Adult outcome in pediatric hydrocephalus

Doctoral Thesis

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Abstract

Introduction: The early outlook of pediatric hydrocephalus has improved over the last decades; however, the adult outcome is still poorly documented. Therefore, we wanted to assess long-term outcome in children treated with permanent CSF diversion. Determing health status in these patients is important in order to organize the management of this population.

Methods: We retrospectively reviewed patients younger than 15 years surgically treated for intracranial hypertension in three different time periods. The two first papers served as basis for the evaluation of adult outcome among cases; including surgical morbidity, mortality, functional and social functioning, work participation, and perceived health. The third paper served as basis for comparing differences in patient characteristics, case-mix, surgical management, and served as background for short-term (2-year) outcome comparison.

Results: In the cohort treated in 1967-1970, ventriculography was the preferred imaging tool, ventriculoatrial shunt was the preferred procedure (94%), and neural tube defect (NTD) was the leading etiology (33%). The overall 2-year survival rate was 76% (non-tumor survival 84%). Almost half of the patients died during 42-45 years of follow-up (non-tumor mortality 39%), and 8% died of shunt related causes. Fifty-eight per cent underwent shunt revision during the first 2 years after initial shunt insertion, but annual shunt revision frequency decreased over time. Functional and social status varied greatly among survivors; the majority were socially independent (56%); almost half was permanently outside the labour marked due to chronic illness, and perceived health poorer compared with healthy controls.
In the cohort treated in 1985-1988, computorized tomography (CT) was the preferred imaging tool, ventriculoperitoneal shunt (VPS) was standard treatment (91%), and the most common causes were intracranial haemorrhage (19%), NTD (17%), and CNS neoplasm. Two-year survival rate was 91% (non-tumor survival 95%). The mortality rate after 20 years observation was 22% (non-tumor mortality 13%), and in total, 3% were due to shunt failure. At 2 years, 60% had at least one revision of their shunt. At follow up, the majority live comparable lives with those of their peers; 56% were employed in the open labour marked or were students; 23% had sheltered employment; and perceived health was slightly lower compared with healthy controls.
In the cohort treated in 2009-2013, magnetic resonance imaging (MRI) was the preferred diagnostic tool, and endoscopic third ventriculocisternostomy (ETV) had become an optional treatment method. As initial treatment, 73% underwent VPS, and 23% ETV. The most prevalent etiology was CNS neoplasm (31%). Four per cent were treated with VPS for Idiopathic Intracranial Hypertension (IIH). The 2-year survival was 92% (non-tumor survival 99%); while none of the deaths were shunt related.

Conclusions: During the last half century mortality rates have decreased substantially in HC children treated with permanent CSF diversion. The case-mix has, however, changed considerably. About 80% of these children can be expected to reach their early adult years. Accumulated mortality increases during young and middle aged adulthood.

The majority of children graduate from regular schools. HC has a substantial effect on later functioning in adult life, with regards to work participation and perceived health in spite of shunt treatment.

Approximately half of the patients need re-do surgery within 2 years after initial procedure, but the need for shunt revision may, however, occur at any time thereafter.

The vast majority of patients seem to be shunt dependent even after 40 years, and many patients require shunt revision during adulthood and interval between shunt revisions exceeding 10 years is not uncommon. Therefore, adults treated for hydrocephalus in childhood require life-long follow-up.

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ABBREVIATIONS

ADL	Activities of Daily Living
BI	Barthel Index
BMI	Body mass index
CI	Confidence Interval
CNS	Central Nervous system
CPC	Choroid plexus cauterization
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
ETV	Endoscopic Third Ventriculocisternostomy
HC	Hydrocephalus
HRQOL	Health-related Quality of Life
ICP	Intracranial pressure
IIH	Idiopathic Intracranial Hypertension
IQ	Intelligence quotient
LP	Lumbar puncture
LPS	Lumbo peritoneal shunt
MCS	Mental Component Summary
MMC	Myelomeningocele
MRI	Magnetic Resonance Imaging
MRV	Magnetic resonance venography
NTD	Neural tube defects
ONSF	Optic nerve sheet fenestration
PCS	Physical Component Summary
PEG	Pneumoencephalography
PTC	Pseudotumor cerebri
PTCS	Pseudotumor cerebri Syndrom
QOL	Quality of life
RCT	Randomized Controlled Trials
SAS	Subarachnoid space
SF-36	36-Item Short Form Health Survey
VA	Ventriculo atrial
VCS	Ventriculocisterno stomy
VGR	Ventriculography
VP	Ventriculo peritoneal
VPS	Ventriculo peritoneal shunt

LIST OF ORIGINAL PAPERS

1. Pediatric hydrocephalus: 40-year outcomes in 128 hydrocephalic patients treated with shunts during childhood. Assessment of surgical outcome, work participation, and health-related quality of life

2. Twenty-year outcome in young adults with childhood hydrocephalus; assessment of surgical outcome, work participation, and health-related quality of life

3. Cerebrospinal fluid (CSF) shunting and ventriculocisternostomy (ETV) in 400 pediatric patients. Shifts in understanding, diagnostics, case-mix and surgical management during half a century

4. Persistent shunt dependency and very late shunt failure in a 3 years old boy with Idiopathic Intracranial Hypertension

1. Introduction

Hydrocephalus (HC) is a condition characterized by the accumulation of abnormally large amounts of intracranial cerebrospinal fluid (CSF), often resulting in abnormally large cerebral ventricles, and typically associated with increased intracranial pressure (ICP). The etiological spectrum is broad, and includes diverse types of diseases, disorders and congenital malformations.
As HC has a heterogeneous etiology and complex pathogenesis, much controversy surrounds its exact definition. Moreover, albeit HC is one of the most common indications for neurosurgery, its standard of care treatment is even today haunted by a significant risk of failures and complications.

Recognized already by physicians in ancient times, one first description of HC is ascribed to Hippocrates (466-377 BC): fluid accumulation in the brain itself. Hippocrates also pointed out associated symptoms and signs which we today identify as signaling increased intracranial pressure (ICP): headache, diplopia, impaired visual function, nausea, and vomiting. The Renaissance anatomist, physician and (neuro!)surgeon Andreas Vesalius (1514-1564) recognized HC as cerebral spinal fluid (CSF) accumulated within the ventricular system, dilating the ventricles and, in small children, enlarging the head [1].
In an attempt to be as inclusive as possible, Anthony Raimondi in 1992 interpreted “hydrocephalus” or, rather translated the Greek term literally. He hence proposed a broad and unifying definition which also includes forms of brain edema, "Pathological increases in intracranial CSF volume, independent of … (intracranial) …. pressure" [1].
Oi and di Rocco defined HC as “…not one unique disease entity, but a pathophysiological condition of disturbed dynamics of CSF with or without underlying disease” [2, 3].
According to Harold L. Rekate, HC is characterized as “...an active distension of the ventricular system of the brain related to inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation" [4]. This definition accentuates HC as **a dynamic** condition which presupposes enlargement of the brain ventricles (ventriculomegaly). For Rekate, absence of dilated ventricles furthermore excludes from the spectrum of HC conditions such as pseudotumor cerebri (aka idiopathic intracranial hypertension), and non-progressive ventricular enlargement of brain atrophies or malformations.

Given the diversity and complexity appearing from the bundle of proposed definitions reviewed above, an in-depth clinical study on hydrocephalus would entail favoring one definition over the others. To minimize the risk of misinterpretation, while realizing that the present work basically concerns neurosurgical management, The Authors have preferred “CSF diversion”, i.e. the surgical treatment modality, as the overarching theme of this present thesis.
The term “CSF diversion” denotes 1) surgically implanted prosthetic shunts, and 2) ventriculocisternostomies, openings created between the brain ventricles and the subarachnoid space with tubes inserted to maintain patency, or without (ETV).

Even though CSF diversion is the most common procedure in the pediatric neurosurgeon`s repertoire, there has been a lack of long-term studies extending fifteen years of duration, i.e. beyond the so-called “pediatric age”, as if it concerned childhood only. Therefore, knowledge is scarce on adult outcome in individuals who were treated with CSF diversion during their early years.
At the time of writing it is 56 years since the first ventriculo atrial (VA) shunt was implanted in Norway, and more than 50 years since shunting became a routinized procedure.

Most workers within this field regularly meet parents of a child in need of CSF diversion surgery. In this challenging setting there are several requirements for this information being passed on to the parents. This involves defusing the acute phase, since obviously, the parents worries focus the weeks and months immediately ahead. There and then concerns on what awaits the child years and decades into the future may not come to the surface until later, e.g. questions on how the child will manage during the school-age, and not least as young and middle-aged adults, when the parents age and can no longer fulfill a role as informal carers. To this end, the present thesis should provide new elements of insight useful to patients and carers as well as to the daily practice of healthcare personnel.

The backbone of the present thesis is may be regarded as selected snap-shots accrued during 50 years of treating children in need of CSF diversion. The description of CSF diversion from the 1960s throughout shifts as to case-mix, patient management and surgical hardware until today may contribute to further improvement in this field, since to foster future improvement calls for knowing the long lines leading from the practice of the past to that of the present.

2. Review of the literature

2.1 Hydrocephalus (HC)

2.1.1 Hydrocephalus - a historical perspective

The natural history of untreated HC

In the first half of the 20th century, prior to any standardized treatment of HC, the condition was associated with substantial brain damage and excessive head growth. Left untreated the child most probable would develop a wide range of neurological deficits and disabilities, such as; mental and physical handicaps, visual impairment, and behavior problems.

A more detailed knowledge of the natural history of HC (i.e. untreated HC) was needed when surgical methods became available. With the introduction of ventriculo-venous shunts with the Spitz-Holter valve, outcome was reported as promising in more than 4/5 cases [5]. Little was known concerning longer-term outcome. The long-term prognosis in non-treated HC children therefore became an important piece of information to compare long-term outcome in operated cases and contribute to a better understanding of the factors influencing both outcome and indications for surgical therapy. In the early 1960s several studies were conducted to describe the natural history of HC, i.e. outcome in non-operated individuals [5-8].

A comprehensive study on outcome in 182 untreated HC children was conducted by Laurence and Coates in 1962 [7]. They found 49% of the patients being alive 1-21 years after their first admittance. Among survivors, 81 was considered having "arrested HC", while the condition was still progressive in 9. The arrest of HC, according to the authors, were likely when: "the head circumference remained the same for 3 months or more coinciding with noticeable improvement of general health; reduced tension of the fontanel; return of orbital axis towards normal combined with a commencement of physical and mental development". In this report they described "HC arrest" taking place between 9 months and 2.5 years with no significant difference among the etiological subgroups.
Among survivors 73% were educable, defined as intelligence quotient (IQ) above 50; 38% had IQ within the normal range (above 85); 14% had severe visual loss or blindness; and 48% were severely handicapped or incapacitated.
The authors calculated the chance of a hydrocephalic child, seen soon after birth, reaching adult life to be 20-23%, with a 10-year life expectancy of 27.5%. There were some important limitations of their study; data was based on the cases seen by only *one* surgeon, allegedly known to not favor surgical treatment; its retrospective structure; and the selectiveness of patients excluding neonatal deaths, among others. According to the authors, their material is representative of the disease in the community after the age of 3 months [7].

Nevertheless, with this study Laurence and Coates introduced the concept of life-expectancy in HC children.

At re-examination of the survivors 6 years later, the average IQ was similar to his primary results, but the distribution was different, with a greater number of patients showing gross retardation [9]. Their results revealed that 45% were severely handicapped or incapacitated; 45% had IQ within the normal range; 32% had normal schooling and employment; and 17% were classified as in a "vegetative existence". There was a close relationship between physical disability, intelligence quotient and later social functioning; the more intelligent and less handicapped cases tended to lead to more normal lives. They concluded that most patients with arrested HC maintained their progress and improved with age, and that the severely brain damaged patients did not improve. Moreover, estimates of the degree of brain damage resulting from the HC itself, or the original insult that led to the HC, could not be clearly elucidated in this series.
Comparable survival data was presented by Foltz and Shurtleff in 1963 [10] comparing 113 HC children with (65 cases) and without (48 cases) operation, calculating a 10-year survival expectancy of 22% in the non-operative group. Compared to Laurence and Coates, their results revealed inferior outcome regarding functional and mental status, thus revealing a lower percentage of competitive children in the group not operated upon. Duration of follow-up and non-similar selection criteria may have influenced their results. However, according to the authors, the predicted course for unoperated hydrocephalic children did show poor correlation to the actual outcome. Of 46 children; 21 were given a prediction of imminent death or a hopeless prognosis, of whom 8 were alive at follow-up five years later and 2 had an IQ of 75 or more; 13 were expected to have a good prognosis, 4 had died and the remaining survivors had an IQ of 75 or less; and 12 were considered to have "arrested HC" of whom 2 had died and 5 were non-competitive at follow-up.

Hadenius et al. analyzed 180 children in southeastern Sweden, diagnosed with HC in the time period 1944-1958 [5]. With an observational period between 2 to 16 years, 53% was dead at follow-up. The most common cause of death was continued progressive head growth. Among survivors, half had normal psychological development; almost half had normal motoric skills; and half of patients were integrated into normal schools. Except from enlarged head circumference, other typical clinical features were such as abnormal fat distribution, pedes valgus, ataxia, spastic diplegia, reduced vision, and strabismus. To describe these children's behavioral deviation with distinctively good verbal fluency, shallow intellect and poor social skills, the term; "The cocktail party syndrome" was introduced. As regard to prognostic factors, infants with pre- or perinatal HC often fared worse. Cortical thickness was not found to correlate with either intellectual or motoric outcome.

In Denmark, Jansen investigated an older HC cohort consisting of both non-surgically (75%) and surgically (25%) treated patients. Spina bifida cases were excluded. The 21-year mortality rate was 43% among 219 patients diagnosed with HC prior to the age of 5 [11]. In general, surgical treatment was offered to patients in whom death was considered imminent without intervention. With 78% of operated cases dying, analysis revealed a negligible effect on outcome. Among the survivors; 53% had attended normal schools; 76% coped independently in regard to more immediate physical needs; more than half (57%) were able to work; half were socio-economically independent; and 54% lived independently. Factors of prognostic importance to survival was asphyxia, a head circumference above the 97th percentile, upward gaze palsy, radiological diagnosis of HC, general seizures, and short lapse of time since diagnosis [12].

The history of surgical treatment of HC

The earliest written reports of HC, is thought to derive from Hippocrates (5th century B.C) [13]. However, the pathophysiology of the condition remained obscure and there were no rational methods of therapy developed until the beginning of the 20th century. Several authors have previously provided comprehensive reviews of the history of HC treatment [13-15]. Due to the limitation of this thesis, we have decided to restrict the historical background, starting with one of the first attempts to establish permanent drainage of CSF.
Current practice is familiar to most readers; with ventriculoperitoneal shunts (VPS) as one of the current preferable methods to treat HC. Therefore, it is interesting to note that the main principles were tried out more than hundred years ago. According to Harsh [16], the first attempt of permanent CSF diversion to the peritoneum was performed by Ferguson in 1898. By using a U-shaped silver wire passing from the lumbar subarachnoid space through a burr hole in the fifth lumbar vertebra into the peritoneum. He reported two cases, the first patient died shortly after the procedure, while the second died after 3 months of improvement. Hartwell, in 1910, was more successful, employing a silver wire as a ventriculoperitoneal wick [17]. This patient died from a brain tumor 2 years later without evidence of raised intracranial pressure, autopsy revealed a patent scarred tube of connective tissue connecting the ventricle and the peritoneum. However, VPS remained a rarity for some time and experience with them was mostly frustrating until some decades later.

The era 1910-1940
In 1913 Dandy and Blackfan first published their innovative research on the physiology of CSF circulation and the pathophysiology of HC, asserting that CSF is formed by the choroid plexus within the cerebral ventricles; that the only escape of fluid from lateral and third ventricles is through the aqueduct of Sylvius to the fourth ventricle; that CSF enters the subarachnoid space via the foramina of Luschka and Magendie; that the absorption of CSF back into the blood stream is from the subarachnoid spaces directly into the rich capillary bed within the subarachnoid spaces [18-20]. Some years previously Key and Retzius proposed that CSF was absorbed via the pacchionian granulations. Dandy and Blackfan then classified HC as either being; 1. obstructive (non-communicating), or 2. non-obstructive (communicating), establishing that an obstruction along the CSF pathways would cause non-communicating HC with the expansion of ventricles proximal to the lesion; and that the cause of communicating HC is impaired absorption of the CSF after reaching the subarachnoid space because of congenital mal development or obliteration caused by inflammation. For clinical use, and to distinguish the two types, Dandy developed a dye test to determine the nature of the HC syndrome, and thereby be able to direct surgical attack advised in either case [21-23]. For the treatment of non-communicating HC, Dandy devised third ventriculostomy, an operation by which a surgical opening is made through the floor of the third ventricle, thus establishing a CSF pathway from the third ventricle and the interpendicular subarachnoid cistern [21]. In Dandy`s series, 24 of 29 patients did well after this approach, 50 per cent of children younger than 1 year died; and the stoma tended to close due to adhesions. Communicating HC proved more challenging to control, and he advocated removal of the choroid plexus from both lateral ventricles and sometimes the fourth ventricle thereby reducing the formation of CSF. None of these treating principles involve other body cavities nor is in need of permanent insertion of foreign bodies into the patient. Dandy`s work inspired to further development within this field and contributed to alternative methods of treatment.

Between 1920 and 1940 several attempts were made to control intracranial pressure directly or indirectly by treating the cause of HC. But a satisfactory surgical treatment was still challenging. Treatment with the Torkildsen shunt, ventriculocisternostomy (VCS), was adapted by several neurosurgeons and various modifications of the original procedure were created [24-27]. Other types of intracranial shunts developed during the 1940s and 1950s including the following: the ventriculo-transcallosal ambient cistern shunt was performed by placing a small rubber tube through the posterior part of corpus callosum into the ambient cistern [13]; the third-to-fourth ventricle shunt accessed through suboccipital exposure placed a spiral of metal wire between the 4^{th} and 3^{rd} ventricle, thus facilitating CSF flow through the aqueduct of Sylvius [28]; the ventriculo-subdural shunt used by placing one end of a short plastic tube between one lateral ventricle and the other flanged edge of the tube between the dura and arachnoid membranes of the cerebral convexity [29]; and the ventriculo-mastoid shunt placed between the temporal horn of the lateral ventricle, transcortically and –durally, through the petrous bone into the mastoid air cells thereby establishing a CSF route into the posterior pharynx [30]. Nevertheless, all methods were discontinued due to relatively high operative mortality and insufficient clinical effect. Moreover, neither of these procedures was applicable in both communicating and non-communicating HC.

