Infantile external hydrocephalus

Epidemiological, radiological, clinical, cognitive, and social aspects

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Thesis for the degree of Doctor Philosophiae (dr. philos.)
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Abstract

Background

External hydrocephalus is a condition sometimes seen in infants. It is characterized by an enlarged head or rapidly increasing head circumference. Neuroimaging shows wide subarachnoid spaces, especially overlying the frontal lobes. The condition has traditionally been termed 'benign', as most children seem to do well, and symptoms and neuroimaging findings normalize over time. Hence, few infants have been treated for this condition. However, limited knowledge exists on long-term consequences of external hydrocephalus, the possible benefit of treatment, epidemiology, and its connection with the very similar conditions chronic subdural hematoma (SDH) and hygroma (SDHy).

Aim

To gain thorough epidemiological data about external hydrocephalus in infants. To explore the long-term consequences of external hydrocephalus, both with and without treatment. To examine the pathophysiology of external hydrocephalus and chronic SDH/SDHy, and their relation to and importance in the investigation of infants with suspected abusive head trauma (AHT).

Methods

Papers 1-4 are based on a cohort of infants diagnosed with idiopathic external hydrocephalus in a relatively well-defined population in Southern Norway during the period 1994-2003. Papers 1 and 3 explored the epidemiology, clinical features, and radiology of external hydrocephalus in this cohort. In papers 2 and 4, long-term neurocognitive and psychosocial functioning were evaluated using neuropsychological tests and questionnaires. Paper 5 is a literature survey exploring the pathophysiology behind external hydrocephalus and chronic SDH. Paper 6 is also a review, focusing on the existing knowledge about bridging veins, thrombosis, and its role in AHT diagnostics. Paper 7 is

based on a cohort of infants with SDH and alleged AHT. Clinical and neuroimaging findings are explored.

Results

The incidence of idiopathic external hydrocephalus was 0.4 per 1000 live births, with a large male preponderance (86.4 %) (paper 1). The main symptom was a large and/or rapidly increasing head circumference, with a mean age at debut of 3.4, range 0-7 months. Neuroimaging showed lateral ventricle enlargement in most cases, with neuroimaging characteristics persisting beyond one year of age (paper 3).

The results on neuropsychological tests were compared with the normative mean (paper 2). Performance IQ and verbal fluency in children with prior external hydrocephalus were better than the normative mean, while attention span, psychomotor speed, executive functions, and fine motor functions were poorer. On quality of life, the children scored themselves better than the normative mean, while the parents scored the children poorer on the school subscore. Operated children performed poorer than non-operated ones on two tests of psychomotor speed. For some of the patients, various cognitive and social problems were reported (paper 4).

Reviewing the literature, the similarities between external hydrocephalus and chronic SDH were discussed, such as neuroimaging and fluid characteristics, and sex and age distribution. A birth-related perinatal SDH was suggested as a common etiological condition (paper 5).

A thorough literature review covering radiological studies, autopsy studies and biomechanical studies could not support the suggestion that neuroimaging signs of thrombosis are markers of bridging vein rupture, and thus AHT (paper 6).

Infants with chronic SDH and alleged AHT had a male preponderance and low mortality, and were associated with external hydrocephalus and stretched

bridging veins. Infants with acute SDH, subarachnoid hemorrhage, or hypoxic-ischemic injury, seemed to comprise distinct groups (paper 7).

Conclusions

Infantile external hydrocephalus occurs in 0.4 of 1000 live births, which is around half of all infants with primary hydrocephalus, and has a marked male preponderance. Although most children with external hydrocephalus seem to do well when growing up, a non-negligible number of patients struggle in various areas, especially related to school functioning. Treatment with a shunting procedure does not seem to improve outcome.

As the epidemiological and neuroimaging features of external hydrocephalus and chronic SDH are similar, a common etiology seems plausible. A small SDH during birth could be one possible common cause. External hydrocephalus should also be kept in mind when investigating infants with chronic SDH and alleged AHT. Our results both question the neuroimaging “evidence” of bridging vein rupture, and show that an underlying external hydrocephalus can mimic symptoms and findings of suspected AHT.

List of publications

Paper 1: **Epidemiology of benign external hydrocephalus in Norway – a population-based study**

Wiig US, Zahl SM, Egge A, Helseth E, Wester K.

Pediatr Neurol 2017. 73:36-41.

Paper 2: **Neurocognitive and psychosocial function in children with benign external hydrocephalus (BEH) – a long-term follow-up study**

Mikkelsen R, Rødevand LN, Wiig US, Zahl SM, Berntsen T, Skarbø AB, Egge A, Helseth E, Andersson S, Wester K.

Childs Nerv Syst 2017. 33(1):91-99.

Paper 3: **Clinical, radiological, and demographic details of benign external hydrocephalus: a population-based study**

Zahl SM, Egge A, Helseth E, Wester K.

Pediatr Neurol 2019. 96:53-57.

Paper 4: **Quality of life and physician-reported developmental, cognitive, and social problems in children with benign external hydrocephalus – long-term follow-up**

Zahl SM, Egge A, Helseth E, Skarbø AB, Wester K.

Childs Nerv Syst 2019. 35:245-250.

Paper 5: **Examining perinatal subdural haematoma as an aetiology of extra-axial hygroma and chronic subdural haematoma**

Zahl SM, Wester K, Gabaeff S.

Acta Paediatr 2020. 109(4):659-666.

Paper 6: **Thrombosis is not a marker of bridging vein rupture in infants with alleged abusive head trauma**

Zahl SM, Mack JA, Rossant C, Squier W, Wester K.

Acta Paediatr 2021. 110(10):2686-2694.

Paper 7: **Neuroradiological findings in a national cohort of alleged abusive head trauma cases suggest different etiologies**

Zahl SM, Andersson J, Wester K, Wikström J.

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Comments on the candidate's contributions

Paper 1:

The candidate conceptualized designed the project together with the senior author. He collected the data. He took part in the review and editing of the manuscript.

Paper 2:

The candidate conceptualized and designed the project together with the senior author. He collected the initial part of the data (from patient records) and investigated them. He took part in the review and editing of the manuscript.

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Paper 6:

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Paper 7:

The candidate analyzed the data and interpreted them. He wrote the manuscript, and took part in the review and editing of it.

Abbreviations

AHT	abusive head trauma
BEH	benign external hydrocephalus
BRIEF	Behavior Rating Inventory of Executive Function
CCW	craniocortical width
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CVT	cortical vein thrombosis
EEG	electroencephalography
HII	hypoxic-ischemic injury
HOQ	Hydrocephalus Outcome Questionnaire
ICP	intracranial pressure
IQ	intelligence quotient
IHW	interhemispheric fissure width
MRI	magnetic resonance imaging
PedsQL	Pediatric Quality of Life Inventory
RH	retinal hemorrhage
SAH	subarachnoid hemorrhage
SCW	sinocortical width
SD	standard deviation
SDH	subdural hematoma
SDHy	subdural hygroma
SSS	superior sagittal sinus
VP	ventriculoperitoneal

1 Introduction

Hydrocephalus is one of the most common neuropediatric conditions, with an incidence of about 0.8 per 1000 births (1, 2). It is commonly defined as an abnormal cerebral ventricular expansion, i.e. a disorder of cerebrospinal fluid (CSF) physiology (3).

