred equally frequently in both cohorts, without any significant statistical difference (Tab. 2 in Paper IV). All these symptoms that are mentioned here, whenever reported by a CMI patient, should therefore always lead to clinical suspicion of elevated pulsatile ICP and potential changes in ICC.

5.6.2 How may alterations of ICP parameters be verified in patients with CMI?

In our practice, we found it well justified to implement diagnostic ICP measurements with analyses of pulsatile ICP into a routine preoperative work-up of patients with symptomatic CMI, particularly of those presenting with symptoms and/or radiological findings indicative of reduced ICC. ICP measurements allow for an identification of the subset of patients with CMI in whom severely reduced ICC (as indicated by significantly elevated pulsatile ICP) requires surgical CSF diversion rather than or prior to FMD. For the same reason, ICP measurements are useful in patients with CMI clinically not responding to FMD, despite seemingly satisfying radiological results.

Despite their value for the choice of the optimal treatment strategy, however, ICP measurements are still an invasive and time-consuming method with some practical drawbacks. Given the demonstrated significant association between pulsatile ICP and the pulsatile pressure gradient as measured invasively (Paper I), we therefore explored whether pulsatile pressure parameters could be assessed by means of non-invasive modalities such as MRI. The non-invasive nature and the out-patient setting of such an assessment would also contribute to better decision-making regarding indications for surgery in cases of radiologically evident CMI with doubtful clinical significance.

The patterns of the CSF flow at the level of the CCJ [193-198] and the upper cervical spine [197, 199] have been studied both directly in phase-contrast MRI as well as in simulation studies by means of computational fluid dynamics [172, 197, 200-203, 276]. However, except for a previously reported effort on measuring ICE (i.e. the inverse of ICC) and ICP non-invasively using MRI [165], no previous study has specifically explored the association between the CSF flow patterns, specifically the pressure gradient derived from phase-contrast MRI (MRI-dP), and pulsatile ICP measured invasively in patients with symptomatic CMI.

By implementing a sophisticated mathematical pixel-by-pixel analysis of phase-contrast MRI as described in detail in Paper II, we could calculate CSF flow volumes and velocities as well as the pressure gradient in a reliable and precise way. Findings from our study are limited by a very small number of study objects and, as we stress in the paper, they should rather be
considered a preliminary observation that gives direction for further exploration. However, by comparing MRI-dP at the CCJ and pulsatile ICP (MWA) measured invasively, we could provide the first-ever evidence of a significant association between these two measures. Surprisingly, however, the MRI-dP gradient was close to identical in patients with CMI and healthy subjects, as were the CSF flow velocities at the CCJ and the occurrence of bidirectional flow. This was an unexpected finding, also because the CMI cases and controls in this particular study - in contrast to Paper IV – were different regarding intracranial volumes (PCFV, VV index, and PCFV index), most probably due to an unequal gender distribution in both groups. Here our results differed from those presented by Haughton et al. [195], who found CSF flow velocities through the FM measured using phase-contrast MRI in patients with CMI (n=8) not as uniform as in control volunteers (n=10), and detected a significantly higher peak systolic velocity in patients with CMI (p=0.01). Furthermore, we found bidirectional flow in healthy subjects as well, with an only insignificant difference compared to the CMI group, which is in contrast to findings of Quigley et al. [196] who reported bidirectional flow in six out of eight patients with CMI, but in none of the healthy volunteers (n=10). We explain the discrepancy between those and our observations by different reference levels for CSF flow measurements applied in phase-contrast MRI. In our study, we computed CSF flow parameters from an axial acquisition plane perpendicular to the upper cervical spinal canal at the level just below the lower tip of the cerebellar tonsils in patients with CMI and, similarly, between the level of C1 and C2 in healthy subjects. We realized that this did not necessarily represent the level where the CSF flow was most irregular in CMI. On the other hand, this tentative reference level was practically identical for both healthy subjects and patients with CMI (given the median ectopy of the cerebellar tonsils of 9 mm below the FM). In our view, the parameters of CSF flow then became methodologically easier to compare between patients and controls than in the studies of Haughton et al. [195] and Quigley et al. [196], where computations were made at the level of the FM in healthy volunteers and at the level of the lower tonsillar tip in patients with CMI, i.e. with a more significant anatomical distance between the two levels.