The era 1950-1970

The classification of HC introduced by Dandy and Blackfan (1914) is still in use. Novel advances from experimental and clinical research still contribute to information and give rice to other definitions and classifications of the condition.

The brilliant idea of establishing a CSF pathway from intracranial or intraspinal sites to other body-sites, were sporadically tried out in the first half century. In the 1950s, CSF shunts gained steadily in popularity as newer plastics became available and a variety of one-way valves appeared. In 1954, Ransohoff described the ventriculo-pleural shunts [31]. Six years later he reported 83 cases treated with this procedure with only 4 % operative mortality and 65% successful arrest of HC during a maximal follow-up period of 3 years [32]. Despite the initial success, the need for repeated surgery due to obstructions, both at the proximal and distal end of the rubber tube, were common. Besides, late complications, some potentially mortal, such as hydrothorax and broncho-ventricular fistulas were reported [33]. CSF drainage into the ureter was also attempted, described by Matson in 1951, who performed a nephrectomy and led a plastic tube from the lateral ventricle, subcutaneously to the perirenal area, subsequently placing the distal end of the tube into the open end of the ureter [34]. He modified this procedure designed for use in communicating HC cases some years later by introducing a lumboureteral shunt. Continuous loss of electrolytes and the adverse effect of having only one functional kidney made Matson abandon both procedures.

The examples of extracranial CSF absorption sites are only a selection by many. The gall bladder, cystic duct, Fallopian tube, ileum, the thoracic (lymphatic) duct and salivary duct were tried [16, 35-38]. Few cases and short length of follow-up made the evaluations deficient and the procedures were discontinued.

A breakthrough in the modern era concerning the treatment of hydrocephalic patients came in 1952. Nulsen and Spitz described a shunting procedure for the treatment of all patients with intracranial hypertension (both communicating and non-communicating cases) developing a shunt system with a valve that would allow CSF shunting from the lateral ventricle to the central veins or right atrium [39]. The valve consisted of two ball-valves permitting one-way CSF flow from the head towards the heart. In this report they also presented a child

operated with this procedure, still alive 2.5 years later without any signs of intracranial hypertension. The essential constituents allowing its success were the availability of improved biomaterial; silicone "rubber" or silicone elastomer, and a robust valve. Interestingly, the acceleration of its development was influenced by military activity during the World War II. To improve the performance of aircrafts and allowing a higher flight altitude a compound was needed to enhance the waterproofness to seal electrical systems. It soon became apparent that this material could have alternative applications.

According to Scarff, Nulsen presented his results [13] on 70 patients shunted due to HC. He reportede no operative mortality; approximately 30% mortality 1-4 years after initial surgery; and survival time in the remaining 70% was between 0.5 to 5 years. Comparable results were later presented by other neurosurgeons adapting this, or a slight modified procedure [40, 41]. Even today, more than 60 years later, the surgical technique and mechanical features remain basically unchanged.

Like other CSF shunts, these shunts had similar drawbacks. Obstructions within, or at the end sites of the tubes, were unavoidable causing repeated surgery to maintain its function. Additionally, serious complications with thrombosis of the jugular vein or of the superior vena cava, septicemia, and meningitis occurred, some even with fatal cardiopulmonary complications [42, 43]. Inevitably, applying shunts in infants and young children with rapid length growth problematized the positioning of the distal tube. Consequently, Nulsen recommended elective frequent (annual) revisions with removal of the distal shunt replacing it with a longer shunt to sustain the optimal distal positioning in the right atrium.

In 1955, Scott and colleagues described a ventriculo-peritoneal shunt for the use in both communicating and non-communicating hydrocephalus [44]. They placed a plastic tube with the proximal end within the occipital horn of the lateral ventricle through a trephine opening, beneath the scalp and further subcutaneously to a point beneath the subcostal region, and through the abdominal wall into the abdominal cavity. In the 32 infants treated, blockage of the system in the peritoneal cavity was frequent and most of the infants needed shunt revisions; operative mortality was 5%; and the mortality rate, with 1-4 years follow-up, was 38%. Matson et al, in 1956, reported 155 re-operations in 64 children treated with VPS during a follow-up of 1-2 years, concluding that the overall success was discouraging [45]. Their results were consistent with other contemporary studies [46, 47] demonstrating the repeated need for surgery due to obstructions, and high shunt failure rates. Due to the rather pessimistic interpretation of the initial results on VPS, the renaissance of its usage appeared several years later. The new shunt material, silicone tubing, and incorporation of valve elements, were essential contributing factors [48, 49].

The era 1970-2010

In this period HC was further classified in some additional manners compared to those categories already existing (age; etiology, clinically, patho-anatomical). In the 1970s computed tomography (CT), and later on magnetic resonance imaging (MRI) was introduced, and these imaging modalities soon after introduction became an indispensable tools in the diagnostics, treatment and follow-up of HC patients.

Studies comparing VAS and VPS conducted in the 1970s and 1980s revealed favor to the VPS [50-53]. Successively, the 1970s saw a gradual shift toward VPS systems, and a wide variety of valve and tube configurations proliferated.

In the 1980s and 1990s the endoscope again became on important instrument in HC treatment. The endoscopic third ventriculostomy era began around 1990 [54]. However, patient selection was still challenging. In children, the effects of age and etiology on outcome were particularly controversial. Some supported age as the most important [55, 56], others etiology [57, 58], while some claimed neither or both being important in terms of successful outcome [59, 60]. Some argued that even with high failure rate, ETV should be the modality chosen in most patients, regardless of age and etiology [61].
However, despite the availability of optional treatment methods, shunting remained the most common first line treatment in pediatric HC in most centers [62].

Furthermore, with the advent of prenatal ultrasonography, better understanding of fetal processes and advances in surgical technique, diagnosis of HC in utero has led to attempts with intrauterine fetal surgery. The rationale for this intervention is that early surgery can prevent progressive injury. From the early 1980s, fetal surgery was attempted in order to treat HC diagnosed in utero [63]. Procedures such as ventriculoamniotic shunts and serial cephalocenteses were attempted to curb the ventriculomegaly [64]. In 1986, the Fetal Surgery Registry reported the results of 41 fetal interventions for progressive HC [65]. They reported technical issues common in postnatal shunting, such as malfunction and dislodgement. According to the authors, repeated procedures addressing these issues unnecessarily increased morbidity for both mother and fetus without providing any established benefit. Due to lack of promising results and few properly designed prospective studies, there has been a delay in the application of fetal surgery in HC cases [63]. Some claim that newer shunt technology combined with ultrasound-guided percutaneous insertion may overcome earlier shortcomings [66]. A prototype has been constructed and has shown positive results undergoing *in vitro* testing [67].

CSF diversion surgery at the National Hospital (Rikshospitalet), Oslo

In the 1910s, at the surgical department at the National Hospital in Oslo, no permanent treatment option was available for children with progressive head enlargement. It is easy to imagine the frustration healthcare workers must have felt when faced with hydrocephalic infants. Thus, temporary solutions were carried out, both in infants and in older patients. By exploring operation protocols from this early period we have found some examples of treatment modalities tried out in pediatric cases.
In April 1911, Augusta, 9 months old, had her meningoencephalocele extirpated. The operation was successful, with minor CSF leak shortly postoperatively. The condition was simply treated with a tightly bandaged head, after drenching the bandage in an antiseptic boric acid solution. Most probable this method did not cure the patient, although information on outcome is not available at present.
In 1913, a eight months old hydrocephalic girl, was treated with ventricular puncture and CSF drainage. Clinical improvement was obvious after the relief of intracranial hypertension, though the effect was transient. Several repeated procedures were needed to preserve her functioning – occasionally at a ten day interval!!
Repeated ventricular punctures provided relief for a limited period of time, but experience indicated its uselessness due to frequent complications such as infection and bleeding.

However, in the 1920s, puncturing the lateral ventricle with subsequent injection of air (or contrast), became an important diagnostic procedure. Lumbar puncture with insufflation of air gave useful information about the ventricular system, but could be dangerous in patients with posterior fossa tumors. From 1930 ventriculography was in regular use in our hospital.

During the 1930s, some neurosurgical operations were performed in the Department of Surgery, Rikshospitalet, by Professor Ragnvald Ingebrigtsen [68]. In 1932, Ingebrigtsen tried to establish communication between cisterna magna and external jugular vein in a 5 year old girl, using a funnel-shaped silver cannula. When this treatment failed, he implanted a silver cannula from the lumbar dural sac into the peritoneal cavity. This first lumbo-peritoneal shunt worked for some weeks, but the girl died from disseminated medulloblastoma.

The availability of equipment and trained staff was limited during this early period. Surgery was mostly done using local anaesthesia, with the additional use of ether or chloroform in children.

In 1933, R. Ingebrigtsen (R.I, 1882-1975), treated a 26 year old male with a non-communicating HC due to a tumor obstructing the aqueduct of Sylvius [69]. He introduced a rubber tube through the aqueduct with the proximal end in the third ventricle, advancing through the fourth ventricle with the distal end in the cisterna magna. The patient improved clinically after the operation and went on to work for another 3 years, before he died, 30 years old, due to an ependymoma in the top of the brainstem. He tried this operative treatment also in a 14 year old girl. Initially her postoperative clinical condition was promising; however, she died within a few days with dramatic symptoms of a brain stem lesion.

In 1934, R.I performed a subtemporal decompression in a patient with brain tumor. After temporal relief of symptoms, ventriculography demonstrated right-sided ventriculomegaly. R.I tried to connect the lateral ventricle and the convexity subarachnoid space by inserting pieces of rubber-sheets to keep the canal open.

While Ingebrigtsen`s method involved re-establishment of CSFs natural pathways, his colleague Arne Torkildsen, some years later, introduced a procedure bypassing the occlusion. From 1935 Arne Torkildsen performed neurosurgical procedures in a small operating room established within the Department of Neurology [68]. A. Torkildsen (1899-1968) was a pioneering Norwegian neurosurgeon and became the first surgeon at The National Hospital devoted only to neurosurgery. He is best known for developing ventriculocisternostomy (VCS). Torkildsen performed his first VCS in 1937, in a patient with non-communicating HC due to tumor in the pineal region [68]. Later, this procedure became regarded as one of the first clinically successful procedure for shunting of CSF, and soon became accepted as a standard procedure for treating hydrocephalus in cases of obstruction of the aqueduct. The method is referred to as the Torkildsen shunt, Torkildsen operation, or Torkildsen tube [13, 70]. In this operation a rubber tube is introduced into a lateral ventricle through a small opening in the skull, beneath the scalp down to the occipital bone, and through an opening of the bone into the cisterna magna – thereby bypassing an occluded aqueduct of Sylvius. His doctoral thesis included 32 cases in which VCS was performed to treat HC secondary to tumors in the pineal region, tumors of the third ventricle, or occlusion of the aqueduct of Sylvius [68]. The results revealed operative mortality of 22%; and a 2 year survival of 56% [71, 72]. A follow-up study, 14-20 years after surgery, revealed that 6 of the original 32 patients (19%) remained alive, all in good condition [73]. Several neurosurgeons started to use this approach in the 1940s [24,

26, 27]. A summary of 136 operated cases was reported by Scarff in 1963 showing an overall reported mortality of 30% during an average follow-up of 2 years; and the initial arrest of HC in 58% [13].
In the 1940s and 1950s, other attempts to drain the 3rd ventricle were done, by establishing a communication between the frontal inferior section of the third ventricle and the subarachnoid space close to the infundibulum. As all these treatments were only suitable for patients with non-communicative HC no sufficient treatment was yet established to treat children with persistently head enlargement of the communicating type.
Drainage of CSF into the ureter was also attempted, using a rubber tube to create communication between the lateral ventricle or the lumbar subarachnoid space, and the free end of ureter after nephrectomy. One major advantage was its usage also in communicating HC. The valve was still not invented; hence the peristaltic movement in the ureter was believed to act as a natural mechanism to prevent excessive CSF drainage. During 1957/ 1958 this procedure was performed in 8 children in the first year of life. The patients, of course, required supplemental salt to make up for the loss in the urine. Seven died within two years after surgery, while 1 survived for 40 years (unpublished data). However, due to the high risk of complications and death, this procedure was also discontinued.
Since existing treatment options implied a noteworthy risk of complications, most patients were offered conservative observation. Among these, a female patient seen in our hospital in 1959, presenting with ventriculomegaly of the communicating type on ventriculography, were sent to her home environment with the agreement on no further action. More than 60 years later she is still alive, paraplegic, being able to speak and answer simple questions, with a mental stage of a child finding amusement by playing with plastic boxes. Impressively, her mother, being in her late 80s, having taken care of her since childhood, received the King`s Medal of Merit for her exemplary care she gave her daughter.

Before 1960 we did not have any standardized treatment for children with HC in Norway. As described earlier the Torkildsen shunt that had been in use some decades earlier was only effective if there was a blockage between the third and fourth ventricle.
In the 1960s, we gained access to a new method that could be implemented in **all** patients with hydrocephalus. The first VA-shunt implemented in 1961was in an adult patient. The same year this method was also applied to pediatric patients. Karl H. Hovind, was the first "pediatric" neurosurgeon in our department. He returned to Oslo in 1967 after two years training with D.D. Matson at Bent Brigham Hospital in Boston [68].
In cases where previously no treatment options existed, there was now surgery to offer the infants with excessive head growth. The available shunt treatment would obviously help some, while of course in the most serious cases, prognosis was uncertain. Nevertheless, a treatment strategy of "shunt and see" appeared a superior option, both to the surgeon and the parents of the child, than doing nothing. A shunting procedure was an attempt to alleviate symptoms in a patient group with an otherwise hopeless prognosis.
Most, but not all, shunted children in this era of 1960s and early 1970s, were followed with regular visits in our department with measurement of head circumference, and imaging to control the position of the radiopaque tip of the atrial catheter. In young children, with rapidly increasing distance between head and heart, elective elongation of the atrial catheter was common, mostly at a 1 to 2 year interval. In later childhood follow-up was less rigid, sometimes with mail correspondence from parent to surgeon containing clinical update on the child.

Contemporary understanding of HC, made many believe that HC in many cases were temporary, i.e. months to several years. "Arrested HC" was a frequently used expression to interpret a clinically stable shunted child who did not have any symptoms of intracranial hypertension nor had been in need for revision of the shunt in many years.

Improvement of neuroimaging techniques by the introduction of CT in The National Hospital of Oslo, Rikshospitalet, in 1977, enhanced and facilitated the HC treatment.

Until 1979, Pudenz VA shunts were almost exclusively used as a primary choice as well as in revisions. Lundar et al. demonstrated that among 450 children treated with VA shunt in our Department during the years 1965 to 1986, fatal complications related to the atrial catheter were seen in 15 patients [42]. Consequently, since 1980, VP shunts has been regarded as standard. Nevertheless, VA shunts have remained a treatment option, usually in cases with repeated distal failure in VP shunts.

We started using endoscopic third ventriculostomy (ETV) in the treatment of HC in 1993. At that time, there was no consensus as to selection criteria. In the years that followed, Helseth and co-workers demonstrated higher ETV success rate in patients > 6 months of age with HC caused by aqueductal stenosis or space-occupying lesions in the posterior fossa [74].

Permanent CSF diversion has also been done in children with Idiopathic Intracranial Hypertension (IIH) during the last decades. During an 8 year period in the 1980s, 2 out of 6 patients with shunt treatment due to IIH, were children [75]. Both were males, aged 3 and 5 years.

2.1.2 The epidemiology of hydrocephalus in children

Prevalence estimates for infantile HC depends both on the definition of HC, population studied, and in the geographical area in which the calculations are performed. A large, population-based investigation of idiopathic congenital HC in Denmark over a 30 year period was estimated by Munch et al. The authors included children within the first year of life without a known causative etiology, including Arnold Chiari and Dandy-Walker syndrome, excluding HC associated with spina bifida estimating a prevalence of 1.1 per 1000 infants [76]. The prevalence of infantile HC born during 1989-1998 in western Sweden was 0.82 per 1000 live births and included HC associated with myelomeningocele [77].

A probable greater prevalence of infant HC is estimated for Uganda and other developing countries in the African continent [78]. Warf [79] described a higher proportion of HC of infectious origin as one of the potential causes for the higher occurrence compared to high-income countries.

2.1.3 The pathophysiology of hydrocephalus

Cerebrospinal fluid (CSF) is mainly produced in the choroid plexus of the lateral, third, and fourth ventricles, and a minor part is derived from the extracellular space of the brain [80]. The CSF flows in a to-and-fro movement with a caudal-directed net flow through the aqueduct of Sylvius and foramina of Luschka and Magendie into the spinal subarachnoidal space (SAS) [81]. The pulsatile brain movements create a "mixing" of CSF in the fourth ventricle, basal cisterns, and upper spinal SAS [82, 83].

The arachnoid villi in the superior sagittal sinus have generally been thought to be the main site for CSF absorption in humans [84, 85]. However, lymphatic drainage pathways have been shown in animal studies to play an important role for CSF clearance [86, 87]. The existence of this pathway in humans remains unclear. Spinal CSF absorption through arachnoid granulations located along the nerve roots, morphologically similar to cranial villi, was suggested by Kido et al. [88], and CSF clearance from the spinal SAS has been demonstrated in sheep and cats [89, 90]. The extent and importance of the spinal absorption pathway in humans remain unclear. According to the CSF bulk flow theory, HC is caused by an imbalance between CSF formation and absorption, or a block at various locations in the major CSF pathway [91].
An alternative hydrodynamic model explains HC as a condition explained from disorder of intracranial pulsations [92, 93]. In this model, HC is caused by decreased intracranial compliance increasing the systolic pressure transmission into the brain parenchyma. Normally, the arterial systolic pressure waves entering the brain within the fixed skull, pressure changes are absorbed by venous capacitance vessels, subarachnoid spaces, and intraventricular pulsations transmitted by the choroid plexus. The intraventricular pulsations are then absorbed through the ventricular outlet foramina. In pathological conditions leading to HC, dysfunction of these pressure absorbers contributes to abnormally high pulsations amplitudes resulting in ventricular expansion [94].

2.1.4 Classification of pediatric hydrocephalus

Congenital (developmental) vs. acquired
In infants, when HC occurs as a complication of other conditions such as hemorrhage, neoplasm or infection, it is often called acquired. The term congenital HC is used when there is no obvious extrinsic cause to the condition. However, obstacles with bleeding or infection may present prenatally, and consequently cause "congenital" HC. Furthermore, some genetic conditions may not be present at birth but develop over time. Therefore, some authors prefer to differentiate between extrinsic (acquired) and intrinsic (congenital) forms of HC [95].