External hydrocephalus can be seen as a form of hydrocephalus where the CSF-filled (subarachnoid) spaces *outside* the brain are enlarged (4). Although the term 'external hydrocephalus' is old (5, 6), it became more common after the introduction of modern neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI).

External hydrocephalus is a condition seen in infants. It is the combination of a large or increasing head circumference, combined with radiological findings of enlarged extracerebral subarachnoid spaces, mainly frontally, with normal or slightly/moderately enlarged lateral ventricles (4, 7, 8). The word 'benign' is commonly used, as the condition is regarded as self-limiting and with a good, natural outcome. Compared to other hydrocephalus subtypes, these children seem to do better and is rarely in need of surgical treatment (4, 9).

Through the years, several terms have been used on this and similar conditions (Table 1).

Table 1: Different terms for external hydrocephalus or similar conditions as found in the literature, with reference to the articles where they were used. Adapted from paper 5.

Benign/idiopathic external hydrocephalus (7, 10)
Benign infantile hydrocephalus (11)
Benign extra-axial fluid/collection (12, 13)
Benign communicating hydrocephalus (14)
Subarachnoid fluid collection (15)
Benign extracerebral fluid collection (16)
Benign enlargement of the subarachnoid spaces (BESS) (17)
Benign familial macrocephaly (18)
Benign subdural collection (19)
Pericerebral fluid collection (20)
Chronic subdural hematoma (21)
Chronic subdural hygroma (22)
External hydrocephalus (23)
Idiopathic macrocephaly (24)
Subdural effusion (25)

In this thesis, the term ‘external hydrocephalus’ will be used.

What follows is a summary of knowledge about external hydrocephalus in infants, as it appeared at the start of this project.

1.1 Definition

In modern textbooks, external hydrocephalus is defined as enlarged subarachnoid spaces seen in infancy, usually accompanied by abnormally increased head circumference with normal or moderately dilated ventricles (26). The term external hydrocephalus was first used by Dandy and Blackfan in

1914 (6). They defined it as increased intracranial pressure (ICP) combined with dilated subarachnoid spaces in infants.

After the introduction of modern neuroimaging modalities such as CT and MRI, external hydrocephalus was finding its present definition as mentioned above. A few articles from late 1970s and early 1980s have been cited numerous times and still serve as important references (7, 14, 17, 23, 27-29).

1.2 Epidemiology

No previous studies have reported the incidence or prevalence of external hydrocephalus, nor the number of hydrocephalic children with this condition, as most of the studies are hospital based. Finding better epidemiological data was a main objective of this project.

1.2.1 Sex

A male preponderance of around two thirds is reported in most studies (13, 19, 21, 27, 30-37). This is thoroughly investigated in this project.

1.2.2 Age

External hydrocephalus occurs during infancy (first year of life), with most cases occurring around six months of age (7, 32). Many reported children are born prematurely (usually defined as a gestational age < 37 weeks). Alvarez et al. concluded that 50 % of their patients had idiopathic external hydrocephalus, while many of the others were premature (7). Yew et al. reported that 20 of the 99 infants with external hydrocephalus in their institution were premature (38). The incidence of external hydrocephalus in very low birth weight survivors were found to be 3.3 per 1000 in a United States high-risk infant follow-up program (15).

1.2.3 Macrocephaly

Of macrocephalic children (head circumference ≥ 95th percentile) investigated at a children's hospital, 16 % had external hydrocephalus (16). In a large radiologic survey, Tucker and colleagues found that 57.8 % of the macrocephalic children in their hospital had external hydrocephalus (39). Two other studies found that around 65 % of macrocephalic children in their cohorts had external hydrocephalus (30, 40).

1.3 Etiology

External hydrocephalus in infants is an idiopathic condition, hence no direct causes are known, although several risk factors and associated conditions exist (chapter 1.3.5). Some theories of pathophysiology have been suggested.

1.3.1 Pathophysiology

A common theory is that the accumulation of CSF is caused by immature arachnoid granulations (or villi), thus causing a reduced filtration of CSF and subsequently an increasing volume of CSF, especially close to the granulations, i.e. on the surface of the brain (29). As long as the skull is compliant (open sutures and fontanelles), the result will be an increasing head growth, rather than more dramatic symptoms of increased ICP (14). The reason for a delayed maturation is unknown, but some heredity has been suggested, which could explain the high degree of "familial macrocephaly" commonly reported (7, 28, 30, 31, 41).

Related to this theory is the idea of 'arrested hydrocephalus', which suggests that external hydrocephalus is a step towards communicating hydrocephalus (23). It has been suggested that cases requiring a shunting procedure are more likely due to agenesis rather than delayed maturation of the arachnoid granulations (42).

Other authors have suggested that the skull might be growing faster than the brain for some time, hence creating a temporary, fluid-filled space between these structures (43). This, however, seems unlikely as common knowledge is that the increasing volume of the intracranial content (brain and CSF) drives skull growth, not vice versa (44).

Robertson et al. found reduced CSF flow over the cerebral convexities in infants with subdural collections, and hypothesized that subdural fluid might obstruct the reabsorption of CSF through the arachnoid villi, creating a local enlargement of the subarachnoid space (19).

1.3.2 CSF outflow

The traditional view of CSF physiology is that it is produced in the choroid plexus in the ventricles, flows through the ventricles, aqueduct and foramina until it reaches the subarachnoid space, where it is filtered by the arachnoid granulations into the venous circulation. Arachnoid granulations develop gradually during infancy and early childhood (45). However, more recent research reveals a far more complex CSF outflow physiology than previously thought. CSF is absorbed along the roots of cranial and spinal nerves, ending in lymphatic vessels (46, 47). A perineural pathway through the cribriform plate into the nasal mucosa is also described (48, 49), and absorption may also occur along the blood vessels (50). Although these last observations of absorbance pathways are mainly based on animal studies, a recent MRI survey found that intrathecally administered contrast “escaped from CSF into parasagittal dura along the superior sagittal sinus” (51).

Some evidence suggest that CSF may be absorbed through the ependyma-lined ventricles, at least when the ICP is increased (52). The recently discovered cell membrane water channels (Aqp4) is thought to play a role in water transport, hence CSF absorption, especially through the ependyma (46).

Prior to the maturation of the arachnoid granulations, CSF is possibly absorbed in the intradural capillary bed, through venous plexuses that later seem to degenerate as the arachnoid granulations form (53).