Alperin et al. provided experimental evidence of a correlation between invasively measured ICP and an MRI-derived elastance index by utilizing a different method [165]. In short, the elastance index was derived from the ratio of pressure-to-volume changes and the authors claimed that the sensitivity of their method allowed for a non-invasive differentiation between normal and elevated ICP. In a pilot study in patients with CMI, Alperin et al. [191] found significant changes in MRI-derived ICC and ICP in only one out of three patients with CMI.
after surgical decompression, but observed significant changes in the dynamics of ICV changes during the cardiac cycle in all three patients. From observations in a larger sample of patients with CMI (n=34) and healthy controls (n=17), the authors later reported significantly (20%) reduced ICC in patients with CMI compared to controls, but - in accordance with our own study - no statistically significant differences in systolic CSF velocity and flow [192]. Likewise, in a recent study by the same group, the MRI measure of ICP was one of the most significant parameters distinguishing the CMI from the control cohort [46].

In summary, further studies and a refinement of computation techniques will be necessary in order to better define reliable parameters and thresholds for MRI-derived CSF flow velocity, pressure, and pressure gradient in CMI.

5.7 Methodological limitations

Obviously, one major limitation of our studies is that the data are derived from a relatively small sample of patients. Although the referral area of the Dept. of Neurosurgery, Oslo University Hospital - Rikshospitalet covers a population of almost 3 million inhabitants, the number of patients with symptomatic CMI requiring treatment is relatively limited, adding up to approximately 10 – 15 patients annually.

Although we consider our patient sample as consecutive, only the study presented in Paper 1 was performed prospectively. Other limitations that need to be mentioned are as follows:

The first point pertains to our choice of method for volumetric measurements (VV, ICV, PCFV). Using volumetric software incorporated in the neuro-navigation tool (Papers I, II, and IV) was relatively simple, effective, and in our view fully appropriate. To our knowledge, however, such a method has not been validated against other methods used in the literature, at least not for assessing PCFV in patients with CMI, as discussed in detail in Paper I.

Furthermore, the investigation protocol for the study presented in Paper I should ideally have included phase-contrast MRI assessments in all patients; a comparison of invasively measured cranio-spinal pressure gradient with the pressure gradient measured non-invasively from phase-contrast MRI (MRI-dP) would be of particular value. Unfortunately, and despite our original intentions, this turned out to be difficult to achieve for practical reasons, mainly due to limited access to the phase-contrast MRI facility and the time-consuming method of computing MRI-dP. Thus, out of the whole CMI cohort (as analysed in Paper IV), there were only five patients who had phase-contrast MRI technically eligible for further analysis, as presented in Paper II.
The findings presented in Paper III are limited by the small sample of patients analysed retrospectively. In addition, perioperative ICP measurements were performed quite selectively in patients whose preoperative ICP scores were abnormal, but in whom we decided to perform primarily FMD and avoid CSF diversion.

Finally, the method of identifying cardiovascular risk factors in patients with CMI and IIH (Paper V) may potentially be questioned. Here, the data were gathered retrospectively and based mostly on the patients’ medical records (for CMI and IIH cohorts). This method might have underestimated the occurrence of cardiovascular risk factors in CMI/IIH. For the part of the data of the HUNT3 cohort, representing the general population, self-reporting of cardiovascular diseases, i.e. the questionnaire, represents another methodological limitation. This is the same kind of limitation affecting similar previous studies based on data from the HUNT3 survey [228, 229].
6. CONCLUSIONS

The main conclusions of Papers I-V included in this thesis may be summarized as follows:

1) More than two thirds of patients with symptomatic CMI seem to present with elevated pulsatile ICP, indicative of reduced ICC, which also correlates significantly with the pulsatile pressure gradient between the intracranial and intraspinal CSF compartments. This gradient is significantly higher in patients with syringomyelia. Pulsatile ICP relates neither to specific symptoms nor to radiological measures, such as the extent of tonsillar ectopy and intracranial volumes including PCFV. Furthermore, preoperatively elevated pulsatile ICP does not necessarily normalize immediately after FMD, a fact that may explain the persistence of symptoms after surgery in many patients and potentially justifies surgical CSF diversion prior to FMD in a subset of patients with CMI with severely elevated pulsatile ICP. How long it takes to restore normal ICC after FMD remains to be explored.