Non-communication vs. communication (obstructive vs. non-obstructive)
This binary classification has existed for over a century and still is in common use [3, 23]. The most classical condition associated with non-communicating HC is aqueduct stenosis.
The classical terminology concerning CSF dynamics may be confusing [2, 3]. According to the definition by Dandy, communication of the CSF pathway is between the lateral ventricle and the lumbar subarachnoid space, demonstrated by injection of dye into the lateral ventricle and detection by lumbar puncture. The term obstructive HC proposed by Russel [96], some decades later, was defined as a condition of disturbed CSF circulation due to a blockage at any region in the major CSF pathway including the ventricular system and the entire cistern/ subarachnoid space. The distinction between these concepts may be important in the discussion of method to treat HC (shunt vs. endoscopic third ventriculocisternostomy). Since blockage in the subarachnoid space in relation to the venous sinus is obstructive due to Russel's terminology, this condition is without interventricular block thereby classified as communicating according to Dandy's classification.

A new, more complex classification of HC, "Multi-categorical Hydrocephalus classification" (Mc HC) was proposed by Oi in 2011[2]. This classification includes ten categories (onset, cause, underlying lesion,

symptomatology, pathophysiology-CSF dynamics, pathophysiology-ICP dynamics, chronology, post-shunt, post-neuroendoscopic ventriculostomy, and others), each category divided into three to thirteen subtypes. A more practical clinical classification of non-tumoral HC, based on etiology and time of onset, was proposed by Mori et. al. in 1995[97]. They classified HC into two groups; Hydrocephalus seen in early life (fetal, infantile congenital, HC associated with encephalocele or myelomeningocele, posthemorrhagic, and postmeningtic), and HC seen in adults (HC following subarachnoid hemorrhage, idiopathic, and posttraumatic)

2.1.5 Clinical features in children with hydrocephalus

The two key determinants of clinical presentation of HC are age of onset and the rate of the rise in intracranial pressure. In infancy and early childhood prior to closure of the cranial sutures (usually between 1 and 2 years of age) progressive enlargement of the head is the most common manifestation of HC as the sutures have not united firmly [98]. Other typical signs are irritability, vomiting, drowsiness, and anorexia. As HC progress, further destruction of the cerebral cortex occurs, the child become listless, stops taking interest in the surroundings, and regression of earlier achieved milestones occurs. Clinical examination may reveal inappropriately increasing head circumference, frontal bossing, bulging and tense anterior fontanel, splayed cranial sutures, scalp vein distension, "Macewen's sign" with cracked pot sound by percussion, and excessive trans-illumination of the skull indicating abnormal collections of fluid [98]. Intermittent or continuous "sun-setting sign" with down-turning of the eyeballs appears when pressure on the superior quadrigeminal plate against the free edge of the tentorium causing supranuclear paresis. Other ocular disturbances include abducens nerve paresis, nystagmus, ptosis, strabismus and diminished pupillary light response. Papilledema is rare because rising tension is easily buffered by suture diastasis. A rarer feature is spastic paraparesis with increased tone in the limbs resulting from stretching and distortion of paraventricular corticospinal tracts. Depression of consciousness may result from compression of the midbrain reticular system [99].

In early and late childhood (2 years and above), the predominant finding is often neurological symptoms caused by raised intracranial pressure or focal deficits referable to the primary lesion. Features caused by intracranial hypertension includes headache aggravated in the morning, improving with upright posture and often associated with nausea and vomiting. Other typical signs are irritability, fatigue, visual impairment, cognitive decline, and delay or loss of developmental milestones.
Perceptual motor deficit and visual spatial disorganization may follow as a result of stretched corticospinal fibers of parietal and occipital cortex due to dilated posterior horns of the lateral ventricles. Consequently, some HC children do have problems with coordination [100-102].
Typical presenting signs in children with HC are papilledema, decreased visual acuity, strabismus, visual field defects, and sixth cranial nerve palsy. Clinical examination may also reveal ataxic gait, and spasticity. In severe cases decreased level of consciousness may be seen.

2.1.6 Diagnostics

Head circumference

Head size should be measured by taking the maximal obtainable circumference with measuring tape. The circumference is plotted on a growth chart. Hence, excessive rate of growth is demonstrated by serial measurements. Children with clinical features indicative of intracranial hypertension and/ or crossing of two or more percentiles should be referred to a pediatrician.

Three sets of Norwegian growth references are available to date. The first Norwegian growth reference was developed by Sundal in the 1950s based on data from the city of Bergen, with the exception of head circumference data that were collected in Oslo. A second set was based on data collected in the 1970s and 1980s where children up to 4 years old were recruited in Oslo and Hedmark during 1982-1984 in the SYSBARN study and data for older children were collected by Waaler in Bergen during 1971-1974 [103]. The third set of growth references constructed for lengths/ heights, weight, BMI and head circumference were collected in the Bergen Growth Study [104].

The Norwegian Directorate of Health (2010) recommends using growth charts based on the WHO growth standard (2006) for the age group 0-5 years [105]. From 6-19 years, growth references from the Bergen Growth Study are suggested [104].

Pneumoencephalography (PEG)

The procedure was introduced by Dandy in 1919 [23] and was performed extensively until the late 1970s. PEG was performed by lumbar puncture draining CSF and replaced with air, oxygen, or helium to allow the structure of the brain and its fluid compartment to show up more clearly on plain X-rays. PEG is very poor at resolving soft tissues, such as the brain. Besides, it is an invasive procedure, often painful and associated with a wide range of side effects, including headache, nausea, and vomiting [106]. It has been replaced by ultrasound, CT scan and MRI.

Ventriculography (VGR)

Before CT, VGRs were commonly performed with indications based on the clinical picture and/or angiography. Rather than inserting air or other gases, water-soluble contrast media was introduced [107].

This led to fewer and less severe reactions and complications. Furthermore, this technique gave a more complete visualization of the ventricles with less alteration of intracranial hyperdynamics. VGR was performed in local anesthesia by inserting a needle through a burr hole near the coronal suture, 2.5 to 3 cm. lateral to the midline. With the tip of the needle directed towards the foramen of Monro contrast media was injected into the lateral ventricle in a single bolus. Hence, radiographs were taken in rapid succession [107]. By rotating the x-ray tube around the immobilized head provided respectable visualization of the desired ventricular areas.

Occasionally infections, temporary exacerbations of clinics, subdural hematomas, convulsions, and porencephaly along the transcerebral mantle track were seen [107, 108].

A supplemental lumbar subarachnoid gas injection could be valuable for visualizing the inferior border of an occlusive lesion.

VGR with water-soluble contrast media had its clinical value from 1964 in Norway [109].

The introduction of CT made VGR almost superfluous in the diagnostics. In some institutions the number of VGRs was reduced by 85% [109]. However, VGRs maintained for some years, giving valuable additional information concerning functional stenosis or occlusion in the aqueduct of Sylvius, whereas this only could be suspected on CT.

The use of newer neuroimaging techniques began in the mid-to-late 1970s. These revolutionized the field by not only being able to examine patients non-invasively but also by examine all parts of the brain and its surrounding tissues in much greater detail than previously.

The current preference at our department is magnetic resonance imaging (MRI). Computerized tomography (CT) and ultrasound are other commonly used methods. When appropriate, ultrasound or MRI, which do not use ionizing radiation, are preferred. Three-dimensional constructive interference in steady-state (3D CISS) MRI sequences provides additional information on CSF pathways and lesions impeding CSF flow [110].
In selected cases, when in doubt, ICP monitoring may assist the diagnostic work-up.

2.1.7 Treatment of hydrocephalus in children

Treatment aims to reduce intracranial hypertension by diverting CSF to other regions of the body through a mechanical shunt implant or the creation of a natural bypass in the third ventricle [94]. The effect of the shunt involves equalization of the pressure in the intracranial space with the pressure in peripheral body cavity like intraperitoneal space. To avoid excessive CSF drainage the shunt tube is normally connected to a valve that imposes a certain resistance to CSF flow. The clinical effect of shunting is linked to normalization of ICP which in turn improves cerebral perfusion pressure, cerebral blood flow, and reduces the distortion of neural tissue [111]. Failure in treatment, such as obstruction, fracture or disconnection of the tubing, valve failures and infection, are common [112-114]. In addition, over-drainage is a challenge associated with treatment [112-114].
The effect of third ventriculostomy has traditionally been attributed primarily to relief of elevated ICP in patients with non-communicating HC. However, several authors describe clinical effect also in cases of communicating HC [61].
In developing counties with economic and human resource constraints, other modes of treatment may be more appropriate than the routine use of shunts, which are prone to failures that require urgent surgical treatment. The combination of ETV and choroid plexus cauterization (ETV/CPC) has proved effective among infants with HC in parts of the developing world [115, 116].
The current preferred type of prosthetic shunt for implementation in pediatric patients at Oslo University Hospital is a VPS. Currently, the most used valves are the adjustable Codman Medos valve, the Medtronic Strata valve, and the non-adjustable OSV2 valve. Type of valve and the valve setting used depend both on age, size, and aetiology.
VAS was the most frequent procedure in earlier decades, but is still used in selected patients. Lumboperitoneal shunts (LPS), and cystoperitoneal shunts (CPS) shunts are examples of other shunts applied in some.

2.1.8 Prognostic factors in shunted children with hydrocephalus

Many factors correlate with final functional and intellectual outcome in children with HC. Although the precise nature of the neuropsychological deficits in HC patients is not completely known, several factors have been issued to influence outcome. In both humans and experimental animals the ependyma offers focal destruction, cerebral blood flow vessels are distorted and capillaries collapse, there is damage to axons and myelin in the periventricular white matter, and occasionally neurons suffer injury [117, 118]. Distribution of pathological changes is dependent on age at which HC develops, and the magnitude and duration of ventriculomegaly and raised ICP [100, 118].

In 1963, Foltz and Shurtleff [10] noted that the IQ may be inversely related to prolonged duration of increase of intracranial pressure, and found the critical range to be between 12 to 14 cm. of water. They also observed that thickness of the cerebral mantle followed the intracranial pressure (ICP), whereas if the pressure was higher than the critical pressure, a decrease in mantle depth took place. While some supported that the thickness of the cortex was a valuable prognostic indicia of the hydrocephalic infant`s intellect [119], this was disputed by others [7, 120].

In fact, the presence of complications and other brain abnormalities, in addition to HC, such as low birth weight, degree of prematurity, birth asphyxia, intracranial infection, intraventricular haemorrhage, epilepsy, visual and hearing impairment, are important determinants of the ultimate cognitive and functional status [100, 121-123].

In 1962 Hadenius et al. reported on 180 untreated HC children. In this analysis, they found that long-term prognosis seemed to depend more upon the nature of the underlying lesion than upon the degree of HC [124]. Also in more recent series concerning children treated with CSF diversion, most agree that the underlying cause of HC is an important predictor on outcome [100, 125-128]. Children who had HC secondary to infection or IVH are more likely to need special schooling than those with congenital HC [100, 125, 126]. Moreover, children with HC secondary to MMC tend to score better in IQ tests and a higher percentage of patients attending regular schools [100, 101]. Results at school are obviously related to IQ. Besides, the co-presence of psychological problems and behavioural disorders, particularly when they are severe, are often a contributory factor in social integration [100].

Most authors have found a correlation between cause of HC and the incidence of epilepsy [77, 129]. In several studies epilepsy appears to be an important predictor factor of poor intellectual outcome in shunted hydrocephalics [100, 101, 129]. Reporting on over 800 patients with transient or recurrent epilepsy, Bourgeois et al. found spina bifida to carry a low risk (7%), cerebral malformations and IVH to carry a moderate risk (about 30%), and infection a high risk (50%) [129].

Some claim that frequency of shunt complications is associated with increased morbidity and less favourable outcome [130, 131], disputed by others [132].

2.1.9 Randomized controlled trials in pediatric hydrocephalus populations

Enhanced outcome for the patient has been the ultimate goal with the implementation of "new" surgical techniques and shunt hardware. Several studies have tried to prove their benefit. A limited number of randomized control trials (RCTs) in pediatric HC populations have been carried out since the early 1990s. A prospective, randomized study on shunt function and infection due to placement of the proximal catheter being placed anteriorly or posteriorly did not favor any of the two [133]. Lack of benefit by endoscopic VP shunt insertion to ensure an optimal positioning of the ventricular catheter was demonstrated by Kestle et al. in 2003 [134], although a secondary analysis found less failures if the proximal catheter was situated away from the choroid plexus, as demonstrated on postoperative imaging. A multicenter study from the Shunt Design Trial, including 344 children, failed to demonstrate any significant difference in shunt failure-free duration among the three valves studied (i.e., a standard differential pressure valves; a Delta valve, which contains a siphon differential pressure component designed to reduce siphoning in upright positions; and a Orbis Sigma valve, with a variable resistance, flow-limiting component), in both a short and longer time perspective (4-6 years) [135, 136]. Similar results were presented by Pollack et al, when comparing programmable- and conventional valves [137].
Furthermore, a systematic review compromised by ten studies, including both children and adults, did not reveal any difference comparing laparotomy and minimal invasive (laparoscopic) placement of the peritoneal catheter in regard to complication rate, shunt failure or infection rate [138], although the authors claimed that lack of studies with high levels of evidence may have contributed to this conclusion.

In a meta-analysis on prophylactic preoperative antibiotics for shunt surgery in pediatric HC patients, the results indicated a protective benefit, although a sub-analysis of higher quality RCTs only, did not, thereby concluding with the recommendation of antibiotics to prevent shunt infection [139]. In our hospital preoperative antibiotics in pediatric shunt surgery has been used routinely since 1995.

2.2 Idiopathic Intracranial hypertension (IIH)

2.2.1 History

The syndrome of increased ICP without HC or mass lesion and with normal CSF composition was previously referred to as pseudotumor cerebri (PTC) or benign intracranial hypertension. In more recent years it is a diagnosis of exclusion, now termed idiopathic intracranial hypertension (IIH).
In 1937 Dandy attempted to describe the disorder and establish diagnostic criteria [140]. Even though he considered the cause of this condition unknown, he stated that the diagnosis was clear in patients with increased intracranial pressure (confirmed by ventricular or lumbar puncture) plus papilledema, given normal findings on ventriculograms, no focal neurological signs (except sixth-nerve palsy), and a normal CSF composition. According to Dandy treatment was purely upon a mechanical basis and performed a right subtemporal decompression only if symptoms and objective signs (eg. progressive vision loss) indicated the need. In the most

severely affected individuals, without operative relief vision could be lost. He broadly understood the disease as a self-limiting disorder with signs and symptoms lasting from a few months to several years.
Otitis media was a common single etiological factor which was recognized to be associated with the condition [141]. Thrombosis of the venous sinus was considered one of the potential mechanisms causing it [141]. The remaining cases, in which no explanation was forthcoming, Foley gave the name benign intracranial hypertension due to his view of an almost invariably good prognosis with the condition subsiding for a few weeks or months [142]. He noted some associating factors of the condition such as female gender with a peak incidence in the fourth decade, mild head injuries, and other infections.
The term IIH arose when the disorder was no longer regarded as benign. As many as 24% of patients have been demonstrated to have permanent visual loss in a 4-41 year follow-up study [143]. If left untreated, the disorder can lead to substantial visual loss [144].
Smith proposed the modified Dandy criteria in 1985 due to advances in imaging technology, including CT imaging as a criterion to set the diagnosis [145]. Further improvements on the diagnostic criteria have been made since then, and the last revision was published in 2013 by Friedman [146].

2.2.2 Epidemiology of IIH in children

The annual incidence of IIH in the general population, including both children and adults, is estimated to be 0.5-2.0 per 100,000 [147-149], rising to 3.3 per 100,000 in women 15 to 44 years, and 7.6 per 100,000 in obese individuals (Body Mass Index (BMI) $>$ 26 kg/m^2) [149]. Due to the absence of large epidemiological studies, the occurrence is poorly documented in pediatric patients. In a hospital-based Croatian survey 19 pediatric patients were diagnosed with IIH during a 12 year period giving an incidence of 1.2 per 100.000 [150].

2.2.3 Pathophysiology of IIH

The pathogenic mechanisms of IIH are still unclear and although no unifying theory exists for the development of the disorder, dysregulation of ICP is an important focus of investigation. There are three major theories of the mechanisms resulting in raised ICP in IIH patients: 1) increased resistance to CSF absorption; 2) increased CSF production; and 3) increased venous sinus pressure [151]. Other potential causal mechanisms has been described it the literature, such as obesity, and hormonal factors.
Results from initial infusion studies suggested the role of increased CSF production in IIH [152]. However, a later trial performed by Malm et al. did not find any significant difference in CSF formation rate between patients and controls [153]. Moreover, the theory of increased CSF production do not fit with the general assumption that in patients suffering from plexus papilloma hypersecretion of CSF is known to occur, developing ventricular enlargement [154], whereas in IIH patients, the ventricles remain small or normal sized.
Studies on isotope infusion in dogs have demonstrated a delay in CSF clearance [155]. Johnston and Paterson proposed that the reduction of the CSF absorption rate resulted either from an abolition of the pressure gradient between CSF and the superior sagittal sinus or from the elevation of resistance to drainage of CSF across the

arachnoid villi. However, others have found that abnormalities in the mechanism of CSF absorption are only present in some IIH patients, therefore concluding that the appearance is non-specific in IIH patients [156]. Other conditions, such as subarachnoidal hemorrhage and meningitis, may also reduce/ block CSF drainage, thereby causing ventricular enlargement (e.g HC) [157, 158], which is not the case in IIH patients.

The presence of venous sinous obstruction in IIH patients is a common feature [159], some even suggesting that elevated intracranial venous pressure may be a universal mechanism in PTC of different etiologies by resisting CSF absorption and thereby leading to elevation of CSF and intracranial pressure [160]. However, Riggeal et al. did not find a correlation between the degree of transverse sinus stenosis and the clinical course, including visual outcome, among patients with IIH [161]. Besides, transverse sinus stenosis, as revealed by MR venography, persists in patients with IIH after normalization of CSF pressure, suggesting a lack of a direct relationship between caliber of transverse sinus and CSF pressure [162].