CSF dynamics is a field still under investigation, with partly diverging hypotheses of CSF drainage (54). See Figure 1.

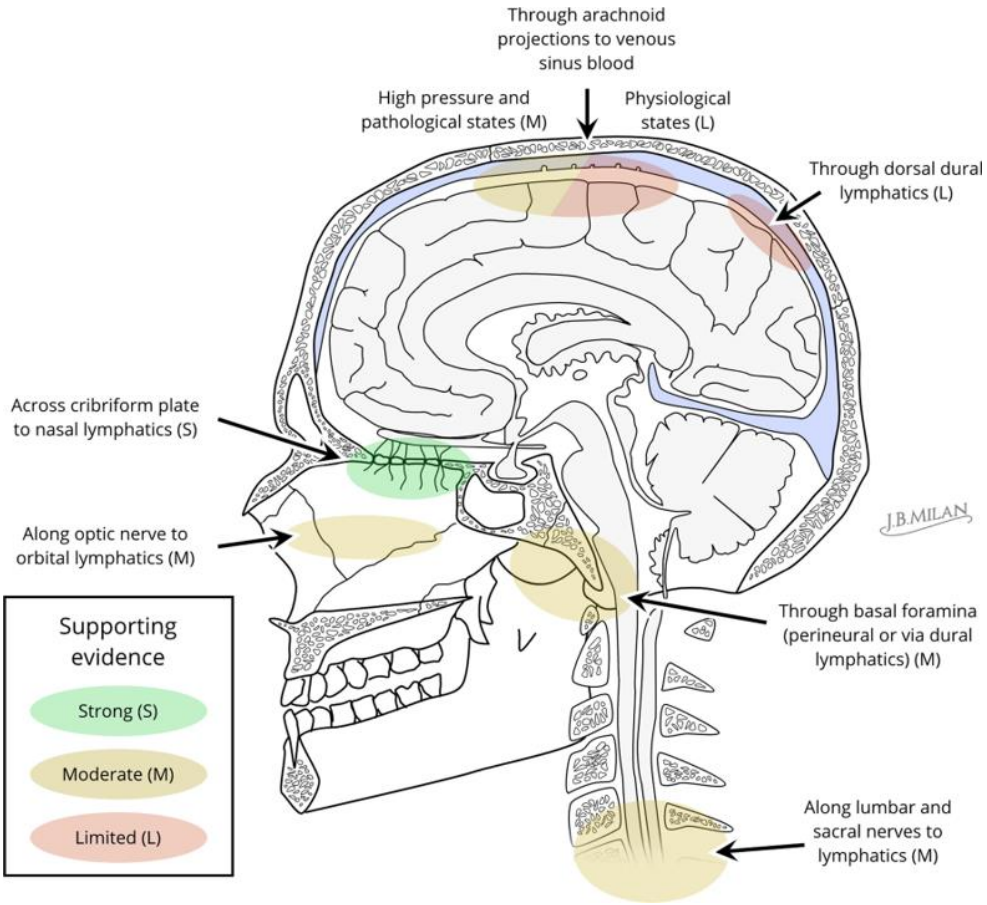

Figure 1: Depicting known routes of CSF absorption. The colors indicate level of evidence for the specific drainage routes, as considered by the author of this review article (55). Reprinted from Proulx. Cell Mol Life Sci 2021. Creative Commons License 4.0.

1.3.3 External hydrocephalus in fetal life

The subarachnoid spaces are wide during fetal life, starting to decrease to normal size around 32 weeks of gestation (56). Girard et al. found that 19 % of fetuses with mild ventriculomegaly and prominent subarachnoid spaces developed external hydrocephalus postnatally (57). They also found that during pregnancy, the fluid is most prominent posteriorly (58). This is thought to reflect the development of the subarachnoid space, which begins as a cavitation of the primitive meninges, spreading from the ventral to the dorsal part of the neural tube. Of fetuses with congenital heart disease, 7 % had increased extra-axial spaces in one report (59). This, however, was not shown in a recent study using 3D ultrasound (60).

Nine fetuses with macrocephaly and wide subarachnoid spaces were followed until two years age, all but one (who had a genetic mutation) developed normally (61). In children with isolated fetal ventriculomegaly, a favorable neurodevelopmental outcome was seen in about 80 % of cases (62).

In a case series of ten fetuses with widened subarachnoid spaces, associations with maternal alcohol use and congenital cytomegalovirus infection were identified. Only one child had a normal postnatal development (63).

1.3.4 Heredity

Many external hydrocephalus children seem to have close relatives with macrocephaly, hence some degree of heredity has been assumed. It is probable that the term “familial megalencephaly” were previously used for external hydrocephalus, although those studies often lacked modern neuroimaging (18, 64). Most studies report that around 40 % of external hydrocephalus children have at least one relative with a large head (28, 30, 31, 34, 43, 65). Case reports of twins and triplets seem to support some heredity (10, 66-70). Both autosomal dominant (7, 71) and multifactorial (72) models of inheritance have been suggested.

1.3.5 Risk factors

External hydrocephalus has known risk factors such as prematurity and intraventricular hemorrhage (14, 17, 32, 73), meningitis (14), metabolic disorders (74), steroid therapy (75), chemotherapy (76), neurosurgery (77), and trauma (14). Raised venous pressure, for instance following cardiac disease, has also been related to external hydrocephalus (78, 79).

Some congenital conditions are associated with external hydrocephalus, such as craniosynostoses (80, 81), achondroplasia (82, 83), Sotos syndrome (83-85), and glutaric aciduria type 1 (86, 87).

1.4 External hydrocephalus and SDH

External hydrocephalus is thought to be a risk factor for developing subdural hematoma (SDH) after minimal or no head trauma (32, 88-94). A suggested explanation for this is that the veins traversing the subarachnoid space ('bridging veins') are stretched in external hydrocephalus, thereby being more vulnerable to injury, and thus bleeding (95). The theory however has been questioned recently. Based on a finite element model of an infant head with enlarged subarachnoid spaces, Raul et al. simulated shaking of the infant, with emphasis on the bridging veins (96). They concluded that the enlarged subarachnoid spaces probably had a *dampening* effect and that it therefore is not a risk factor for developing SDH. Fingarson and colleagues did not find enlarged subarachnoid spaces to be associated with SDH in children with minor head traumas (97).

SDH is commonly divided in chronic and acute. Chronic SDH and external hydrocephalus are both chronic subdural collections, which is reflected in the literature where both terms have been used for similar conditions (Table 1). This subject has been thoroughly investigated during this project, and is reviewed in detail later in the thesis.

1.5 Neuroimaging

As a prerequisite for the condition, the typical external hydrocephalus patient has enlarged extracerebral spaces, especially overlying the frontal lobes, and normal or moderately enlarged ventricles. Common imaging modalities are cranial ultrasound, CT and MRI (Figure 2).