2) CSF flow velocities and volumes as well as the pressure gradient across the CCJ as derived non-invasively from phase-contrast MRI seem to be comparable in patients with CMI and healthy subjects. However, given the significant correlation between MRI-dP and pulsatile ICP measured invasively in patients with symptomatic CMI, phase-contrast MRI may potentially allow for an assessment of ICC to be done non-invasively. For that, however, further studies in larger samples of patients will be necessary.

3) The findings from this thesis challenge an established theory of CMI as a disease of ‘mesodermal’ origin, characterized primarily by distorted anatomy of PCF and FM, where syringomyelia and hydrocephalus, if present, are the secondary events. Instead, and well aware of the still insufficient evidence supporting this alternative theory, we suggest that reduced ICC may be a primary pathological event in a significant proportion of CMI cases, leading secondarily to ectopy of the cerebellar tonsils and the clinical picture typical of CMI. Due to different treatment strategies, the clinical identification of this subset of patients with CMI appears crucial and must be further refined. Based on current knowledge, our own findings, and pathophysiological considerations, we also advocate the use of the term ‘Chiari syndrome’ rather than ‘malformation’.
7. Future directions

The findings from the studies presented in this thesis offer several possible directions for further exploration:

- Although the assessment of particularly pulsatile ICP in the preoperative work-up of patients with CMI appears beneficial, the value of diagnostic ICP measurements for the choice of the optimal treatment strategy and, subsequently, for the long-term outcome following surgical treatment remains to be evaluated in a separate study. In cases where an indication for primary treatment with CSF diversion exists, the effect of endoscopic third ventriculostomy as an alternative to CSF shunting should ideally be investigated in a prospective, randomized study.

- In a continuing search for a reliable non-invasive modality for the assessment of pulsatile ICP in CMI, a larger prospective study with computation of MRI-dP and CSF flow velocity derived from phase-contrast MRI should be conducted. As soon as non-invasive assessments of ICP will be further refined and reliable CSF flow and pressure parameters better specified, based on phase-contrast MRI, it will also be easier to distinguish symptomatic from incidental cases.

- A potential link between still ‘idiopathic’ intracranial conditions presenting with disturbed CSF circulation and/or reduced ICC (including iNPH, CMI, and IIH) and systemic cardiovascular risk factors needs to be further explored.

- The use of the term Chiari syndrome instead of malformation (in case of Type I) should be established and promoted by further specifications of existing clinical, radiological, and particularly pathophysiological criteria, the latter being critical for the understanding of the condition. In order to further support the hypothesis that CMI is not actually a congenital condition, it would be beneficial to perform a study comparing the prevalence of CMI in infants with similar data from older children and young adults, as evaluated with MRI.
REFERENCES


140. Yeh DD, Koch B, Crone KR. Intraoperative ultrasonography used to determine the extent of surgery necessary during posterior fossa decompression in children with Chiari malformation Type I. *J Neurosurg* 2006;105(1 Suppl):26-32.


228. Eide PK, Pripp AH. Increased prevalence of cardiovascular disease in idiopathic normal pressure hydrocephalus patients compared to a population-based cohort from the HUNT3 survey. *Fluids Barriers CNS* 2014;11:19.


251. Linge SO, Mardal KA, Helgeland A, Heiss JD, Haughton V. Effect of craniovertebral decompression on CSF dynamics in Chiari malformation type I studied with computational fluid dynamics: Laboratory investigation. *J Neurosurg Spine* 2014;21(4):559-64.