A strong association of IIH with weight has been demonstrated in several epidemiological studies on adults showing that 59 to 70 per cent of newly diagnosed IIH patients were obese [148, 149]. A cross-sectional study on pediatric patients in Southern California found that increasing weight class was associated with increasingly higher OR for IIH among children aged 11 years and older. The magnitude of this effect was not significant in the younger age group (2-10 years) [163]. A possible cause could be that the increased abdominal mass raises the intrathoracic pressure, thereby increasing the venous pressure. A prospective cohort in a study on adults found a significant reduction in ICP levels, papilloedema, and headache after weight loss [164], also supporting the importance of weight on the disease. However, BMI and lumbar opening pressure has been demonstrated to only have a weak, but non-significant, relation by Whitely and colleagues [165]. This theory also fails to explain why only a small proportion of obese individuals develop IIH. Therefore, bodyweight alone is an unconvincing explanation.

Several authors have reported patients developing intracranial hypertension, mostly in case reports, secondary to other causes. These could be exemplified by; antibiotics (tetracyclin) [166, 167], excess vitamin A [168], vitamin A deficiency [169], other drugs (corticosteroids) [170], and associated disorders such as; anaemia [171], Addison disease [172], chromosomal (Down`s syndrome) [173], and autoimmune (systemic lupus erythematous) [174]. In spite of identification of these various etiological agents the mechanism by which they are causing the condition still remain ambiguous.

2.2.4 Clinical features in children with IIH

Clinical presentations of IIH in pediatric patients vary greatly in severity of symptoms and the time aspect in which they develop. Symptoms of IIH that reflects generalized intracranial hypertension include headache, pulsatile intracranial noises and double vision. The most predominant presenting symptom is headache (57%-94%) [150, 163, 175]. The IIH headache is typically holocranial, frontal or retroorbital, worse in the morning, and improved with CSF removal. Double vision, usually resulting from abducens paresis, has been reported to appear in 16-31% of pediatric IIH patients [150, 163].

Other nonspecific symptoms of meningeal irritation may be present, including photophobia, nausea, and vomiting. Other less common symptoms include dizziness, visual loss, and horizontal diplopia.

Typical signs of IIH include papilledema, papilledema-associated visual loss, and ophthalmoplegia from sixth cranial nerve palsy [176]. Abnormal examination of the optic discs varies from blurring of the disc margins to gross papilledema with hemorrhages. In pediatric cases papilledema has been reported to be present in 95% of the cases [150]. Focal neurologic signs are usually not consistent with IIH. However, children with IIH sometimes develop signs that suggest a posterior fossa lesion, including ataxia, facial palsy, nuchal rigidity, irritability, torticollis, or Babinski sign [177]. However, none of these signs is typically present in adults.

2.2.5 Diagnostics

The latest revision of diagnostic criteria for IIH in children was published by Friedman in 2013[146]. These state that required for diagnosis are; 1) papilledema; 2) normal neurologic examination except from cranial nerve abnormalities; 3) neuro-imaging showing normal brain parenchyma without evidence of HC, mass, or structural lesion and no abnormal enhancement on MRI, with or without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others. If MRI is unavailable or contraindicated, contrast-enhanced CT may be used; 4) normal CSF composition; 5) elevated LP opening pressure (>280 mm CSF [250 mm CSF if the child is not sedated and not obese]) in a properly performed LP. Additionally, criteria in cases without papilledema were made. If intracranial hypertension arises from a secondary cause he termed the condition *pseudotumor cerebri syndrome* (PTCS). Increased cut-off level of LP opening pressure, and questioning of the need for the term PTCS, has been criticized by others [178, 179]. In the pediatric population, no large-scale normative data regarding normal cerebrospinal opening pressure exist. The influence of age, body-mass index (BMI), and depth of sedation on opening pressure may influence the results [180]. However, Avery et al. performed a prospective study on 197 children aged 1 to 18 years, to determine the reference range for CSF opening pressure in children undergoing diagnostic lumbar puncture. They found that 90 % of the measurements was between 11.5 and 28 cm of water [181]. A later prospective study, performed by the same authors, compared LP opening pressure in children with papilledema and compared them with controls. Among cases, 98% had LP opening measures above 28 cm of water [182], while only 5% in the control group did. Whereas the upper limit of normal LP opening pressure in neonates probably is lower, one study set the upper threshold at 7.6 cm of water [183].
In the revised criteria of Friedman a LP opening pressure greater than 28 cm of water is therefore considered abnormal in children, whereas the value is set to be 25 cm of water in adults [146].

If raised intracranial pressure is suspected, initial neuroimaging, usually MRI or CT, should be performed. MRI with and without gadolinium and magnetic resonance venography (MRV) should be performed in all to rule out any secondary causes [146]. As long as there are no contra-indications on MRI, an LP with CSF samples and measurement of the CSF opening pressure should be performed. Lumbar infusion tests and continuous ICP monitoring can give additional information. Further workup should be directed to rule out secondary causes

guided by the history and examination findings. When initial workup suggests possible IIH, urgent neurologic and ophthalmologic evaluations are mandatory.

2.2.6 Treatment options in children with IIH

Preserving vision, controlling symptoms, and lowering the ICP is the mainstay of treatment. There are no randomized clinical trials for the pediatric population and the treatment of IIH in children is largely based on evidence obtained from the adult population. Individualizing treatment by identifying and directing treatment at the underlying cause, if any, is important. In general, medical management is used first and surgical treatment is reserved for the cases in which medical therapy fails to control ICP or if visual function is threatened. A multidisciplinary team including at least a neurologist and an ophthalmologist is essential.

Disease modification

In some patients, especially in obese individuals, weight loss has been an important factor in managing the disease, along with low-salt diet. Reduced energy diet has been demonstrated to reduce ICP, improved symptoms and reduced papilledema [164] .

Medical therapy

Acetazolamide, a carbonic anhydrase inhibitor, is frequently used in the management of IIH due to the characteristic of the drug to reduce CSF secretion [184]. A RCT in adult patients has demonstrated its effect regarding visual field measurements, grade of papilledema, CSF pressure, and quality of life measure [185].
Furosemide, a diuretic drug, has been demonstrated in animals to reduce CSF formation [186]. A pediatric case series combining acetazolamide and furosemide found this treatment to be an effective method of treating IIH in children [187].
Topiramate, an antiepileptic drug, is another management option. Except from one case report [188] suggesting a potential benefit, the effict of Topiramate in treating childhood IIH is lacking. An open label trial on the use of Topiramate versus Acetazolamide in adults showed that both were comparable in improving visual field grades in patients with IIH, as well as in regard to headache relief, and papilledema improvements [189].
Corticosteroids, may be useful in managing raised ICP, however, the evidence for the use in pediatric IIH is poor. However, recurrence with withdrawal, weight gain, and gastric ulcer are potential side effects. If clinically indicated in patients with rapid visual deterioration, short term use is preferred [190].

Operative therapy

IIH children who fail to have effect from medical therapy and have intractable headaches, or have progressive or acute visual deterioration are candidates for surgical treatment [191].
CSF shunting and optic nerve sheet fenestration (ONSF) are the two main procedures in pediatric cases, while venous sinus stent placement [192] and bariatric surgery [193] has been reported only in case-reports.

In retrospective studies on IIH in children, 0 to 16% requires surgical intervention [194-196].

To date, there are no randomized controlled trials to compare ONSF to CSF shunting. A comprehensive review of the literature supported ONSF as the preferred procedure of visual loss from IIH [197], perhaps because visual outcomes was better documented with this procedure. It is generally accepted that patients with headaches undergo CSF diversion procedure and those with prominent visual symptoms undergo an ONSF procedure [198]. Supporting evidence underlying this practice is less well defined [199].

ONSF

The mechanism may be related to the localized reduction in pressure on the optic nerve head as CSF is allowed to leak through the dural window cut in the nerve sheath [200]. A systematic analysis of case series published between 1980 and 2013 noted that only 37 % of the pooled patients experienced improvement of headache following ONSF, while visual field assessment improved in 72% [199]. A generalized reduction in ICP via a persistent orbital fistula is disputed.

In a retrospective study of 12 children aged below 16 years, 75% had improvement in visual function and papilledema within 3 months following ONSF [201]. In addition, some patients had improvement in optic nerve edema and some even in visual acuity, in the contralateral eye after unilateral surgery. ONSF in children is regarded as a relative safe and effective procedure in stabilizing visual acuity and visual loss, although complications, including further visual loss, may occur [201, 202].

CSF diversion

There are several CSF shunting options. Diversion from Cisterna Magna has been used, but the two most frequently used approaches to-day are lumboperitoneal shunt (LPS) and VPS. CSF shunts is generally accepted as being effective in arresting visual deterioration in IIH patients, while its effect on alleviating headache is more debatable. The use of LPS is well described [203, 204] and commonly used due to its minimally invasive nature. Besides, small ventricular size in IIH patients often makes the ventricular placement of the catheter more challenging. Image-guided stereotactic techniques have contributed to a more common use of VP shunts in more recent decades [205, 206]. Besides, lower shunt revision rates in VP shunted patients have been reported [205].

2.2.7 Prognosis in children treated for IIH

Fortunately, most children with IIH respond well to treatment.

Initial remission. The duration of resolution of clinical symptoms and/ or papilledema in the majority of treated children after diagnosis of IIH vary from one week to six months [187, 194, 207, 208]. Other studies have reported 43% of pediatric IIH with continuing headache and 9-33% with persisting papilledema for more than 10 months, despite interventions [195, 209].

Recurrence rates. Rates of relapse of symptoms and/ or signs of IIH in children range from 5-22% [194, 195, 207, 208, 210] and are related to different duration of follow-up. In adults shunted due to IIH, the presentation without papilledema and the duration of symptoms for >2 years preoperatively were associated with an increased risk of symptom recurrence [205].

Visual outcome. Visual prognosis in pediatric IIH is generally good. However, a small percentage will have some degree of permanent visual loss [211]. In a review of 79 children in 1971 Grant concluded that permanent impaired vision appeared to be less of a danger in children than in adults [175]. None of the children in his series required decompressive operations for preservation of visual acuity. In more recent pediatric case-series there has been reported permanent subnormal visual acuity or narrowing of visual field in 6 to 16 per cent [194-196]. Vision may remain impaired also in shunted cases [212].
Determinants of favorable long-term visual outlook in childhood IIH are not yet established.

Long-term outcome in surgically treated patients: Treatment failure is not an uncommon feature. In seven children receiving a LPS due to IIH [212] all needed subsequent surgery due to shunt malfunction within 2.5 years. After a mean follow-up of 26 months, the two patients presenting with acute visual loss had persistent impaired visual acuity, and only one patient became headache free. In studies on adult patients marked headache relief postoperatively has been reported in 82-100% [203, 205, 213], but almost half had reoccurrence within 3 years [205]. In some patients, adequate headache relief has persisted up to 20 years post shunting [205]. Whether these patients represented spontaneously improvement of the disease, or represented a group with persistent shunt dependence with a functioning shunt, were not discussed in this report.

Because long-term results in children shunted for IIH are scarce and the question of shunt dependency in such individuals remain unanswered, we have included a case-report describing a male patient diagnosed with IIH in our department in early childhood (paper 4). He experienced shunt failure no less than 17 years after initial treatment followed by another failure after 20 years. To our knowledge, limited documentation on long term outcome in patients demanding permanent CSF diversion due to pediatric IIH exists. Moreover, knowledge upon the persistent nature of the disease is still an unanswered question.

3. Aims of the thesis

The main objective of this thesis is to explore long-term outcome in individuals treated with CSF diversion due to intracranial hypertension during childhood.

For this purpose, the thesis is composed of four sub-objectives by discussing the following;
1. Explore the outcome in middle aged adults shunted for HC in early life.
2. Explore the outcome in young adults shunted for HC during childhood.
3. Shunt treatment was established in Norway more than 50 years ago – are there any relevant differences in whom we treat, and the way we treat them? Explore and compare short-term outcome in the three different time periods; the 60s, the 80s and the 21st century.
4. Can CSF diversion in IIH individuals (children) lead to life-long shunt dependency?

Ad. 1. In the first paper we examine forty-year outcome in adult HC individuals treated with permanent CSF-shunts during childhood by assessing survival, the need for re-surgery, work-participation and health related quality of life.

Ad.2. In the second paper we examine twenty-year outcome in young adults with childhood HC by assessing their functional status and health related quality of life. We determine short and long-term survival, surgical outcome and explore to what degree these individuals live comparable lives with those of their peers.

Ad.3. In the third paper we examine shifts in patient characteristics, diagnostics, surgical management, surgical outcome and short-term survival data in pediatric patients treated with permanent CSF diversion due to intracranial hypertension in three different time periods covering a time span of more than fifty years.

Ad.4. At least in this particular patient, presented in paper 4, it appears that he most likely is permanently shunt dependent.

4 Patient population, materials and methods

4.1 Patient population

In our three first studies, all children less than 15 years of age who underwent first-time permanent CSF diversion to treat intracranial hypertension, were included. All of our patients were treated surgically with permanent CSF diversion (shunt or ETV) at the Department of Neurosurgery, Rikshospitalet, Oslo University Hospital (OUS) in the calendar years; 1967-70, 1985-1988, and 2009-2013. All types of CSF shunts were included.

Our hospital function as a third line health care unit in Norway. This implicates that which children are treated with permanent CSF diversion necessarily depend on these patients being referred to our department.

In the Neurosurgical Department located at Rikshospitalet, Oslo University Hospital, the catchment area in paper 3 (2009-2013) is restricted to the south-eastern part of Norway. Prior to 1998 children were also treated for HC in the other neurosurgical department in Oslo (Ullevål hospital). There has furthermore been an increase in neurosurgical centres treating children in Norway over time, including Bergen from 1968, Trondheim from 1973, and Tromsø from 1986. From 1998 all children from south eastern Norway has been treated at Rikshospitalet (population of around 2.8 million inhabitants). Each unit treats patients within their geographically restricted areas. Our non-selected cohorts of patients can thus be viewed as epidemiologically representative according to case-mix. On the other hand, data on the annual incidence of shunt treated children may vary according to the actual catchment area in each time period.

In our two first studies (paper 1 and 2), all relevant patients were identified in our surgical protocols for the relevant time periods. These surgical books contain information on all surgical procedures performed in our department with detailed information of patient name, date of birth, and type of surgical procedure performed.

In our third paper the patients were identified from electronic surgical protocols according to relevant surgical codes, including all types of permanent CSF shunt procedures.

In all three papers (paper 1, 2 and 3), the diagnosis of HC was based on increased head circumference, characteristic symptoms and signs indicative of intracranial hypertension. In paper 1, diagnosis was often confirmed with pneumoencephalography/ ventriculography. In paper 2, ventriculomegaly was verified with cerebral CT scans. In paper 3, supplemental brain imaging with CT and/or MRI was performed in all patients. In ambiguous cases, intracranial pressure recording was used. IIH patients had papilledema, and normal sized ventricular system on neuroimaging. The indications for CSF diversion were lack of improvements after medical therapy, stationary or progressive visual impairment and/ or intractable headache.

Paper 1, 2 and 3, have a retrospective descriptive design.

The fourth article is a case report on a boy shunted due to IIH in early childhood.

4.2 Exclusion

The exclusion criteria in paper 1-3 were previous shunt implantation or ETV.

4.3 Research ethics

The studies (paper 1 and 2) were approved by the regional committee for medical health research ethics (REC), and Data Protection Official at Oslo University Hospital (paper 1, 2 and 3). In paper 1 and 2, informed written consent was obtained from all study participants; in incapacitated patients, consent was obtained from a person authorized to give such.

4.4 Data collection

In our three retrospective papers, information was collected from the patients' medical charts; age at initial surgery, type of CSF diversion procedure, cause of intracranial hypertension, re-surgeries, surgical complications (e.g. shunt infections), mortalities, and if available; cause of death. In cases where patients had been partly followed or treated in other neurosurgical care units during the follow-up period, relevant information were obtained from these departments.
In paper 1 and 2, all patients was contacted by phone before mailing the questionnaires to their home address, and requested to give additional information on functional status, scholastic outcome, employment attendance, and perceived health.

4.5 Patient assessments

Reoperations in paper 1, 2 and 3 included all surgical procedures involving the shunt, including shunt malfunction, exploration of the shunt system, elective revisions (e.g. elongation of the atrial catheter), and shunt removal (e.g. in patients with infection). Shunt infection was defined as clinical diagnosis of infection, with or without positive culture, leading either to shunt removal or externalization of the shunt (e.g. abdominal infection).
In paper 1 and 2, we assessed the patients' functional status according to the Barthel Index (BI) score. The Barthel is a 10-item ordinal scale that measures functional independence in the domains of personal care and mobility. Patient score ranges from 0-100; a score of 100 indicates the persons` independence in basal activity of daily living (ADL), specifically, it measures self-care, sphincter management, transfers and locomotion.
Schooling was rated as; normal schooling, school for mentally handicapped children, and school for physically handicapped children.
Social status was rated as; normal job (employment in the competitive labor market), sheltered job, currently unemployed (job seeker on the competitive labor market), or not employed due to chronic illness.
Perceived health was assessed by using the questionnaire Short-Form Health Survey (SF-36).This is a generic, non-disease specific questionnaire assessing health related quality of life in eight domains; physical functioning, social functioning, role limitations due to emotional problems, pain, mental health, vitality, and general health perception. Higher domain scores indicate higher functioning and health-related well-being. Patients whom were unable to express independent view on their own health were not asked to complete the SF-36.

In paper 1, patients lacking clinical or neuro-radiological follow-up since year 2000, were invited to our outpatient clinic to obtain CT or MRI images and radiographs of the shunt system in order to assess shunt function.

4.6 Outcome measures

Improvement of pre-operative symptoms indicative of intracranial hypertension was regarded as clinical effect of treatment. To the greatest possible extent, complications to surgical treatment, such as re-surgeries and unwanted surgical complications, were recorded. Overall mortality was calculated from the time of initial surgery until the time of death by any cause. Shunt-related deaths included deaths due to acute and late shunt failure. Probable shunt related deaths accounted for patients who died short time after the last shunt revision (within 7 days), and those who suffered from sudden death without any other obvious cause.

4.7 Statistical analysis

Statistical analyses on survival analysis were conducted using Kaplan-Meier curves. Student`s t-test were used to assess paired data. The level of statistical significance was set at <5% in all analyses. Statistical analyses were conducted in SPSS 18.0 for Windows (IBM Corp., Armonk, NY, USA) and Excel.