0.6 % of the children in a pediatric neurology practice had external hydrocephalus in a survey of intracranial incidental findings on MRI (98).

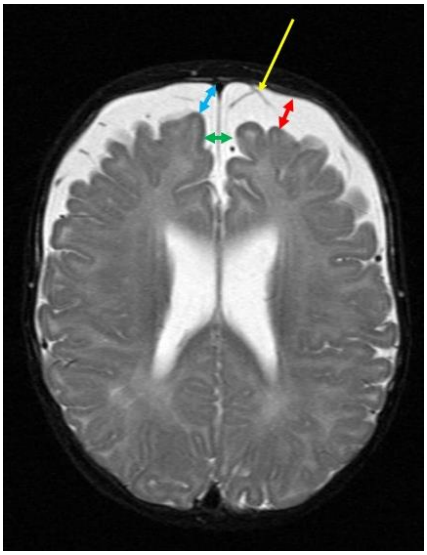

Figure 2: An MR image of a 6.5-month-old boy with external hydrocephalus. The investigation was undertaken due to a rapidly increasing head circumference. The frontal subarachnoid spaces are enlarged - increased craniocortical (CCW – red arrow), sinocortical (SCW – blue arrow) and interhemispheric (IHW – green arrow) widths - and there is slight ventriculomegaly. There is no flattening of adjacent gyri. Bridging veins can be seen traversing the subarachnoid space (yellow arrow).

1.5.1 Size of the extracerebral space

The definition of a normal extracerebral or subarachnoid space size varies in the literature. There also exist different ways of measuring this space. Lam et

al. defined craniocortical width (CCW) as the widest vertical distance between the calvarium and the cortical surface, sinocortical width (SCW) as the widest distance between the lateral wall of the superior sagittal sinus and the cortical surface, and interhemispheric width (IHW) as the widest horizontal distance between the hemispheres (99). See Figure 3 for common measuring options, and Table 2 for published upper limits of normal subarachnoid spaces. The wide range reflects the rather divergent measures published. This lack of consensus will lead to uncertainty both when comparing studies of external hydrocephalus, and between cases examined by different radiologists. What is a pathologically increased subarachnoid space?

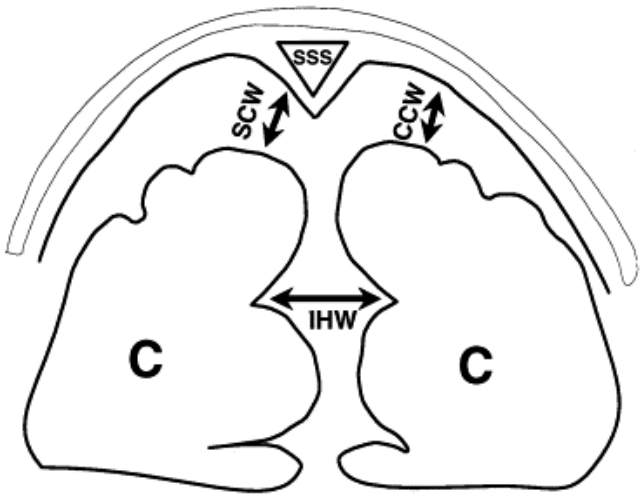

Figure 3: Schematic view of the subarachnoid space. C = cerebral cortex; SSS = superior sagittal sinus; CCW = craniocortical width; IHW = interhemispheric fissure width; SCW = sinocortical width.

Reprinted from Lam et al. Pediatr Neurol 2001. With permission from Elsevier.

Table 2: Published upper limits of normal subarachnoid space size in infants (99-107), above which the subarachnoid space has been regarded as abnormally large.

Craniocortical width (CCW)	4 – 10 mm
Interhemisferic fissure width (IHW)	5 – 8.5 mm
Sinocortical width (SCW)	2 – 10 mm

Another important aspect is how the size of this space develops over time. Yu et al. recently published percentiles of "cerebrospinal fluid width" in normal children 1-24 months of age, divided in two-month intervals (106). They found that the frontal CSF width was largest at 5-6 months of age.

1.5.2 Ventricular enlargement

Some degree of dilatation of the lateral ventricles is commonly found in external hydrocephalus, although the amount of patients with ventricular dilatation varies considerably between studies (8, 13, 24, 29-31, 84, 89, 108). One study found that the degree of ventricular enlargement was proportional to the width of the frontal subarachnoid space (109). Maytal et al. reported that ventricular dilatation was a later finding than subarachnoid enlargement, i.e. that the enlargement 'spread' in a reverse direction of the expected CSF flow, like a stasis of fluid (84).

Enlarged third ventricle and basal cisterns have also been reported (8, 10, 29).

The excess subarachnoid fluid seems to decrease and disappear spontaneously within 2-3 years of age (8, 24, 31, 36, 41, 65, 84, 110). Once the subarachnoid fluid disappears, it does not seem to recur (35). Muenchberger et al. did the longest follow-up (24). All nine patients with long-term neuroradiological follow-up (mean age 19 years old) had normal MRI findings.

1.5.3 Radiological differentiation

To differentiate between external hydrocephalus and other subdural fluid collections can be challenging. A cortical vein traversing the fluid is thought to show external hydrocephalus, as a subdural collection (such as SDH) would compress the subarachnoid space and the veins in it (20, 111). Furthermore, in an early CT era survey, the authors observed that enlargement of the basal cisterns was often seen in external hydrocephalus, but not in SDH (17). Finally, based on fluid intensity, differentiation between CSF and other fluids can often be made on MRI (20, 112).

1.6 Other investigations

Some early studies of external hydrocephalus performed additional investigations of these children:

1.6.1 Fluid composition

The composition of the fluid found in the enlarged extracerebral space varies from normal CSF (7, 43), to xanthochromic fluid with high protein concentration (113, 114). The latter is possibly due to an older hematoma, also known as chronic SDH.

1.6.2 ICP measuring

ICP measurements in external hydrocephalus vary from normal (43) to slightly increased pressure (37, 68). In one study, a normal baseline pressure was found, but abnormal rises above 20 mmHg occurred intermittently (42).

1.6.3 Electroencephalography (EEG)

Seizures are not an uncommon symptom in external hydrocephalus (see chapter 1.7.2), and some studies report abnormal EEG findings – often as non-specific slowing of electric activity (37, 42, 43, 110).

1.7 Clinical presentation

1.7.1 Macrocephaly

Most often, a large head or rapidly increasing head circumference is the first symptom in infants with external hydrocephalus, sometimes followed by other symptoms. As head circumference is measured regularly during infancy, a deviating growth curve is often the initial sign leading to referral, typically when crossing two or more percentile lines. This is similar to children developing any type of hydrocephalus during infancy. Hydrocephalus is the most common cause of increased head circumference (115). Most of the head circumference increase in external hydrocephalus seems to occur around the age of 3-6 months (7, 36). The amount of children ending up with macrocephaly on long-term follow-up varies considerably in the literature, from just a few (24) to almost everyone (30, 31, 108).

1.7.2 Other signs and symptoms

Besides macrocephaly, several other signs and symptoms have been reported, as shown in Table 3.

Table 3: Reported signs and symptoms in children with external hydrocephalus, besides increased head circumference (with references).

Tense anterior fontanel (23, 28, 29, 35, 37, 43, 68, 110)
Dilated scalp veins (23, 37, 116)
Frontal bossing (an unusually prominent forehead) (89)
Irritability (8, 13, 43, 68, 110, 117)
Hypotonia (10, 36, 41, 42, 109, 116, 118)
Vomiting (8, 32, 43, 110)
Gross motor delay (10, 17, 24, 31, 33, 35, 37, 41, 43, 65, 109, 116-118)
Ataxia (8, 37, 110)
Poor head control (8, 33, 34)
Seizures (30, 32, 37, 43, 110, 119)
Fever (32)

1.8 Long-term effects

A psychomotor developmental delay is often reported during infancy and early childhood in patients with external hydrocephalus (7, 24, 34, 35, 89, 120). It seems to affect mainly gross motor development and to a lesser extent language development, and most studies report a gradual decrease and disappearance of delay – normalization – within 1-4 years (8, 41, 121). Identified studies of external hydrocephalus children with follow-up beyond one year of age are listed in Table 4.

Table 4: Identified studies of external hydrocephalus children with a follow-up time beyond one year of age.

Authors (reference)	No of patients (males/females)	Age at last follow-up	Outcome	Treatment
Alper et al. (30)	13 (9/4)	Mean 17.6 months	Fine motor deficit in two children, language delay in one.	No treatment
Alvarez et al. (7)	36 (19/17)	About 24 months	One with developmental delay, three more suspected. 14 with transient motor delay, five with transient language delay.	No treatment
Andersson et al. (28)	9 (3/6)	Mean 48 months	Three initially suspected of having a slight psychomotor retardation. All normal at follow-up.	Seven patients had exploratory craniotomy, three of these shunted.
Babcock et al. (121)	41 (N/A)	Up to 60 months	Initially, seven had neurological abnormalities. On follow-up, one had speech problems, three had developmental delay.	No treatment
Barlow (29)	5 (1/4)	Mean 33.2 months	Follow-up available for four infants, all were doing well.	Three treated with acetazolamide.
Bosnjak et al. (120)	9 (N/A)	12 months later	Most had developmental delay at presentation, all described normal at follow-up	No treatment
Briner and Bodensteiner (113)	4 (2/2)	Mean 13.9 months	Normal development in all.	No treatment
Camerota and Rash (66)	3 (0/3)	Mean 12 months	Normal development (dizygotic triplets)	No treatment
Carolan et al. (13)	15 (11/4)	Mean 15.8 months	Normal development initially and at follow-up	No treatment

Castro-Gago et al. (31) (abstract only)	39 (23/16)	Mean 48.7 months	Motor retardation in five patients, psychomotor retardation in one.	No treatment
Cundall et al. (10)	2 (2/0)	Mean 22 months	Gross motor delay and hypotonia initially, normal at follow-up (identical twins)	No treatment
Gherpelli et al. (108) (abstract only)	18 (17/1)	Mean 56 months	At follow-up one was "neurologically abnormal" and another had an IQ of 77	No treatment
Halevy et al. (122)	20 (14/6) [a]	Mean 2.7 years	Normal development in 18, hypotonia in 2	No treatment
Hamza et al. (16)	13 (9/4)	Mean 23.5 months	All patients were asymptomatic initially and at follow-up	No treatment
Handique et al. (123)	3 (3/0)	Mean 21.7 months	Two presented with motor delay. One of them also with seizures, and with hypotonia and motor delay at follow-up	One treated with acetazolamide
Haws et al. (124)	177 (N/A)	Mean 3.6 years	30.5 % with developmental delay at last follow-up	No treatment
Hellbusch (32)	39 (27/12)	Mean 56 months	Two children with developmental delay at 26 and 78 months. One with speech delay at 84 months.	Two had subduroperitoneal shunts, one VP shunt
Karantanas and Bakratsi (67)	2 (2/0)	Mean 23 months	Developmentally and neurologically normal initially and at follow-up (twins)	No treatment
Kendall and Holland (14)	14 (N/A)	24 months later	9 with minor to moderate degree of retardation initially, and at follow-up	No treatment

Kumar (8)	5 (2/3)	Mean 37 months	One child delayed, but improving on last follow-up	All treated with acetazolamide
Laubscher et al. (89)	22 (12/10)	'School age'	Developmental delay in 12/22 children. One mentally retarded. Normal school outcome in 11/12 children	No treatment
Ment et al. (17)	12 (N/A)	Mean 17.5 months	Normal at follow-up.	No treatment
Mori et al. (91)	20 (15/5)	About 24 months	"Almost all patients eventually reached normal developmental milestones."	Three underwent surgery, not fully specified.
Muenchberger et al. (24)	9 (7/2)	Mean 19 years	One hypotonic youth. Several minor problems, see text. Four with transient motor or speech delay	One VP shunt
Neveling and Truex (33)	10 (6/4)	Mean 19 months	All patients grouped together: developmental testing showed below average results for gross motor skills	No treatment
Nickel and Gallenstein (34)	9 (6/3)	Around 25 months	One with gross motor and speech delay, two more with speech delay. Seven with transient motor delay	No treatment
Nishimura et al. (35)	20 (14/6)	3-10 years	Four patients had mild motor delay, three of them improved with time	Three operated because of SDH
Nogueira and Zaglul (43)	58 (44/13) [b]	Mean 22.8 months	14 children had abnormal development on follow-up. One was dead	No treatment
Pettit et al. (27)	7 (5/2)	Mean 16.4 months	One delayed gross motor function at follow-up	No treatment
Robertson et al. (23)	6 (6/0)	Mean 20.7 months	One mildly developmentally delayed	Two shunted

Sahar (37)	7 (4/3)	Mean 4.4 years	At last follow-up, five showed various degrees of mental retardation or delay. One more had motor problems	No treatment
Segal-Kuperschmit et al. (41) (abstract only)	5 (5/0)	24-30 months	All had transient hypotonia and language and motor delay (resolved at about 4 years)	No treatment
Shen et al. (125)	6 (4/2)	Mean 18.7 months	Two with mild psychomotor retardation at follow-up	No treatment
Smith et al. (126)	7 (N/A)	Mean 17.9 months	One developmentally delayed initially, none at follow-up	No treatment
Suara et al. (127)	2 (2/0)	Mean 18 months	Normal development in both	No treatment
Yew et al. (38)	99 (55/44) [c]	Mean 13 months after diagnosis (8.9 months)	Eight non-premature patients had delayed verbal or gross motor development at follow-up	No treatment

[a] Six patients born prematurely (gestational age 32-35 weeks).
[b] Sex undetermined in one patient.
[c] 20 patients born prematurely.