5 Results

5.1 Survival and surgery-associated complications in children treated with permanent CSF diversion

In our first paper (40-year outcome) we find that the survival rate at 1 and 2 year was 84% and 76%, respectively. Almost half of the patients dying within two years after initial shunt insertion had malignant disease. Forty years after primary shunt treatment, 48% had died, and the estimated shunt-related mortality was approximately 9%. Approximately 1/5 deaths occurred during the last two decades. The vast majority was caused by intercurrent disease, while 2 deaths were related to shunt treatment.
In our second paper (20 years outcome) we find that the survival rate at 1 and 2 years was 93% and 91%, respectively. Of the 138 patients evaluated, 17% died during the first decade and 22% during the 20-year study period. Shunt related deaths were estimated to be 3%.
In our third paper (2009-2013) we find that the survival rate at 1 and 2 years was 96 and 92%, respectively. The patients were followed between 2 to 7 years and a total of 16 deaths were registered. No shunt related deaths were seen. Except from one patient with severe malformations (anencephaly), the other fifteen died due to malignant central nervous system (CNS) tumors.

5.2 Case-mix in children treated with permanent CSF diversion

In the cohort from the 1960s the most common cause of HC was Neural tube defects (NTD), accounting for 33 per cent. CNS tumors and communicating HC of unknown origin accounted for 20% and 16%, respectively. HC following intracranial bleeding accounted for 7% of the cases.
In the cohort from the 1980s the three most common causes was Hemorrhage, NTD, and CNS tumors, accounting for 19%, 17% and 17%, respectively.
In the most recent cohort (2009-2013) the far most common underlying condition was CNS neoplasm (31%). Hemorrhage and Neural tube defects accounted for 12% and 8%, respectively. Patients shunted due to IIH accounted for six patients (4%).

5.3 Initial permanent HC treatment, longevity of primary surgical treatment, and shunt “in place” at follow-up

In the first paper (40 years) the vast majority of the primary shunts were the VA type (94%) while only 4% was VPS. Following from VAS as standard treatment, elective revisions with lengthening of the atrial catheter accounted for 26% of the total number of re-surgeries. The need for revision of the shunt in cases of suspected shunt failure was common; 58% during the first two years. Although the annual revision frequency decreased over time, 10% were performed in the last decade. Four patients (3%) had no revisions of their primary shunt at follow-up. In 3 out of 67 patients (4%) still alive at follow-up, the shunt has been explanted, and they are considered shunt independent.

In the second paper (20 years) the vast majority had VPS as their first-line treatment (90%). Other primary treatments were; VA shunts (4%); VCS ad modum Torkildsen (2%); and others (4%). Although no patient underwent primary ETV, endoscopic third ventriculocisternostomy was tried in two patients in cases of shunt malfunction, but due to lack of improvement, both had a shunt re-inserted. Although more than half of the patients (60%) needed to undergo at least one revision within two years after primary shunt treatment, 10 patients, all alive at follow-up, still had their primary shunt in place. We found a significantly higher number of revisions in the youngest age group (less than 6 months). As VP shunts were now standard, elective elongation of the distal catheter accounted for only 6% of the total number of re-surgeries. Twelve patients (9%) were living without any artificial CSF diversion at follow-up, all had their shunt explanted during the observation period, most of them without symptoms indicating raised ICP for more than ten years.

In the third paper (2009-2013) 77% of the patients were initially treated with prosthetic shunts, thus ETV was the preferred first treatment in the remaining 23%. We find that more than half of the patients (52%) needed to undergo at least one re-do surgery within two years after initial shunt insertion or ETV. None of the patients have been found to be independent of CSF diversion during the 2 to 7 years they have been followed, and none of the patients have had their prosthetic shunts explanted on a permanent basis.

5.4 Functional outcome and social integration

In paper 1 and 2, the results revealed notable variances in the level of independence, with Barthel Index (BI) scores ranging from 5 to 100. In both papers, the mean BI score was just above 80. In paper 1, the majority were able to walk independently, but almost one in three was in need of a wheelchair. Especially in the NTD- and Hemorrhage-group impaired motor function was common. In paper 1, the majority of the patients reported to be socially independent (56%). One third required daily assistance from caregivers, either by family members if living at home or in sheltered units/ institutions. Similar results were found in paper 2, with 59% being fully independent in daily living.
In the cohort of young adults (paper 2), with the majority being in their mid-20s, 22% reported being in a relationship. In paper 1, a slightly higher proportion (27%) reported to be in a relationship, and 27% had at least one offspring.

5.5 Educational achievements and work participation

In the first (40 years) paper, we found that approximately 2 in 3 were attending the regular school system during their childhood, including those requiring additional support. Being middle aged adults, 42% reported to be employed; 31% were employed in the open labor market; and 10% were in sheltered work places. Fifty-eight per cent of the patients were unemployed, and almost half (46%) were outside the labor market on a permanent basis due to chronic illness.

In the second (20 years) paper, we find that among the 95 respondents, 56% were students or employed in the open labor market, 23% were in sheltered work places, and 21% were not in contact with the labor market due to chronic illness. Regular secondary school was completed by 76%, while 28% had completed or was currently students at a higher educational level.

5.6 Perceived health in children treated with shunt during childhood

In the first paper (40 years), the response rate regarding self-perceived health was 90%, 6% was unable to answer the questionnaire due to severe mental handicap, and 4% were non-responders. Compared with the reference group, the HC cohort reported poorer results in 6 out of 8 surveyed domains; *Physical functioning*, *role physical*, *general health*, *vitality*, *social functioning*, and *role emotional*. We find some differences among the genders and within the different etiological subgroups.

In the second paper (20 years), SF-36 was completed by 77 individuals (71%); in 18 patients (17%) measuring perceived health was not feasible due to severe mental handicap, and 13 patients (12%) did not respond. Compared to the reference group, we find that young adults (median age of 23 years) with childhood HC reported a poorer perceived health in 2 out of 8 SF-36 domains. In two domains; *Physical Functioning,* and *General Health*, they had significantly lower scores for both genders, when compared to the reference population. Females also scored lower in one additional category; *Role limitations due to physical functioning*. Additionally, we find some significant differences within the etiological subgroups: *CNS tumors* and *NTD* patients reported inferior results in physical domains; *Other malformations* reported inferior results in mental domains; and *HC of unknown origin* reported superior results in the *physical functioning* domain.

Due to the young population in the third paper (2009-2013), where the mean age at follow-up was less than 7 years, no testing on perceived health was performed.

6 Discussion

6.1 Some aspects that makes it challenging to compare results from different time periods

HC is not one disease entity. Several diseases are associated with the condition, which makes it challenging to evaluate this group as one "whole". Influences on outcome may in some cases be credited to HC only, but might as well be caused by the underlying condition/ co-morbidities.

There are some challenging aspects regarding comparison of outcome in different time periods. The emergence of new and better treatment options, given that the new method has therapeutic effect, i.e. relieves disease symptoms more effectively, and implies lower complications rates/ less dangerous complications, though, the new method does not treat the cause, but are symptom-oriented as the previous method, may influence the results.
The treatment practice changes preferably by a growing proportion of patients treated with "new method". Disease perception modifies when the disease is considered "less threatening" because the treatment involves less risk. Referral practice alternates, still comprising those with manifest or "probable" disease, but also those who could conceivably have the diagnosis, cases with "possible" disease. This may lead to "new" groups of patients, with less dramatic clinical picture, being referred to surgery. Also, the most seriously affected patients already suffering from irreversible brain damage obviating useful survival may be excluded. Published results may now appear more favorable than in the original treatment group.

Technical devices and materials, as well as surgical techniques, have developed over time. Curiously, despite several attempts to prove the superiority of "new", more modern surgical techniques or innovative valves, positive results to prove their benefits have so far not been convincing [134-137]. We therefore argue that any revolutionary improvement in surgical techniques or shunt devices made available during the last three decades, is ambiguous.

Whereas in the past, air and dye contrast studies were required to determine the presence or absence of HC, the introduction of CT imaging of the brain, clearly benefited HC children by being a less hazardous modality and providing a more accurate diagnosis [108]. Given a higher specificity of the etiology causing HC, a more correct and direct treatment was feasible. While approximately 1 in 4 patients were diagnosed with *HC of unknown cause* in our fist paper (1967-1970), this diagnosis was less common in the cohorts from the 1980s and 21st century (14 and 17%, respectively). With the introduction of MRI, the specificity improved again leading to the gradual increase in diagnosis of tumors as cause of HC [214].

When studying outcome in three different time periods, these factors may have influence the results.

6.2 Case-mix in pediatric patients treated with permanent CSF diversion

See; discussion in paper 3 (2009-2013).
In 2013 Kulkarni presented a comparison between two pediatric HC cohorts, with a 15-year interval between them. The trend towards a higher proportion of CNS tumors, and the decrease of MMC patients, are the same as our results [215]. Also, age at initial surgical treatment was higher in their most recent cohort.

6.3 Mortality in pediatric patients treated with permanent CSF diversion during childhood

The concepts of long-term follow-up, outcome, prognosis, and survival in the pediatric HC population have been subject for several studies throughout modern history [215-217], and these concepts have been used alternating as regards to both time frame and what specific conditions they account for. This may cause hitches when comparing different series.
However, prior to shunting various studies yielded 10 years mortality rates of 50-80% [7, 11, 12, 124, 218]. After the introduction of ventriculo-venous shunting the mortality rates was reduced. In 1963 Foltz and Shurtleff conducted a comparative study in HC children with and without operation calculating the 10-year mortality rate to be 38% and 78%, respectively. [10].

In paper 1, we found an overall 2-year mortality rate of 24%, while 31% of the patients died within 10 years after initial shunt procedure. These results are comparable with other studies with treatment performed during the same time period; Overton and Snodgrass` series presented a mortality rate of 25% within 5 years [219]; Stark et al. lost 22% in the same time period [220]. Despite new methods to treat HC children, the mortality rate remained relatively high during the first decade after its introduction.
The operative mortality and deaths in the early post-operative period still remained a challenge, accounting for approximately 4% of deaths [48, 221, 222]. Early deaths caused by meningitis, pneumonia or cardiopulmonary failure (e.g. pulmonary embolism) were not uncommon. The shift towards the use of VP shunts contributed to the decrease in operative mortality in shunting procedures [223], as did the development of surgical techniques. In a cohort shunted in the late 1970s, Amacher and Wellington reported a 5-year mortality rate of 16.5%, reduced to 14% if omitting the tumors [224]. Lumenta and Skotarczak reported on 233 patients in whom shunts were placed for congenital HC in the years 1964 to 1984. Fourteen per cent died during the follow-up period, of which more than one third of deaths were associated with infection [130]. Some years previously, O`Brian and Harris concluded that shunt infection contributed to 20% of deaths, whereas shunt malfunction led to 30% of deaths [225]. In a Canadian survey, 707 pediatric CSF shunted individuals were followed for 11 years, a multivariate analysis revealed a significant association between deaths and a history of shunt infection [128].
In paper 2, the 2, 5, and 10-year mortality rate was 9, 12, and 17%, respectively. In a comparable study including shunted HC children from the late 1980s, Casey et al. found an overall 10-year mortality of 18%, reduced to 11% when tumors were excluded [216]. In 1998 Hoppe-Hirsch presented inspiring results with a 10-year mortality rate of less than 5 % in 129 non-tumor HC children [100].

In more recent studies; Heinsbergen reported a mortality rate of 8% in all-cause HC children followed 1.5 to 5 years [126]; Tuli et al. calculated the 10-year mortality to be 12% when studying all pediatric patients requiring CSF shunts over an 11-year period, excluding patients with CNS neoplasms [128].
In paper 3, the 2-year mortality rate was 8%, reduced to 1% if CNS neoplasms were excluded.

Although no deaths due to shunt failure were registered in paper 3, this may be due to limited time of observation (2-7 years). In paper 2, the cause of death is primarily due to the underlying condition, still deaths due to shunt failure accounted for 3%. In paper 1, the identification of the precise cause of death was more challenging, because not all children died in the hospital or were autopsied. The shunt related mortality at 8.6%, may represent an underestimation. However, it is interesting to note that cases of late shunt related deaths were seen even two to three decades after initial shunt insertion. Similar results were found by Sgouros; "despite long periods of apparent stable shunt functioning, death from raised intracranial pressure due to shunt malfunction remains a risk throughout adulthood" [226]. Moreover, retrospective studies from the 21st century, reported death due to sequela of shunt failure in 1-2 per cent [131, 227].

In papers 1 and 2, the majority of deaths occurred during infancy and preschool years. In cohort 2, during school-age and early teens, the death rate seemed to level off. However, in paper 1 with more than 40 years of follow-up, we found that the death rate flattened for a 10-year period (24 to 34 years after initial surgery); thereafter a continued climb was seen. Similar results have been demonstrated in a cohort consisting of spina bifida patients [228]. They also found a continued increase in death rate as the cohort was ageing.
Thus, is seems that mortality continues to climb as the pediatric cohort become adults.

6.4 Longevity of the initial permanent CSF diversion – time to first re-surgery

In all papers (paper 1, 2, 3), more than half of the patients had at least one re-surgery, due to suspected shunt failure, within 2 years after initial procedure. How can we interpret the results regarding consistently relative high re-surgery rate? In the second paper (1985-1988) a significantly higher revision rate was seen in children initially treated before 6 months of age. Similar observations is described by other authors, pointing out that shunt revision rate is correlated with age at initial surgery [131, 216, 229], and that the longevity of initial shunt increase with higher age [227]. Other predisposing factors leading to the higher number of revisions in the youngest group could be reduced resistance to infections, and predisposing underlying causes of HC (e.g. NTD, IVH). Besides, increased distensability of the infant head possibly reduces the pressure gradient across the shunt.

Despite the fact that the median age at initial shunt procedure was clearly higher (14 months) in our third paper (2009-2013), the proportion of patients in need of repeat-surgery within 2 years remained disappointingly high. Nevertheless, the results are comparable with a multi-center randomized trial from the late 1990s with an overall shunt survival of 52% at 2 years [136]. Stone et al. found that more than half of the children experienced failure within the first year after VP shunt insertion [230].

However, both in paper 1 and 2, we do see that the revision rate decreases with time, although it never reaches zero. In our studies, mean revision rate was 3.3 (paper 1) and 4.2 (paper 2). The reason for the lower revision rate seen in the cohort with more than 40 years of observation is not obvious, but may reflect the closeness of follow-up. To claim that the threshold for repeat surgery has changed with time is speculative. In cases of doubt, when patients present with subtle clinical complaints and radiological findings are inconclusive, the surgeon may be more inclined to recommend surgery in current practice, compared with previous decades.
In pediatric series extending 17 years of observation, mean number of shunt revisions per patient are between 2.6 and 2.7 [130, 230, 231]. Prolonged observation in pediatric HC cohorts have shown that shunt failure can occur very late [218]. In paper 1, one patient experienced first shunt failure as long as 29 years after initial procedure. Moreover, it was not unusual that patients experienced stable shunt function for ten to fifteen years, after which shunt failure occurred (paper 1 and 2). There were even a few patients who were considered to be shunt independent for many years, since they were clinically doing well despite images showing fracture or displacement of the tubing system. However, they later proved to be shunt dependent and in need of shunt revision. Others have demonstrated similar findings [219]. A possible theory is that the shunt material, silicone, induces a fibrous connective tissue sheath around the tubing defect. As demonstrated by Sugar et al., these sheaths can convey CSF for some period when the tube is disconnected or pulled out of the abdomen [220].
In Stones` series as many as 12.5% had their first shunt revision more than 10 years after initial shunt insertion [230]. In a French cohort on 456 patients followed up for a mean of 24.2 years, 18% experienced shunt failure after 20 years or more [231].
However, the “ever-lasting” high numbers of failures shows that shunt problems may happen at any time. The risk of shunt failure persists into adulthood.

While shunt failure is proof of shunt dependence, the lack of such may lead to questions regarding whether the shunt is still functioning or not. In paper 1 and 2, 4 and 10 patients, respectively, have never presented with symptoms of shunt failure, nor have they had any revisions of the initial shunt. In addition, more than one in four patients had no revision during the last 30 years of follow-up (paper 1). Theoretically, the shunt may have been blocked a long time ago and the patients have become shunt independent. Thus one is bound to question whether the shunt is still functioning. However, without using invasive methods, this is hard to prove. In our department there is no tradition for performing further surgical procedures in these cases.

With this thesis, confirming that many shunted patients treated during childhood require reoperation when they are adults, we claim that the absence of shunt failure should not be interpreted as shunt independence.
The majority of patients are considered to be still dependent on their shunt at follow-up. Nevertheless, shunt removal has been performed in some cases. In paper 1, only 4.5% acquired shunt independence, i.e. removal of the shunt without subsequent endoscopic treatment. In paper 2, the proportion of shunt independent individuals were surprisingly high – 11%. To our knowledge there has not been a change in practice in this regard. Random fluctuations may partly explain some of this difference.

ETV has several advantages in the treatment of children with HC. Statistically, Kulkarni et al demonstrated that the relative risk of ETV failure is initially higher than that for shunt. But after the early high-risk period of ETV

failure, ETV was shown to have better long-term survival advantage compared to shunts [62]. In paper 3, the patients treated with ETV required fewer re-do surgeries compared to those with shunts. Patient selection bias may influence these results. Longer term data is less clear, but delayed obstruction of the stoma has been reported 7.8 years after initial procedure [232]. Despite its rareness, late failure of ETV in children does occur with the scenario being a fatal outcome [233].

6.5 The understanding of HC and follow-up routines

HC has in the past been regarded as a disease of childhood [234]. In the middle of the last century ventricular shunts were adopted in pediatric HC patients [39, 41]. As a result, HC patients experienced a considerably improved prognosis with regards to survival leading to a higher proportion reaching adolescence and adulthood. However, shunting is not a curative treatment, but a symptom-relieving treatment transforming an acute/ sub-acute condition, into a chronic and life-long condition [235]. This understanding was already established by Foltz and Shurtleff in the early 1960s [10]. It appeared to them, that "once a shunt was established in a progressing hydrocephalic, it may mean life-long need for such". Several series published in the 1980s described the difficulties in establishing whether a shunt is non-functional [236, 237], thereby indorsing a greater caution before the diagnose of "arrested HC" was set.
Conversely, some supported Laurence claiming the frequent occurrence of "arrested HC". Holtzer et al conducted a study over a ten-year period in the 1960s demonstrating "shunt-independent arrest" in 34 out of 127 children (27%) who all successfully had their shunt removed, half of whom had non-communicating HC [238]. The confirmed arrested state was demonstrated in part by performing a contrast study to check the patency of the shunt system. Other reports published in the 1980s found similar results, one in five becoming shunt independent within 5 years, all with a shunt "in place". The compensated HC was judged on clinical status and radiological findings [224].