1.8.1 Preschool age

Ten of the studies shown in Table 4 have followed children with external hydrocephalus for 2-5 years (14, 29, 31, 32, 34, 35, 37, 41, 108, 121). Around 15-20 % of all children reported in these ten studies were described as having an abnormal psychomotor development at last follow-up. Seemingly, most studies base their evaluations on clinical examination, while some standardized tests have been used.

Two studies have used the Denver Developmental Screening Test, testing four developmental domains: gross motor, language, fine motor-adaptive, and personal-social (7, 33, 128). Alvarez et al. found that many of the infants showed transient delay in either gross motor or language development. It was typically present at 5 to 12 months of age and disappeared by 15 to 18 months of age (7). Another study also reported delay in gross motor development, while the other domains were within the normal range (33).

A revised version of the above-mentioned test, the Denver II, was used by Alper and colleagues (30, 129). One of 13 infants were reported with “language delay”, while two had “fine motor deficit”. The remaining ten had a normal development (30).

The Milani Comparetti, a gross motor assessment survey (130), was used in one study (33). The authors reported that the infants “were lacking in belly crawling and sitting skills”. They found the gross motor developmental pattern to be abnormal, and hypothesized this to be secondary to the increased head size.

The Gesell Developmental Schedules (131) and the Movement Assessment of Infants (132) were used by Nickel and Gallenstein (34). They reported nine infants where seven of them showed gross motor delay during the first year of life. At around two years of age, three were delayed in speech/language, one of them also with persistent gross motor delay.

The French Brunet-Lézine scale (133) was used in one study of nine infants (120). Six had “abnormal neurodevelopmental findings” at presentation, but

the majority was considered normal at follow-up. Further details about test findings are not available.

1.8.2 School age

Very few studies have followed children up to school age. Muenchberger et al. did a long-term follow-up of nine patients with external hydrocephalus (24). At final follow-up (mean 19 years), all nine were considered neurologically normal and the neuropsychological assessment showed an intellectual ability within the normal range. Nevertheless, reduced performance was noted on tests of attention, and several patients reported learning problems in reading and mathematics. Three of the nine patients had been diagnosed with a psychiatric disease.

Laubscher et al. investigated 22 'megalencephalic' children with dilated pericerebral subarachnoid spaces (89). Twelve of them were classified as developmentally delayed (type of delay and age not specified). Eleven of the twelve who had reached school age at time of study end had a normal school outcome.

Yew et al. received Hydrocephalus Outcome Questionnaires (HOQ) from some of their patients (mean age 7 years). They reported slight reduction in quality of life, but less so than in shunted hydrocephalus (38).

The aim of this project was to further explore the long-term effects of external hydrocephalus.

1.8.3 Adulthood – idiopathic normal pressure hydrocephalus

Bradley has suggested that idiopathic normal pressure hydrocephalus could be a "two-hit" disease: external hydrocephalus during infancy, leading to increased intracranial volumes, followed by a second hit during late adulthood, possibly ischemia or other ageing variations, leading to decreased outflow of CSF (134, 135). This was partly based on the finding of significantly increased

intracranial volumes in adults with idiopathic normal pressure hydrocephalus, compared to age- and sex-matched controls, indicating that the large head must have been contracted during childhood (136). No studies have followed children with external hydrocephalus into adulthood.

1.9 Treatment

Most children with external hydrocephalus have been managed conservatively, i.e., they have only been observed. Some studies have reported shunting procedures in external hydrocephalus (23-25, 32, 35, 42, 65, 68), usually ventriculoperitoneal or subduroperitoneal shunts. Symptoms and signs of increased ICP are the most common causes of shunting, while no studies have been found that report developmental delay as treatment indication alone. No studies have compared treatment versus non-treatment in children with external hydrocephalus. Yew et al. compared their external hydrocephalus patients with a previously published cohort of shunted hydrocephalic children (38). They found that external hydrocephalus children reported slightly better HOQ scores than the shunted patients, although not significantly so.

Only a few studies have reported outcome after shunt surgery in external hydrocephalus, mostly stating “clinical improvement” (23, 42, 68). Some authors advocate temporary shunting (25, 137).

Other treatment options have been found in the literature, such as various forms of external drainage (117, 138), repeated subdural taps (113), and acetazolamide as monotherapy (8, 29, 139) or in combination (110). Even craniotomy is described (22, 28).

We have compared treated and untreated patients with external hydrocephalus.

2 Aims of the study

- To find the incidence and other epidemiological data of infantile external hydrocephalus in a well-defined population.
- To find the long-term effects of external hydrocephalus regarding neurocognitive and psychosocial function, and quality of life.
- To compare treated and untreated patients with external hydrocephalus.
- To examine the pathophysiology of external hydrocephalus and chronic SDH in the light of recent knowledge of perinatal subdural hematoma, and the possible consequences for suspected abusive head trauma (AHT).
- To explore the assumption that ruptured and thrombosed bridging veins indicates AHT, and how this could be related to external hydrocephalus.
- To examine clinical and neuroimaging findings in infants with alleged AHT, and a possible connection with external hydrocephalus.

3 Methods

For papers 1-4, a retrospective and population-based study from southern Norway was performed, identifying patients with external hydrocephalus. For paper 5, existing literature was the basis for a discussion of possible pathophysiological mechanisms leading to external hydrocephalus and chronic SDH, as well as a comparison between the epidemiology and neuroimaging of these entities. For paper 6, literature regarding bridging veins were reviewed, and discussed regarding its role in AHT investigation. In paper 7, clinical and neuroimaging findings in a national cohort of infants with alleged AHT were studied.

3.1 Study population (papers 1-4)

During the study period Norway consisted of four health regions. Each region had a three-level hospital structure with local hospitals, central hospitals (with pediatric departments), and university hospitals (with neurosurgical departments). This study covered the two largest health regions in Norway, covering the southern part of the nation. During the study period (1994-2003) the mean population for these two regions was 3.34 million, about 75 % of Norway's total population. The regional annual average of live births during this period was 44,225 (140).

All infants in Norway are seen at local health centers at regular intervals. During the first year of life, it is recommended that head circumference is measured at each visit. Children with rapidly increasing head circumference, defined as crossing two curves on the registration sheet, or a head circumference > 97.5th percentile, should be referred to a specialist. The national head circumference reference chart used during this period was published in 1988 (141).

Children with any neurosurgical condition in our study region were evaluated and treated at the neurosurgical departments in either Oslo (Oslo University Hospital – Rikshospitalet) or Bergen (Haukeland University Hospital). Medical records at these two centers were searched for relevant diagnoses (Table 5) in the 10-year period from January 1, 1994, to December 31, 2003.