In our first paper, most children were followed routinely by clinical visits for some years. The need for frequent elective elongation at the atrial catheter contributed to this. Nevertheless some patients were sent to their home environments without any further controls. Why is this? The experience on how to follow these children was not yet established. Our first paper (1967-1970) demonstrates this immaturity in practice. A decent tradition to capture the lack of good results, or interpreting these as failure to surgery was not yet estabished, as most patients had substantial comorbidities. With regards to maintaining shunt function and following these children on a regular basis, the routines were less strictly formed in this period compared to later decades. If a child remained clinical stable for several years, without symptoms of raised ICP, further controls were discontinued. In paper 1, several of these cases were considered to have "arrested HC".

With follow-up, the symptoms of acute shunt failure are usually simple and straightforward to diagnose. However, the symptoms of insidious failure or intermittent failure can be missed with disastrous consequences. Discharging these patients from regular visits, may have fatal costs [239]. Today, there is more or less consensus on the need of controls throughout childhood, but still no guidelines exist for adult long-term follow-up.

Complications are legion and can happen at any time [231], implying the need for prolonged follow-up in these patients. Some clinicians propose that many of these patients could be followed by pediatricians or general practitioners [240], while others recommend a continued neurosurgical approach [231]. The expertise of the follow-up team is important for the successful identification of problems as it is more difficult for those with little experience of the condition to make an accurate diagnosis. The best possible option may be that these patients should be followed by an interested and dedicated neurosurgeon.

Due to the dynamic nature of the condition, HC never should be regarded as quiescent. Therefore, regular visits contribute to remind patients of symptoms that necessitate review, provide a safe route for re-attendance, and remind both the patient and the doctor that alertness should be maintained [226, 239, 241].

As discussed in our second paper, we recommend a life-long follow-up organized and adapted to the specific need of each patient. As a suggested template we recommend frequent visits in the initial years after shunt treatment, with intervals gradually increasing from 6 months to 1 year, later 2 years, until the age of approximately 16 years. Thereafter, control examinations, with supplemental radiological MRI or CT of the brain and radiographs of the shunt system, should be performed at a 4- to 5-year interval.

Have the results regarding shunt failure rates in pediatric patients improved with time?

When comparing results from the three different time periods in our institution, we did not find any improvement in longevity of initial treatment. Similarly, in a study published in 2008, Stein and Guo did not find evidence of reduced shunt failure rates in the published literature covering a period from the 1960s into the 21st century [242].

However, both Stein and others state that shunt failures attributable to infection has probably decreased over the years [243, 244].

To our knowledge, consistent improvement in shunt survival over time has only been demonstrated by few authors. Kulkarni et al. reported improvements in longevity of initial shunt, when comparing pediatric cohorts from the 1990s and the 21st century [215].

6.6 Functional outcome in adults treated with CSF shunt during childhood

Life-long morbidity associated with shunt placement to treat childhood HC is substantial, including the initial severity of HC, shunt-related complications and comorbidities that adversely affect both social and functional functioning. In paper 1 and 2 we found that the profile of motor handicap was markedly different between the etiological groups; patients with NTD being overrepresented in the group of wheelchair-users. Platenkamp reported that 13% needed a walking aid and 17% needed a wheelchair [245].

Epilepsy is a common finding in HC patients and may be caused by the initial brain disease or by insertion of the ventricular catheter as attested by the presence of epileptic foci on postoperative electroencephalography (EEG) [129]. Having epilepsy may have a negative effect on perceived health, as reported by Kulkarni [246].

Endocrine sequelae in adult HC populations are described by some authors. Hypothalamic dysfunction may influence gonadostimulin axis reducing fertility. Among adult women in Gupta`s series, 26% of adult women reported to have been pregnant [125], which was close to our findings (27% of female patients).

Other common conditions are underreported in this thesis. The presence of depression has reported to be as high as 43% in adult HC patients [125]. Moreover, chronic headache has been reported to be a problem in 44% of adults with shunts (Rekate; Headaches in patients with shunts, 2009).

6.7 Educational outcome and work participation in adults treated for HC during childhood

Children with HC frequently experience physical, social, emotional and cognitive health issues [100, 247]. While it is true that hydrocephalic patients do not often reach superior intellectual abilities, there are some who do [224]. Nor is it always possible to predict from initial examination of the child how it will fare. Learning disabilities are fairly common and these children are often credited with better verbal IQ than performance IQ [101, 248]. The severity of HC can differ considerable between individuals; some have average or even above-average intelligence. Schooling and social integration of HC patients are contributed to their cognitive deficits. Many agree that the severity of initial brain damage has an impact on later intellectual performance [249].
In several studies, IQ has been used as a measure of mental development. To document specific areas of dysfunction, neuropsychological tests also have been used [250].
However, Hirsch pointed out that another good measure might be whether the child is able to attend regular schools or not [217]. In paper 1 and 2, we used school type and ability to work as a measure of mental development. In paper 1, we found that 2 out of 3 patients had been integrated into the regular school system. Cause of HC such as CNS tumor, meningitis, and IVH were associated with poorer educational outcome. As middle aged adults one third had "normal" jobs, 10% were in sheltered work places, and nearly half of the patients (46%) were permanently outside the labor market. The high proportion of individuals not working reflects the chronicity of HC and its related causes. It seems clear that problems with integration into society persist into adulthood.
In an adult outcome study on 70 patients shunted during the mid-1970s Sgouros et al. found that the majority of children graduated from a normal school (63%) [226]. In 1974 Raimondi et al. presented a study of 200 consecutive children shunted for HC. Poorer IQ scores were found in children with Dandy Walker syndrome and porencephaly; MMC children had the highest mean scores; no relationship between number of shunt revisions and outcome were found, but the earlier HC was brought under control, the better the outcome [251]. Shurtleff et al. reported that 72% of 5-year survivors with HC and MMC had normal intelligence, but only 50% of 15-year survivors did [252]. Of the children with HC only, 66% of 5-year and 76% of 15-year survivors were in the normal range, intellectually.
In a study of the level and pattern of intelligence in hydrocephalic children, excluding children with mental retardation (IQ < 70), Dennis et al. found that performance intelligence developed less well that the verbal intelligence; ocular and motor deficits significantly affected performance IQ values; and that IQ levels seemed to remain stable over a age range of 5 to 15 years [121]. Amacher et al., found that 64% of HC children, followed for 5-12 years, had normal intelligence as indicated by psychological assessment and school performance. Consistent with previous reports, they also found higher verbal performances; while performances IQ values tended to be lower [224].

In paper 2, approximately 3 out of 4 had completed regular secondary school.
In a cohort of young adults followed-up for a mean of 25 years, Vinchon reported that 32% required schooling in special institutions; and 6% could not be schooled at all. Being young adults, 34% were employed in the competitive labor market, 18% were employed in sheltered jobs, while the unemployment rate was 25% [231]. National differences with regard to social services may attribute to some of the discrepancies.
Lumenta analysed 233 children with congenital HC, MMCs were included, as hemorrhage, tumors and infection were excluded, 115 of 201 survivors were investigated 5 to 27 years after initial procedure. Psychological evaluation revealed normal performance in 63%, while 30% had mild retardation. Severe retardation was seen in 7% of cases. Those being treated with early shunt implantation seemed to achieve better outcomes, while no correlation was found between shunt revision rate and psychological results [130]. In contrast, Halliwell et al. did find some differences in regard to intellectual and educational and number of shunt revisions in HC children with NTD [253]. A recent meta-analysis performed by Arrington et al. in 2016 found a statistically significant inverse association between number of shunt revisions and IQ, but the power of association was small [254].

6.8 Perceived health in adults shunt treated in childhood

Quality of life (QOL) data may be useful for several reasons. It may help when counseling families and provide them with a more concrete and realistic picture of what to expect for their child`s long-term outcome, beyond the information regarding the chance of requiring repeated shunt surgery and mortality rates. Besides, QOL data provide information about the efficacy of our treatment. QOL assesses how the subjects feel about their own level of functioning, thereby providing a more personal perspective on how function affects the life of that individual. Some even claim that QOL data may be useful in performing decision analysis or more complex economic evaluations [255].
Interestingly, "*the disability paradox"*, described by Albrecht, describes that this type of evaluation may reveal surprising results, such as subjectively high personal ratings among those who objectively seem to have poor functioning [256].

The lack of studies regarding QOL in the adult HC population makes comparison difficult. However, a cohort of young adults with spina bifida, of whom 70% also had HC, reported poorer perceived health in six out of eight SF-36 domains [257]. The difference was largest for the physical functioning domain. The subgroup of patients with *spina bifida associated with HC* scored significantly worse in the physical functioning domain. The mental health domains (role limitations due to emotional problems, mental health) did not deviate from those of the reference group.
Gupta et al published the results from a self-reported survey completed by 403 patients older than 20 years of age [125]. Limitations such as selection bias, and lack of ability to validate their data may have an impact on the generalizability of their results. Nevertheless, they reported high rates of depression and impaired social functioning among the adult survivors. These impairments appeared to be generally worse in those diagnosed with HC before 18 months of age.

In paper 2, young adults with surgical treated HC during childhood had lower scores in 2 out of 8 domains. The relative high percentage of survivors with NTD (17%) contributes to this finding, and also supports Verhoef`s findings [257]. In paper 1 (1967-1970), self-perceived health in middle aged adults was even worse. They reported poorer outcome in 6 out of 8 SF-36 domains. When interpreting these results it is important to note that the two different cohorts represent treatment standard in two different time periods with almost 20 years in between.
Therefore, the discrepancies may not necessarily indicate that self-perceived health deteriorates with age. A potential contributing factor may be that twice as many individuals were permanently outside the labor market due to chronic illness in the oldest cohort (46% (paper 1) vs 21% (paper 2)). The association between unemployment and poorer self-perceived health has been demonstrated [258].

Kulkarni et al. developed a disease specific outcome measure, Hydrocephalus outcome questionnaire (HOQ), to estimate Health Related Quality of Life (HRQL) in pediatric HC patients. Perceived health was measured by using parental proxy respondents, i.e. mother or father of the child. The internal consistency of the child's and their parents scoring was good according to the same authors, although they found a tendency of parents to underestimate their child's outcome [259]. They presented their first analysis in 2004 with a mean HOQ overall health score of 0.68 in 80 patients [260]. No association with age or cause of HC was seen. Epilepsy was associated with poorer outcome in all domains.
In a later series, assessing HOQ in 340 patients, the overall outcome was found to be highly variable with notably lower cognitive scores than physical and social-emotional scores [261]. Despite a publicly funded health care system in Canada, health outcome advantages for children from high income families were seen [261]. Besides, prolonged hospital stays and repeated episodes of shunt malfunction were associated with poorer outcome. The latter could be related to pathophysiological effect of intracranial hypertension on the developing brain, and also to the effect of prolonged absence from school and other normal activities. Convincing evidence of a difference in QOL outcome between children treated with ETV or shunt has not yet been found [262].

The HOQ seems useful, but the disease specific measure may be difficult to interpret. Whether a value represent good or bad health is hard to say, given the absence of other comparable measures. Kulkarni has proposed to convert the score into a health utility score. Additionally, there are no longitudinal studies. It would be interesting to see whether HOQ scores remain stable as the child grows, and also to identify aspects influencing each individual score, i.e. episodes of acute shunt failure.

7 Conclusions

- When reviewing our children treated for intracranial hypertension in three different time periods, we found that the case-mix in pediatric patients treated with permanent CSF diversion has changed over the last half-century. With the higher proportion of children with CNS tumor; inclusion of IIH; the gradual decrease in proportion of NTDs; and the proportion of HC caused by Hemorrhage changing from 7 to 19 to 12%, respectively, there has been a shift in median age at initial treatment from 3.2 to 14 months.
- Between the late 1960s and the most recent cohort (2009-2013), the overall short-term mortality (at 2 years) has fallen from 24 to 8%. The causes of death in all periods studied were mainly because of severe comorbidity.
- Shunt-related mortality was 8 and 3% in our first and second paper, respectively, and should still be regarded as a potential risk.
- Despite the decline in demand for elective procedures in the most two most recent cohorts, the re-surgery rate 2 years after primary surgery, is similar.
- Prolonged asymptomatic periods extending 15 years are relatively common and in 1 patient primary shunt failure episode were observed more than 29 years after initial surgery. This underlines the importance of life-long follow-up.
- Our first paper (with more than 40 years follow-up) demonstrate that 96% of living patients still have an artificial CSF diversion forty years after initial treatment, 75% of which have experienced at least one episode of acute shunt failure, indicating that the vast majority of patients are still shunt dependent. This support the dictum; "Once a shunt-always a shunt".
- Despite the fact that all three cohorts are diverse with the individual patients representing a wide range of comorbidities, we conclude that being treated for HC during childhood have a substantial effect on function and perceived health in adulthood. When compared to the reference populations, perceived health was more profoundly reduced in middle-aged adults than in young adults.

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III

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ORIGINAL PAPER

Cerebrospinal fluid (CSF) shunting and ventriculocisternostomy (ETV) in 400 pediatric patients. Shifts in understanding, diagnostics, case-mix, and surgical management during half a century

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Abstract
Objective To characterize shifts from the 1960s to the first decade in the 21st century as to diagnostics, case-mix, and surgical management of pediatric patients undergoing permanent CSF diversion procedures.
Methods One hundred and thirty-four patients below 15 years of age were the first time treated with CSF shunt or ETV for hydrocephalus or idiopathic intracranial hypertension (IIH) in 2009–2013. This represents our current practice. Our previously reported cohorts of shunted children 1967–1970 (n = 128) and 1985–1988 (n = 138) served as backgrounds for comparison.
Results In the 1960s, ventriculography and head circumference measurements were the main diagnostic tools; ventriculoatrial shunt was the preferred procedure (94 %), neural tube defect (NTD) was the leading etiology (33 %), and overall 2-year survival rate was 76 % (non-tumor survival 84 %). In the 1980s, computerized tomography (CT) was the preferred diagnostic imaging tool; ventriculoperitoneal shunt (VPS) had become standard (91 %), the proportion of *NTD* children declined to 17 %, and the 2-year survival rate was 91 % (non-tumor survival 95 %). Hydrocephalus caused by *intracranial hemorrhage* had, on the other hand, increased from 7 to 19 %. In the years 2009–2013, when MRI and endoscopic third ventriculocisternostomy (ETV) were matured technologies, 73 % underwent VPS, and 23 % ETV as their initial surgical procedure. The most prevalent etiology was *CNS tumor* (31 %). The proportion of *NTD* patients was yet again halved to 8 %, while *intracranial hemorrhage* was also reduced to 12 %. In this last period, six children were treated with VPS for *Idiopathic Intracranial Hypertension* (IIH) due to unsatisfactory response to medical treatment. They all had headache, papilledema, and visual disturbances and responded favorably to treatment. The 2 years of survival was 92 % (non-tumor survival 99 %). In contrast to the previous periods, there was no early shunt related mortality (2 years). *Aqueductal stenosis* was a small but distinctive group in all cohorts with 5, 6 and 3 % respectively.
Conclusions The case-mix in pediatric patients treated with permanent CSF diversion has changed over the last half-century. With the higher proportion of children with CNS tumor patients and inclusion of the IIH children, the median age at initial surgery has shifted substantially from 3.2 to 14 months. Between the 1960s and the current cohort, 2 years of all-cause mortality fell from 24 to 8 %. Prolonged asymptomatic periods, extending 15 years, were relatively common. Nevertheless, 18 patients experienced shunt failure more than 15 years after last revision, and first-time shunt failure has been observed 29 years after initial treatment. This underscores the importance of lifelong follow-up.

Keywords Pediatric CSF diversion · Shifts in case-mix and management

Abbreviations

ETV	Endoscopic third ventriculocisternostomy
IIH	Idiopatic intracranial hypertension
VPS	Ventriculo peritoneal shunt
VAS	Ventriculo atrial shunt
CSF	Cerebrospinal fluid

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CPS	Cysto peritoneal shunt
LPS	Lumbo peritoneal shunt
S-DPS	Sub-dural peritoneal shunt
NTD	Neural tube defect
ICP	Intracranial pressure

Introduction

Despite significant advances that have transpired in the treatment of hydrocephalus during the last six decades, most neurosurgeons still regard the management of pediatric hydrocephalus as a challenge. Albeit hydrocephalus has been clinically recognized since antiquity; the current understanding of its pathophysiology is mainly a product of the 19th and 20th centuries [1]. In a classical study, largely valid even today, Key and Retzius in 1875 suggested that the cerebrospinal fluid (CSF) was secreted by the choroid plexus, flowed out of the ventricular system, and was reabsorbed through the subarachnoid villi and pacchionian granulations [1]. Once hydrocephalus was recognized as a mechanical hydraulic disorder, it was realized that theoretically treatment might be through any of the following three means: reducing CSF production by deactivating the choroid plexus, reopening intracerebral blocked fluid pathways with a bypass or a surgical removal of the causative lesion, or shunting CSF into body cavities of normally low pressure using a valved tubing system.

Today's treatment has resulted from discoveries within numerous fields underlining an inextricable mutual bond between basic science and clinical therapy.

Before CSF shunting became common, i.e., in the 1940–1950s, the mortality rate was about 50 % (about one in two children died), and many of the survivors has debilitating deficits [2]. Technological breakthroughs made silicon shunts possible, providing biocompatibilities [1, 3]. At the same time, improved valve technology emerged which explains why between 1956 and 1961 valved shunts had become standard of care [1].

It soon transpired, however, that in most cases shunt surgery could relieve the acute life-threatening disorder while converting it to a chronic condition. Nowadays, mortality is mostly due to the underlying cause of hydrocephalus.

For a period, ventriculoatrial shunts (VAS) were standard, superseded by ventriculoperitoneal shunts (VPS) from about 1980.

In our department, Arne Torkildsen introduced ventriculocisternostomy in 1937 using rubber catheters. These proved to be effective in selected cases [4]. Following the advent of reliable valved shunts, ventriculocisternostomy was performed only occasionally, but since the 1990s advanced neuroendoscopic techniques have resulted in a renaissance of ventriculostomy.

We have chosen a procedure-centered focus rather than concentrating on a more or less well-defined disease entity. The aim of the present work is thus to portray some long lines from the evolving practice of CSF diversion procedures. To this end, we present representative snapshots from three different epochs spanning one-half century of pediatric CSF diversion surgery from the 1960s until today.