Inclusion criteria: Head circumference crossing two percentiles or more, or a large head circumference (> 97.5th percentile) during the first year of life, and typical neuroimaging findings.

Exclusion criteria: History of head trauma, intracranial hemorrhage, CNS infection, other known causes of hydrocephalus, or prematurity (< 37 weeks of gestation).

The following information was collected from the medical records: age, sex, symptoms and signs, head circumference, neuroimaging reports, treatment, follow-up, and other information deemed relevant.

Table 5: Diagnoses used in the search for relevant patients.

ICD-9	331.3; 331.4; 741.0; 742.3; 742.4; 432.1; 852.2
ICD-10	G91.0; G91.1; G91.2; G91.3; G91.8; G91.9; Q03.0; Q03.1; Q03.8; Q03.9; Q75.3; I62.0; S06.5

3.2 Neurocognitive and psychosocial functioning (papers 2 and 4)

For papers 2 and 4, external hydrocephalus patients and their families were invited to participate in the neuropsychological assessment and evaluation of quality of life. Neurocognitive functioning was assessed for the domains *verbal fluency*, *attention span*, *psychomotor speed*, *learning and memory*, and *motor speed and coordination*. *General IQ* (divided in *verbal* and *psychomotor IQ*) as well as performance-based *executive functioning* were

evaluated. Parental scoring of the latter was obtained using BRIEF (The behavior rating inventory of executive function) (142).

Quality of life was assessed using the Pediatric Quality of Life Inventory (PedsQL) questionnaire (143). The self-report versions for teenagers (13-18 years) and children (8-12 years), and the parental version were used. A total score and four subscores (physical function, emotional function, social function, function at school) were calculated and compared with normative data from a Norwegian validation study (144). Table 6 gives an overview over domains and the respective tests used.

Table 6: Neuropsychological tests and questionnaires used when examining children with external hydrocephalus.

Domains	Tests
Verbal fluency	Delis-Kaplan Executive Function System (D-KEFS) (145)
Attention span	Children's Auditory Verbal Learning Test 2 (CAVLT-2) (146) *and* Wechsler Intelligence Scale for Children-IV (WISC-IV) (147) *or* Wechsler Adult Intelligence Scale-IV (WAIS-IV) (148)
Psychomotor speed	WISC-IV/WAIS-IV *and* D-KEFS
Learning and memory	CAVLT-2
Motor speed and coordination	Grooved pegboard (149)
General IQ	Wechsler Abbreviated Scale of Intelligence (WASI) (150)
Executive functioning	D-KEFS *and* The Behavior Rating Inventory of Executive Function (BRIEF) (142)
Quality of life	Pediatric Quality of Life Inventory (PedsQL) (143)

3.3 Additional medical information (paper 4)

All Norwegian inhabitants are registered with a family physician providing primary health care. The doctor also receives medical information about their patients from specialists and hospitals. The doctors of the included patients were contacted by letter and asked for medical information about their patients, with emphasis on developmental, cognitive, and social status.

3.4 Study population (paper 7)

A national registry of children suspected of AHT in Sweden is managed by the Swedish National Board of Forensic Medicine. During the period 1994 – 2018, a total of 1380 infants (< 1 year of age) were included in the register. The study population included both live and deceased infants with suspected AHT. Information from medical records including neuroimaging, autopsy reports, and medico-legal investigations were assessed.

3.5 Statistics

The neuropsychological scores (papers 2 and 4) were transformed into *z*-scores and *T*-scores based on normative data. One-sample *t* test and Student's *t* test were used to compare patient groups. For the quality of life data (PedsQL), means from raw scores were compared with the normative mean. A score below 70 was considered clinically relevant (151).

For paper 7, the following statistical tests were used: chi-square, Mann-Whitney *U*, Fisher exact test and *t*-test.

Analyses were conducted using IBM SPSS Statistics, versions 22 – 27.

The level of significance was set to $p < 0.05$.

3.6 Ethics

Papers 1-4: After the initial medical records search, eligible patients and families received a letter with information about the study and an invitation to participate. On the day of testing (papers 2 and 4), they signed an informed consent form. The project was approved by the Regional Committee for Medical and Health Research Ethics, as well as the Norwegian Centre for Research Data, and the Norwegian Directorate of Health.

Paper 7: The study was approved by the Regional Ethics Review Board in Uppsala, Sweden.

4 Results

4.1 Paper 1

Epidemiology of benign external hydrocephalus in Norway – a population-based study. Wiig US, Zahl SM, Egge A, Helseth E, Wester K. *Pediatr Neurol 2017. 73:36-41.*

176 children were identified with external hydrocephalus during the study period. This gives an incidence of 0.4 per 1000 live births. 86.4 % were males.

161 (91.5 %) of the children were referred because of a large or rapidly increasing head circumference, in 38.6 % this was the only finding. Other commonly reported (>5 %) signs and symptoms were frontal bossing, delayed development, distended scalp veins, bulging fontanel, hypotonia, and sunset gaze.

The mean age at referral to hospital was 7.3 months (median 7 months, range 1.5 to 23 months).

Neuroimaging showed, in addition to the mandatory enlarged subarachnoid spaces, some degree of ventricular enlargement in 79 % of the patients. No correlation was found between ventricle size and clinical findings.

49 (27.8 %) of the children were treated surgically, mainly with ventriculoperitoneal shunting.

4.2 Paper 2

Neurocognitive and psychosocial function in children with benign external hydrocephalus (BEH) – a long-term follow-up study. Mikkelsen R, Rødevand LN, Wiig US, Zahl SM, Berntsen T, Skarbø AB, Egge A, Helseth E, Andersson S, Wester K. *Childs Nerv Syst 2017. 33(1):91-99.*

Of 171 available patients, 86 (76 males) were included in the study. Age range at inclusion was 8-18 years (mean 13.90, SD 2.60). 26 children (30.2 %) had been treated with ventriculoperitoneal shunt (mean age at follow-up 14.80 years, SD 2.28), and the rest (60 patients) had not been operated (mean age at follow-up 13.44 years, SD 2.58).

For the external hydrocephalus group in total, performance IQ ($p = 0.047$) and verbal fluency ($p = 0.027$) were significantly above the normative mean. For the following neuropsychological domains, the external hydrocephalus group scored significantly poorer than the normative mean: attention span ($p = 0.001$), psychomotor speed ($p < 0.001$), executive functions ($p < 0.001$), and fine motor function ($p = 0.003$). On executive functioning according to BRIEF, no scores were significantly different than the normative mean. On quality of life (PedsQL), the children scored themselves significantly higher (better) than the normative mean on total score, as well as the subscores emotions, social and school. The parents, however, scored their children significantly lower (poorer) on the school subscore.