Material and methods

All patients under 15 years of age who underwent initial treatment for hydrocephalus and IIH with either a prosthetic shunt system or endoscopic third ventriculocisternostomy (ETV), in the Neurosurgical Department, Oslo University Hospital, Oslo, Norway, between 01 January 2009 and 31 December 2013, were retrospectively analyzed. The patients were selected from surgical protocols according to the NOMESCO (Nordic Medico-Statistical Committee) classification of surgical procedures (NCSP) [5]. The codes selected were the following: ventriculostomy (AAF00), ventriculoperitoneal shunt (AAF05), lumboperitoneal shunt (AAF10), ventriculoatrial shunt (AAF15), shunt of intracranial cysts to peritoneum (AAF40), and other shunt operation (AAF99) (Subduroperitoneal shunt), i.e., all types of prosthetic shunts, and ETV procedures were included. The diagnose of hydrocephalus was based on increased head circumference, typical clinical signs of raised intracranial pressure, and enlargement of the ventricular system on neuroradiological imaging; and in ambiguous cases, intracranial pressure (ICP) recording was used. All the IIH patients had papilledema, and the indication for shunting was stationary or progressive visual field defects despite medical treatment, intractable headache, or both.

The following details were ascertained from the case records: name, age, gender, indication of initial permanent CSF diversion, later CSF diversion procedures, hardware removal with subsequent re-implantation, surgical complications (e.g., shunt infection), survival, and cause of death. CSF diversion procedures due to presumed treatment failure were performed in the presence of moderate to severe clinical symptoms of shunt dysfunction, in most cases, supported by radiological findings. In some patients with vague clinical symptoms and/or non-conclusive radiological findings, ICP monitoring was used to verify the presence of drainage failure, (over- or under drainage) or not, prior to revision.

Two previous cohorts of children, both including children younger than 15 years of age, initially shunted for hydrocephalus in the same institution during the years between 1967–1970 ($n = 128$) and 1985–1988 ($n = 138$) and formed the basis for our comparison [6, 7].

The results from these three time epochs were used to describe our experience as well as shifts in diagnostic work-up, case-mix, and surgical management during half a century.

Statistics

These cohorts include children considered to be in need for CSF diversion referred to our department in the actual time periods. There are obvious differences as to case-mix and surgical approach. Besides, we assume that there are unknown confounders. Statistical probability analysis may therefore seem inappropriate and has therefore not been performed.

Results

Recent cohort

In this first section, we present results from children treated with CSF shunt or ETV in the calendar years 2009–2013. We identified 134 patients (81 males, 53 females) first time treated with CSF shunting or ETV in our department in 5 years, 2009 to 2013. The patients were followed between 2 and 7 years or until death - follow-up was complete in all cases. Last available follow-up was at an average of 8 years 4 months (median 6 years 10 months, range 2.5 to 20.5 years).

The cause of intracranial hypertension is summarized in Table 1. The most common underlying condition was *CNS neoplasm* (31 %). The vast majority of children in need for CSF diversion in the *Hemorrhage* (12 %) group were infants, born preterm with intraventricular or/and intracerebral hemorrhage. Neural tube defects (NTD) accounted for 8 % of the children. The group, here referred to as *Other malformation* (22 %), included a wide range of causes, see Table 1. Patients with IIH accounted for six patients (4 %). Other children without any obvious cause to their elevated ICP were denoted as *Unknown* (17 %).

The mean age at first-time treatment (prosthetic shunt or ETV) was 3 years 11 months (median 1 year 2 months, range 1 day to 14 years 12 months). In 43 (32 %) patients, first treatment was performed during their first 6 months of life; and in 64 (48 %) patients, within the first year of life. Time of initial treatment varied considerable within the different subgroups; whereas, the mean age was 6 years 11 months (median 6 years 11 months) in the *Tumor* group and 6 months (median 10 days) in the *NTD* group. If excluding the patients with *Tumor* and *IIH*, the mean age at first surgical treatment for hydrocephalus was 2 years 1 month (median 7 months).

Within 2 years of initial surgery (prosthetic shunt or ETV), more than half of the patients (52 %) needed to undergo at least one re-do. Repeat surgery was more frequent in the *Hemorrhage* group (mean 2.4), lower in the *Tumor* group (mean 1.1), while no revisions were performed in the three patients with hydrocephalus due to *Infection*. In total, 59/134 (44 %) patients did not require further hydrocephalus-related surgery, and 51/118 (43 %) of whom were alive at follow-up.

Table 1 The underlying cause for permanent CSF diversion in 134 pediatric patients during the calendar years 2009–2013

Cause		No. of patients (%)
CNS Neoplasm		42 (31)
Intracranial neoplasms		
Supratentorial loc.	19	
Infratentorial loc.	17	
Supra- and infratentorial loc.	2	
Intraspinal neoplasms	1	
NF type 1/TS	3	
Hemorrhage		16 (12)
IVH and/or ICH	13	
SAH/other vascular malformations	2	
Acute subdural hemorrhage	1	
Neural tube defects (NTD)		11 (8)
Myelomeningocele		
Lumbosacral loc.	8	
Thoracal loc.	1	
Encephalocele	1	
Anencephaly	1	
Aqueductal stenosis		4 (3)
Other malformations		29 (22)
Syndromal associated HC	11	
Intracranial cysts		
Fossa posterior cysts	3	
Arachnoidal cysts	3	
Chiari 1	5	
Craniosynostosis, non-syndromatic	3	
Dermal sinus tract	1	
Septum pellucidum cysts	1	
Other	2	
Postinfectious		3 (2)
Unknown		23 (17)
Idiopatic intracranial hypertension (IIH)		6 (4)
Total		134 (100)

Patients initially treated with a prosthetic shunt

In 103 (77 %) patients, a prosthetic shunt was placed to treat the child's intracranial hypertension (98 VPS, 2 CPS, 1 LPS, 2 S-DPS). All of whom had clinical symptoms indicating raised intracranial pressure and the vast majority presented with ventriculomegaly on neuroimaging. In some patients ICP recording was used as an adjuvant diagnostic procedure prior to permanent CSF diversion. Furthermore, continuous over-night ICP-recording was used for all the 6 IIH patients to reveal mean ICP pressure and mean wave amplitudes. The mean age at shunt insertion was 3 years 8 months (median 11 months, range 1 day to 14years 7 months). The proportion of children without any revision of initial shunt between 1 and

2 years was 53 % (52/98) and 44 % (41/94), respectively. In times of shunt failure, eight patients were treated with ETV. Two of them did not need further treatment, while six later received a prosthetic shunt. At follow-up (2–7 years), 89 out of 103 initially shunted children were still alive. Twenty-five of these (28 %) had no revision of their prosthetic shunt during the study period.

Idiopatic intracranial hypertension (IIH) was the cause of shunt placement in six patients (three boys, three girls). The mean age at shunt insertion (VPS) was 9 years (median 9 years 8 months, range 4 years to 12 years 3 months). Due to further worsening of vision despite shunt placement, orbitotomy was performed bilaterally in one male patient followed by 11 shunt revisions during follow-up. In the remaining five patients, only one revision was registered. Except from one female patient who in the following has been diagnosed with a hereditary eye condition, the remaining patients reported relief of headaches, improved vision and resolution of chocked disks.

ETV as initial treatment

In 31 (23 %) patients, ETV was the preferred choice of initial surgery. Almost half of them (15 children) had intracranial tumor, of which ten in the posterior fossa. The patients being primarily treated with ETV tended to be slightly older than the individuals first time treated with a prosthetic shunt system with a mean age of 4 years 7 months (median 1 year 6 months). Two patients, both with malignant tumor, died within 2 years of follow-up.

The proportion of children with no re-dos (repeat ETV or conversion to prosthetic shunt) at 1 and 2 years was 67 % (20/30) and 62 % (18/29), respectively. Mean revision-free time in those 11 patients who needed further revisions was 5 months (median 2 months, range 1 day to 2 years). In one patient, a re-stoma was successfully performed, while in the remaining ten patients, VPS was placed.

Shunt related morbidity and mortality

Two hundred and thirty-three surgical procedures (shunt revisions, ETVs, and re-ETVs), with a range of 1–14 procedures for each of the affected children, were recorded. Shunt infection did occur in 14 cases in 12 (9 %) patients, with an incidence of infection per procedure of 3.8 %.

Of the 134 patients evaluated, 16 (12 %) died during follow-up. Analyses revealed survival rates of 98.5, 95.5, and 91.8 at 0.5, 1, and 2 years, respectively (form initial treatment until death), see Table 2. In all 16 cases, the most probable cause of death was due to their underlying condition; 15 patients died due to malignant CNS tumors, and one patient shunted in palliative care died due to severe malformations (anencephaly).

Excluding the tumor patients revealed, survival rate was at 100 % at 1 year and 99 % (91/92) at 2 years.

Patients with CNS tumor

In total, 42/134 (31 %) patients had hydrocephalus associated with CNS tumor. This subgroup differs from the others due to the high mortality rate of 15/42 (36 %), and age at initial treatment. We found a predominance of boys with a male/female ratio of 24/18 = 1.33. There was an even distribution of patients with tumor located supra- and infratentorially (21/42, 50 %), and there was a predominance of high-grade WHO III/IV (24/42, 57 %) tumors. Except from eight patients, all with low-grade tumors, the remaining 34 patients had adjuvant chemo- and/or radiotherapy.

Endoscopic third ventriculocisternostomy was selected as initial intervention for the child's hydrocephalus in 15/42 (36 %) instances. In all 15 patients, nine of whom had an infratentorial location of their tumor, intracranial hypertension was relieved *before* tumor surgery. Preoperative ETV was persistently successful in 12 patients, and three patients were in need for re-surgery due to their hydrocephalus; in one patient, a re-stoma was subsequently performed, while in the remaining two patients, a VP-shunt was inserted.

Prosthetic shunt systems (VP) were inserted in the latter 27 tumor patients, *before* (14 patients) or *after* (13 patients) tumor resection.

Comparison of results in the three different cohorts—from the 1960s, 1980s, and the twenty-first century

The cause of the hydrocephalic state raised intracranial pressure in pediatric patients differs greatly in the three cohorts

Table 2 Survival rates in pediatric patients treated with permanent CSF diversion in three different time epochs

Time epoch	No. of patients (non-tumor)	Overall survival rates (non-tumor)	
		At 1 year	At 2 years
1967–1970	128 (103)	84 (88)	76 (84)
1985–1988	138 (115)	93 (96)	91 (95)
2009–2013	134 (92)	96 (100)	92 (99)

studied. Table 3 gives a brief overview of our major findings. Males outnumbered females in all three cohorts with a male/female ratio of 1.2, 1.9, and 1.5, respectively. Figure 1 demonstrates the etiological factors for each given time epoch. In the 1960s, NTD was accounting for one third of the children requiring shunt insertion [7]; in the 1980s, the proportion was nearly halved to 17 percentages [6], and in the twenty-first century, the proportion of children was only 8 %. Hemorrhage was the cause of shunting in 7 % in the 1960s, increased to 19 % in the 1980s, and reduced to 12 % in the years 2009–2013 [6, 7]. The most common distinct etiological group in the third cohort was CNS neoplasm (31 %) which accounted for 20 and 17 % in the first and second period. Aqueductal stenosis was a small but distinctive group in all the cohorts with 5, 6, and 3 %, respectively. Consequently, there were divergent results regarding age at initial treatment in the three cohorts. The median age in the most recent cohort was 14 months, compared to 6 months in the 80s, and 3.2 months in the 60s.

Our findings concerning preferred initial surgical treatment in children with HC raised intracranial pressure are illustrated in Fig. 2. VA shunt was the initial surgical procedure in 94 % of the cases in our study conducted in the 1960s. In the 1980s, VP shunts was the most common procedure and accounted for 91 %, and the proportion treated with VA shunts had diminished to 4 %. In the third cohort from the twenty-first century, 73 % underwent VPS and 23 % ETV as the first surgical treatment due to raised intracranial pressure.

Event-free survival rate of the primary shunt at 2 years in children treated in the late 60s was 34 % (33 patients of 97 still-alive patients). Excluding elective elongations of the atrial catheters, 42 % of the patients had not experienced shunt failure. In the cohort treated in 1985–88, event-free survival rate after 2 years was 40 % (50 patients of 125 still-alive patients), and in the cohort from 2009 to 2013, event-free survival rate of initial treatment (prosthetic shunt or ETV) at 2 years was 48 %.

Table 3 Comparison of three cohorts of children treated with permanent CSF diversion in different time epochs

			Time epoch		
	Variable		1967–1970	1985–1988	2009–2013
Cohort (no. patients)			128	138	134
Follow up (years)			42–45	20–24	2–7
Median age at follow up (years)			44.6	23.6	6.8
Diagnostic work-up[a]			Ventriculography	CT	CT/MR
Demography	Median age, initial treatment (months)		3.2	6	14
	sex-ratio (M/F)		1.2	1.9	1.5
Etiology (%)	Determined	Neural tube defect	33	17	8
		Hemorrhage	7	19	12
		CNS neoplasm	20	17	31
		Aqueductal stenosis	5	6	3
		Postinfectious	2	6	2
		Other malformations[b]	9	18	22
		IIH	0	0	4
		Trauma	0	3	0
	Undetermined	Unknown[b]	24	14	17
Event-free survival (%)[c]		at 1 year	64	61	56
of the shunt		at 2 years	42	40	48
Mortality (%)	Overall	at 1 year	16	7	4
		at 2 years	24	9	8
	Non-tumoral	at 1 year	12	4	–
		at 2 years	16	5	1
Mortality (no)	Shunt-related	at 2 years	4	1	–

[a] Besides head circumference measurements and clinical signs, this was the most common used neuroimaging technique at time of inclusion

[b] Patients amounting for the *Congenital communicating HC*-group in the cohort from the 1960s were included in the *Unknown*-group, while patients shunted due to posterior fossa cysts/porencephaly, multiple malformations, chromosome defect, Arnold-Chiari malformation, and CNS disease in the late 1960s were included in the *Other malformation*-group

[c] Elective shunt revisions are excluded

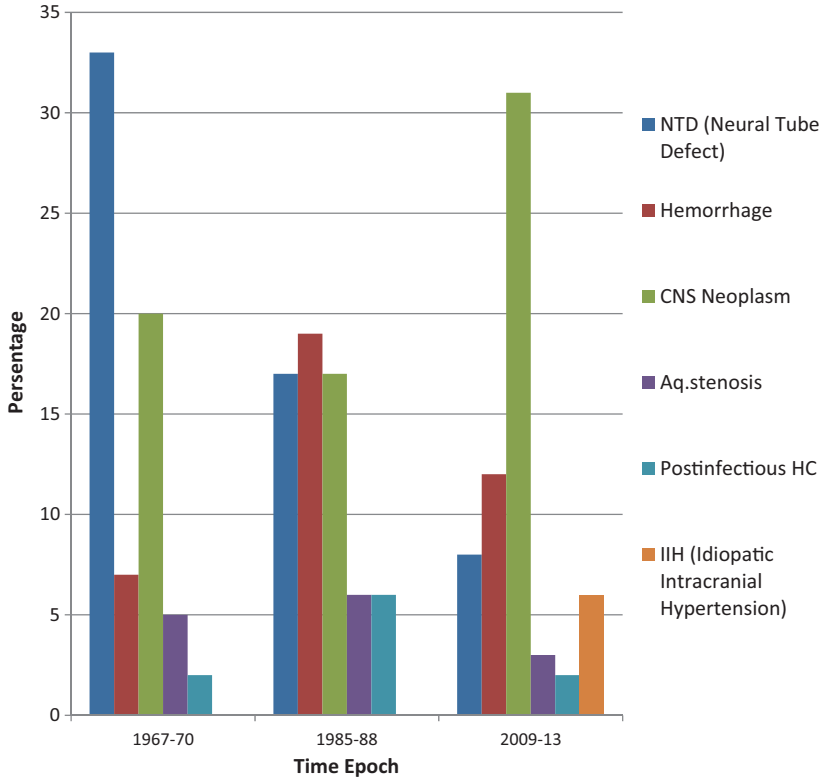

Fig. 1 Case-mix in children less than 15 years of age are in need for permanent CSF diversion (prosthetic shunt or ETV) due to intracranial hypertension in three different time epochs

The overall and non-tumor survival rates (between 1 and 2 years) in the three different time epochs are presented in Table 2.

A long interval between episodes of shunt failure was seen in a number of cases. Fifteen patients in the cohort from the late 1960s and three patients in the cohort from the 1980s experienced stable shunt function for 15 years or more, where after shunt failure occurred. Additionally, one patient experienced first-time shunt failure no less than 29.2 years after initial treatment. This patient had intracranial hemorrhage following intake of amphetamine.

Discussion

This report includes *all* pediatric patients who received permanent CSF diversion during 2009–2013. All patients presented with a variety of typical clinical features indicative of

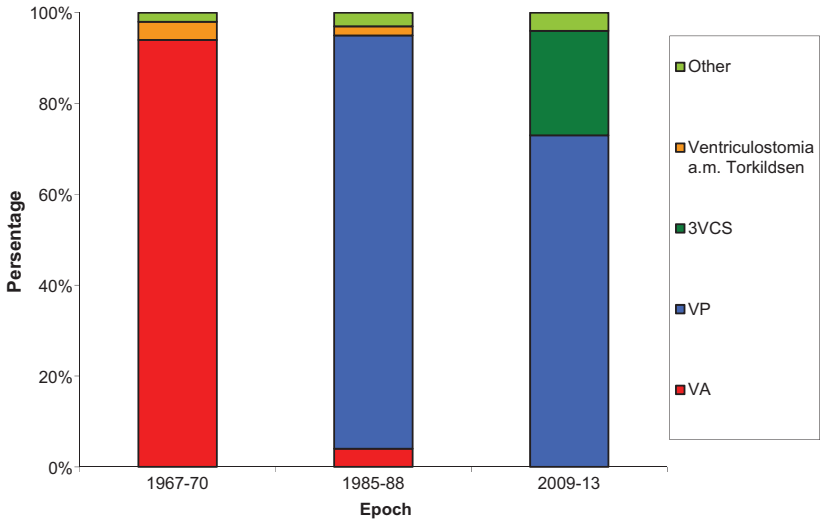

Fig. 2 CSF-shunting in pediatric hydrocephalus patients changing practice patterns 1967–2013

raised intracranial pressure, and the vast majority had mild to severe ventricular enlargement on neuro-imaging. The six patients diagnosed with IIH presented with small or "normal sized" ventricles according to their age. The inclusion of IIH patients may be found controversial by some colleagues claiming that these patients differ from the traditional concept of hydrocephalus. Still, the need for CSF diversion was evident in both entities; and since, there was no children with IIH (Pseudotumor cerebri or benign intracranial hypertension) in our previous two cohorts in the years 1967–1970 and 1985–1988, we found them most proper to include in this historical review, not least, as a supplement for describing differences in case-mix throughout time.

In Norway, as in Sweden and other western countries, the incidence of NTD has decreased over the past decades. Nikkilä et al. did perform a population-based study in Sweden covering the years from 1973 to 2003 showing that the rate of spina bifida in newborns diminished gradually from 0.55 to 0.29 per 1000 [8]. In theUSA, between 1970 and 1989, the neural tube defect rate declined from 1.3 to 0.6 per 1000 births [9]. The decline is probably, to a great extent, a consequence of prenatal ultrasound screening and selective abortion of affected fetus. Better nutritional intake, usage of folic acid supplement before and during early pregnancy, amniocentesis, and screening for alpha-fetoprotein may also have been contributing factors [9, 10]. The gradual decreasing number of shunted individuals with NTD in our three cohorts from the 1960s, the 1980s and further, or until today corroborate with their findings [6, 7].

The advances in neonatal intensive care seen during the 1970s and 1980s reduced perinatal mortality, and more very preterm infants with IVH survived and developed hydrocephalus [11]. Consequently, we encountered more preterm newborns with IVH in need for CSF diversion in the 1985–1988 compared to in the 1967–1970. Despite a continued reduction in perinatal mortality throughout the 1990s, the prevalence of hydrocephalus in infants born very preterm decreased. This was most likely due to improved peri and neonatal care, described by Fernell et al. [12]. The reduced number of newborns in the most recent cohort in need for CSF diversion due to IVH corroborates with those findings.

Summarizing the proportion of patients with *NTD*s and *Hemorrhage* in need for permanent CSF diversion in 1967–1970 and 2009–2013, we find that this proportion has been halved during a time span of 50 years, from 40 to 20 %. At the same time, in the cohort from the twenty-first century, we found a higher proportion of hydrocephalus associated with CNS tumor compared with our previous series [6, 7]. Some studies have found a gradual increase in the incidence of pediatric brain tumors during the last decades [13]. In the USA, a similar increase in childhood brain tumors was reported occurring in the mid-1980s and was explained by an increase, primarily in the detection and reporting of low-grade astrocytomas secondary to improved diagnosis and registration [14]. Likewise, an increase in pediatric brain tumors has also been found in Norway in recent years [15].

During the past five decades, there has been a national increase in the number of hospitals with a neurosurgical care unit, and changes has been made regarding the national geographical distribution of pediatric patients with brain tumor. Therefore, the higher proportion of CNS tumor in this cohort does not necessarily indicate a higher annual incidence of pediatric brain tumors. Yet, our studies only concern *hydrocephalic* CNS tumor patients. Due-Tønnessen et al. performed a study on 100 consecutive children surgically treated for low-grade cerebellar astrocytomas where 15 % experienced a persistent hydrocephalic problem after resection of the tumor [16].

Comparing the three cohorts did reveal a step-wise increase in age at initial treatment. The changing case-mix represented by fewer patients, with NTD and preterm neonates with IVH in need of CSF diversion, explain some of this difference. Further, patients with CNS neoplasm and IIH contribute to increasing the average age. Since the decision for CSF diversion is made by the surgeon on an individual basis, a change in policy over time cannot be fully excluded.

Surgical management

Since the late 1950s, hydrocephalus treatment became more standardized, and shunts into the venous system (usually into the right atrium) were the preferred procedure. Not surprisingly, 94 % of the shunts in 1967–1970 were VAS. Nevertheless, the unavoidable problem of children with longitudinal growth caused gradual retraction of the atrial catheter and serious side effects such as thromboembolic events, pulmonal hypertension, shunt nephritis and sepsis, which led to a negative trend [17–19]. In the 1970s, the use of VP shunts steadily gained ground, and it became the most commonly used variety of shunt. Figure 2 clearly illustrates this shifting practice, and in 1985–1988, we found that 91 % was VPS. Progress in neuroendoscopic technique has been one important contributor to the fact that ETV has gained widespread acceptance as an effective way to manage hydrocephalus in selected pediatric patients. Kulkarni et al. [20] did show that age, etiology, and the presence of previous CSF shunt were each important and independent factors in predicting success of ETV in children and thereby have proposed an ETV success score calculated on these three strata. However, Buxton et al. [21] reported a 23 % success rate in a group of children (with communicating and non-communicating HC) less than 1 year of age (mean age 3.7 months) and suggested that, despite the fact that the majority fail, ETV should be considered as the first-line treatment for hydrocephalus in this age group to spare some individuals the added morbidity of having a shunt (avoid future shunt-related morbidity). Drake et al. conducted a

multicenter study in Canada including 368 pediatric HC patients (34 % brain tumors) and found a 1-year ETV success rate of 65 %, when successful outcome hinged on the absence of further CSF diversion procedures [22].

In our most recent cohort, 38 % of the ETV patients had undergone subsequent surgical procedure for CSF diversion within 2 years. This does not imply a 2-year success rate of 62 %, since 15 out of 31 were tumor patients who underwent initial ETV before tumor removal. Previous reports have demonstrated that the cure rate of hydrocephalus in children with tumor in the posterior fossa was 59 % after tumor resection alone [23]. In our series, two of these patients died within the 2-year period, while some of the other 13 most probably were cured for their hydrocephalic problem after tumor removal. On the other hand it seems clear that the ETV eliminated the acute hydrocephalic problem before tumor surgery.

In some cases of secondary hydrocephalus, improvement may appear after treatment of primary cause due to the reestablishment of CSF pathways. This may cause overestimation of ETV success rate and should therefore be taken into account when comparing ETV outcome.

Nevertheless, treatment with valved shunts has remained the most common procedure in recent years. Our 2009–2013 cohort reveals that VP shunts are used in almost three fourths of the children.

Re-do surgeries

In the most recent cohort, the tumor patients had a lower revisions rate compared to the other etiological subgroups. This could be due to the average shorter observational time caused by deaths shortly after initial treatment, and the fact that some patients, especially those with infratentorial tumors, were cured for their hydrocephalic condition after resection of its origin (tumor).

Pediatric shunt failure rates may be one of several parameters used to evaluate the treatment standard. When VAS was the treatment of choice, elective revisions for lengthening of the atrial catheter were needed in times of growth of the child, whereas the necessity of elective elongations became rarer/non-existing after the introduction of VPS. Moreover, there are essential differences in terms of shunt hardware and the availability of diagnostic tools in our three series which make the comparison challenging. Consequently, comparing revision rate and event-free shunt survival to investigate whether any progress has been made in preventing shunt failure over the past decades are contaminated by differences in practice. Besides, the high early mortality rate in our study on children shunted in the late 1960s, and the high proportion of successfully procedures with CSF diversion among the tumor patients prior to resection of tumor in the posterior fossa in the most recent cohort may both influence our results. Thus, considering our results regarding shunt survival rate at 2 years of 42, 40, and 48 %, in the first, second, and third period, respectively, the results has not clearly improved.

Similar findings were presented by Stein et al. [24] who performed a structured search in the literature to determine whether failure rates of hydrocephalus shunts had fallen in the period from the late 60s and up until the twentieth century, excluding elective lengthening of VAS, where they concluded that no convincing evidence in a reduction of pediatric shunt failure rates were found.

In our two previous series (1967–1970 and 1985–1988), both with more than 20 years of observation, more than one out of ten patients being shunt dependent at follow-up experienced shunt failure after 15 years or more. This substantiates the need for lifelong follow-up.

Early mortality

Due to limited observational time in our latest study, this makes us unable to calculate mortality rates extending 2 years of duration. Since our results from the late 1960s did reveal rather discouraging findings concerning overall short-term survival with only 76 % of the patients surviving at 2 years, our two more recent cohorts from the 1980s to the twenty-first century did present with a higher survival rate of 91 and 92 %, respectively.

The shunt-related mortality rate of 3 % at 2 years in patients treated with VAS in 1967–1970, combined with the fact that there were a high proportion of children dying of unknown cause, made us to propose that treatment with shunt in the 1960s was associated with a higher risk of mortality due to treatment compared with more recent years. No early shunt-related mortality was registered in the most recent cohort.

Follow-up

CSF diversion for hydrocephalus matured in the late 1950s and became established during the 1960s. Although shunt failure was a recognized problem even in the early phase, the most common practice was to wait until blockade of the shunt forced intervention [25]. The awareness upon preventive strategies to avoid complications to shunt treatment and improve outcome in shunted individuals became clearer with time. Becker et al. introduced a program for elective revisions to maintain shunt function in 1960, i.e., elongation of the atrial catheter in growth periods of the child [25]. Besides, Foltz emphasized the importance by periodic and thorough evaluation of the functioning status of the shunt (irrespective of symptomatology) by measurement of ventricular pressure, comparison of ventricular size, psychometric tests, and physical status of the flushing device [26].

Although the majority of the patients in the cohort from the 1960s were routinely followed, there were some exceptions. The higher early mortality rate in the 1967–1970 cohort could

reflect that at the time, management and follow-up had yet to reach maturity.

Still, even today, more than 50 years later, there is no consensus regarding the optimal mode of controlling these patients in regard to frequencies of visits and imaging.

The complexity and rarity of the condition make the follow-up a specialist's role. The role of brain imaging is much debated. It is important to obtain a baseline cerebral imaging to provide adequate comparison when suspicion of shunt malfunction arises. Some authors advise a clinical visit in older children being asymptomatic of shunt failure every second year [27]. In our institution, newly shunted infants have scheduled control at 1 month, and then at 2 to 6 months. Thereafter, in the absence of symptoms of possible shunt malfunction, we currently perform controls at 1 to 2 years, with the frequency decreasing as the child grows.

Limitations of the study

The retrospective nature of this study poses several methodological limitations. First, patient selection was determined by the treating surgeon. Varying individual thresholds for determining both the need for operative intervention for hydrocephalus, decision upon prosthetic shunt or ETV, and the need for repeat intervention could have an impact on patient selection, choice of treatment, and the observed failure rates. Second, comparing results of CSF diversion in pediatric patients in three different time epochs will inevitably also reflect the inherent differences in practice patterns and thereby influence the results. Due to the complexity of confounding factors, we have refrained from using multivariable statistical analyses in this series. Third, because the most recent series were performed relatively recently, the length of follow-up is rather short, thereby limiting our ability to make comparisons extending 2 years of duration. Taken together, these limitations force us to be cautious in the interpretation of our results and emphasize the empirical nature of our study.

Evolvement is continuous, and understanding current practices in order, hopefully, to foster future improvement calls for knowing the long lines leading from the practice of the past to that of the present.

Conclusions

The case-mix in pediatric patients in need for permanent CSF diversion has evolved during half a century. There has been a marked decline in the proportion of infants with neural tube defects and IVH in need for treatment due to intracranial hypertension. Almost one third of the children in need for CSF diversion in 2009–2013 were diagnosed with CNS tumor. Patients tend to be older at initial treatment in the twenty-first century compared to 50 years ago. Although the need for re-do surgery does not differ notably in the three time epochs, early-mortality (at 1 and 2 years) seems to have been lowered. Severe shunt failure may take place at any time, even after prolonged periods of stable shunt functioning, indicating the need of life-long follow-up.

Compliance with ethical standards

Conflict of interest The authors decleare no conflicts of interest.

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IV

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LETTER TO THE EDITOR

Persistent shunt dependency and very late shunt failure in a 3-year-old boy with idiopathic intracranial hypertension (IIH)

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Dear Editor:
This letter reports an unexpected clinical experience of persistent shunt dependency in a 3-year-old boy who underwent cerebrospinal fluid (CSF) diversion for IIH.

In 1937, Walter Dandy published a series of 22 patients treated surgically for intracranial hypertension without a tumor [1]. Among his cases treated with subtemporal decompression during a period of 10 years, there were three children. Later on, this condition with papilledema, headache, and visual disturbances was called benign intracranial hypertension, and many of them could be managed favorably by medical treatment [2]. In more severe cases, it soon became clear that this obscure disease is not always that benign [3]. In severe cases, the term malignant pseudotumor was introduced [4].

Later on, the term idiopathic intracranial hypertension (IIH) was introduced [5].

Neurosurgical treatment with CSF diversion has been performed in severe cases where the response to medical treatment has been unsatisfactory, or as primary treatment in patients with severe visual affection [4, 5]. Unlike the situation for hydrocephalic children treated with CSF shunts who for the most become shunt dependent, clinical results on long-term shunt dependency in IIH are unavailable.

We have treated a boy with IIH giving us a remarkable clinical experience:

> In 1989, a 3-year-old boy was admitted with a short history of lost vision for 36 hours, reduced pupil reactivity, ataxia, and poor general condition. Fundoscopy demonstrated choked discs, and cerebral MRI was normal including unobstructed venous outflow. Lumbar puncture revealed normal CSF composition and increased CSF pressure, but the intracranial pressure (ICP) level was difficult to measure due to lack of cooperation. A lumbar infusion test during general anesthesia demonstrated increased CSF opening pressure as well as slightly increased outflow resistance.

Due to the dramatic clinical symptoms with complete visual loss, corticosteroid treatment was implemented, and an acute shunt procedure was performed during the same general anesthesia. A proximal catheter was introduced into cisterna magna and connected to a low pressure Holter valve with diversion to the peritoneal cavity.

His vision gradually reappeared within days, and after 1 week, there was normal vision and pupillary reactivity to light. Some ataxia and clumsy motor function persisted for weeks, but after 6 months his clinical condition was quite normal. During the first 2 years of treatment, he experienced a few episodes with headache, ataxia, and diplopia (sixth nerve paresis) which resolved spontaneously within a couple of days or after pumping on the Holter valve. At the age of 5 years (1991), he demonstrated episodes of overdrainage in the upright position, which subsided after implementation of an ASD (anti-syphon device) distal to the valve.

He grew up in a family with a large repertoire of sport activities. At the age of 19 years, he joined the technical university of Norway and fulfilled a master's degree. During his

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university studies (in 2006), he became acutely ill with signs of increased ICP (headache and vomiting). There was no choked discs, but lumbar puncture revealed markedly increase CSF pressure level (50 cm H_2O) and no signs of infection. Once more, MRI was normal (Fig. 1). After a shunt revision (LP-shunt), his clinical condition normalized within a few days. In 2009, he experienced shunt failure once more, again followed by rapidly improvement after shunt revision. Thereafter, he has been working full time and has been clinically quite well for another 7 years.

The present case with a very rewarding clinical result indicates that this 30 year-old man in excellent condition most likely is permanently a shunt dependent.

Neurosurgical treatment by CSF diversion is well established in IIH patients with severe visual affection as well as in cases with unsatisfactory response to medical treatment. The present case report describes the full return of vision after complete blindness in a 3 year-old boy. While the initial response to shunt implantation is usually good, shunt failure as well as symptoms of overdrainage has been reported.

When the clinical result is good over years, as in this case, it is difficult to know if the shunt is still functioning or the underlying condition has normalized spontaneously.

Shunt implantation in children with severe IIH raises the question of making these children permanently shunt dependent [3]. While some authors have addressed this question, no cases with late or very late shunt failure has been reported.

This case with 27 years follow-up, indicate that individuals shunted for IIH can be persistently dependent on their shunt, and may experience acute shunt failure even after many years of treatment.

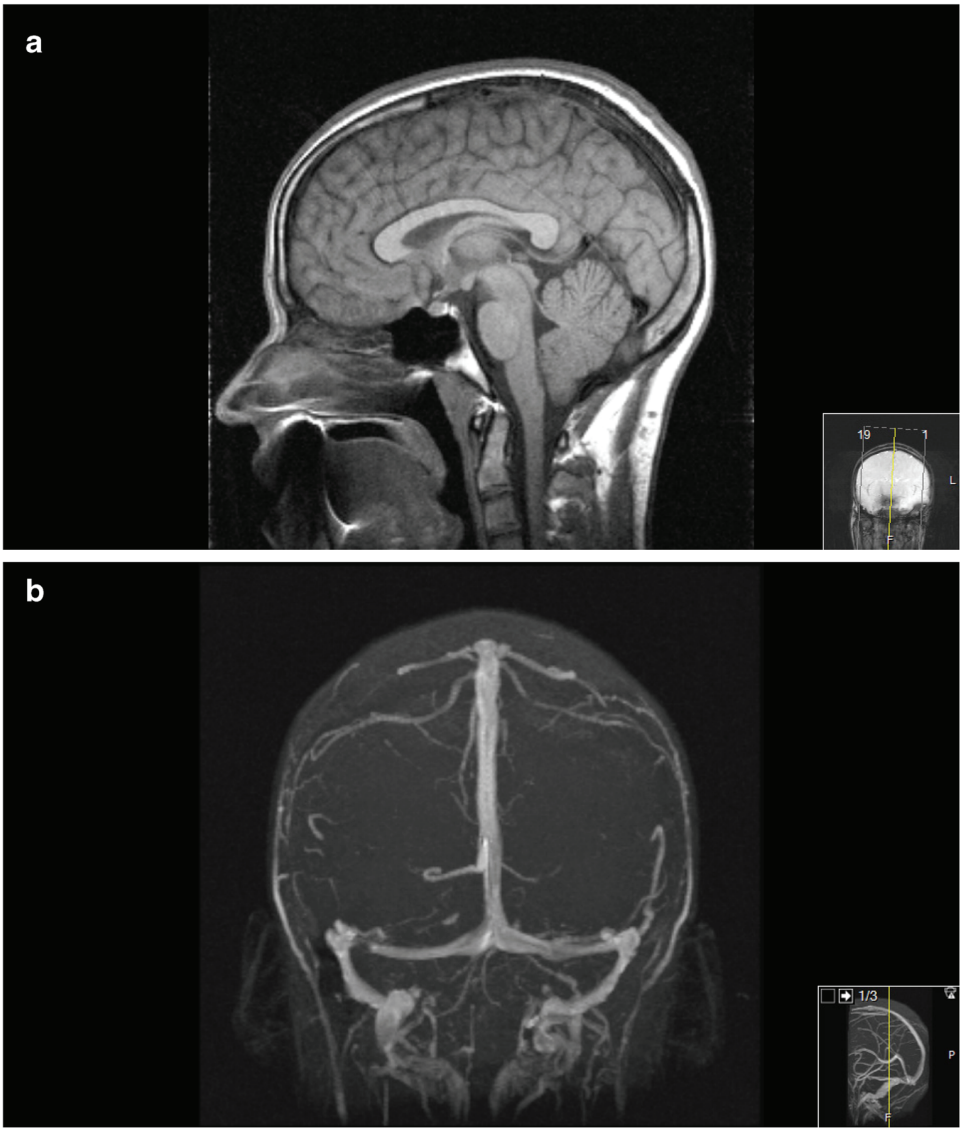

Fig. 1 Normal MRI including venous outflow taken in 2006 during episode of shunt failure

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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