When comparing operated with non-operated patients, the operated children performed significantly lower on one test of attention span (CAVLT memory span, $p = 0.010$) and two tests of psychomotor speed (CWIT1, color naming, $p = 0.034$. CWIT2, word reading, $p = 0.043$). Otherwise, there were no differences between the groups regarding neuropsychological and IQ scores.

Non-operated children scored themselves significantly higher on the PedsQL school subscore than the operated children ($p = 0.011$). Otherwise, there were no significant differences for self-reported and parent reported PedsQL scores and BRIEF scores between operated and non-operated external hydrocephalus patients.

4.3 Paper 3

Clinical, radiological, and demographic details of benign external hydrocephalus: a population-based study. Zahl SM, Egge A, Helseth E, Wester K. *Pediatr Neurol 2019. 96:53-57.*

176 children (152 boys) with external hydrocephalus were identified for this study.

Detailed studies of the development of head circumference for 107 of the children showed that mean age of symptom onset was 3.4 months (median 3 months, range 0 to 7 months). At final measurement, 52 % of the children still had large heads (at or above the 97.5th percentile). For 24 % of these, head circumference continued to increase too rapidly beyond 12 months of age.

For the 77 children with neuroimaging available beyond 12 months of age (mean 21.7 months), 74 % still had enlarged subarachnoid spaces, while 61 % also had dilated lateral ventricles. 10 % had dilated lateral ventricles only, while 16 % had normal neuroimaging.

13 % of external hydrocephalus patients had a history of complicated birth. 13 children were twins, but only one infant from each pair.

4.4 Paper 4

Quality of life and physician-reported developmental, cognitive, and social problems in children with benign external hydrocephalus – long-term follow-up. Zahl SM, Egge A, Helseth E, Skarbø AB, Wester K. *Childs Nerv Syst 2019. 35:245-250.*

176 patients (152 boys) with external hydrocephalus were identified for this study.

103 teenagers and children (8-18 years old) answered the quality of life (PedsQL) questionnaire. Self-reported total score and all subscores (physical health, emotions, social, and school) were significantly higher than the normative mean, i.e., they reported better quality of life than the normal population (144). 86 parents answered the proxy version of PedsQL. For parent reports, the school subscore was significantly lower (poorer) than the normative mean.

For 142 (81 %) of the 176 patients, medical information was obtained from their family physicians. For 104 of these children, no relevant problems were reported. The remaining 38 patients had various reported problems, such as delayed speech (9.2 %); social behavioral problems (8.5 %); motor impairment (7.7 %); mental retardation (5.6 %); and concentration problems (5.6 %). Less than 5 % reportedly had cognitive deficits; epilepsy; ADHD/ADD; autism spectrum disorders; anxiety and depression; and dyslexia.

4.5 Paper 5

Examining perinatal subdural haematoma as an aetiology of extra-axial hygroma and chronic subdural haematoma. Zahl SM, Wester K, Gabaeff S. *Acta Paediatr 2020. 109(4):659-666.*

Perinatal subdural hematoma is an intracranial bleeding inside the dura or subdural compartment occurring during birth. A prolonged or complicated birth process probably increases the risk of such events. An MRI study found perinatal SDH in 46 out of 101 asymptomatic term neonates (152).

We hypothesize that this condition in some patients can develop into both external hydrocephalus and chronic SDH. This theory of a common cause is based on several observations.

- Neuroimaging and fluid characteristics: the terms chronic SDH, external hydrocephalus and hygroma are sometimes used interchangeably for subdural collections. Studies analyzing the fluid also report differing protein concentrations, possibly indicating various stages of disease.
- Epidemiology: age and sex distributions of SDH and external hydrocephalus are very similar, with a marked male preponderance and a mean age of symptom debut at around 3.5 months.
- Pathophysiology: the dural capillary bed is responsible for CSF absorption during early infancy. A bleeding within the dura will obstruct this absorption, creating a local hygroma. These formations could lead to external hydrocephalus as CSF absorption is hampered, as well as chronic SDH, as small hemorrhages within the dura could lead to continued or bigger leaks of blood, creating a process of chronic SDH. These subdural collections are prone to rebleed, creating an inflammatory response with formation of neomembranes, which could lead to new rebleeds.

The possible misinterpretation of such SDHs as signs of AHT is discussed.

4.6 Paper 6

Thrombosis is not a marker of bridging vein rupture in infants with alleged abusive head trauma. Zahl SM, Mack JA, Rossant C, Squier W, Wester K. *Acta Paediatr 2021. 110(10):2686-2694.*

Abusive head trauma (AHT) is often suspected in infants with SDH without a known trauma. Bridging veins traversing the space between the cortex and venous sinuses are assumed to rupture during trauma, leading to SDH. Thrombosis of bridging veins has been suggested to be a neuroimaging marker of bridging vein rupture, and thus AHT. Our literature review concluded that:

- Radiological studies claiming that cortical vein thrombosis (CVT) indicates traumatic bridging vein rupture lack pathological verification, and have to a little degree considered other, medical causes for thrombosis.
- Autopsy studies have not provided evidence for trauma as a cause of thrombosis resulted from bridging vein rupture.
- No biomechanical studies have shown that shaking can cause bridging vein rupture.

In addition, the literature on biomechanics and pathology is mainly based on adult patients. Altogether, we conclude that CVT cannot be considered a neuroimaging marker of AHT.

4.7 Paper 7

Neuroradiological findings in a national cohort of alleged abusive head trauma cases suggest different etiologies. Zahl SM, Andersson J, Wester K, Wikström J. *(Submitted manuscript.)*

96 cases were included, 65 were males (68 %). 69 infants had chronic SDH, of whom many with radiological characteristics compatible with external hydrocephalus, as well as stretched bridging veins on neuroimaging. 16 had acute SDH and were more prone to have skull fractures.

16 % of the infants had HII, which was associated with SAH, acute SDH and higher mortality. While the sex distribution in infants with HII was even, a clear male preponderance was seen in the external hydrocephalus group.

The children were referred because of several signs and symptoms, and were grouped in acute and non-acute symptoms. Neuroimaging signs of CVT, as well as bilateral retinal hemorrhage, were found in the acute group, while

external hydrocephalus was significantly more common in the non-acute group.

5 Discussion

This project has investigated external hydrocephalus in infants. We have found some new epidemiological information, including incidence, of external hydrocephalus. Details about the long-term consequences have been presented, as well as the effect of treatment. Some theoretical considerations regarding pathophysiology of external hydrocephalus, and its relation to chronic SDH and AHT, is put forward.

Our findings will be discussed in detail below, in relation to existing knowledge. Finishing off, some perspectives for the future will be presented.

5.1 Definition

No well-established definition of external hydrocephalus exists. According to Rekate's definition of hydrocephalus ("..distension of the ventricular system..") (3), one might argue that only external hydrocephalus children with enlarged ventricles are truly hydrocephalic. Other authors have proposed that external hydrocephalus children with no other symptoms/findings than macrocephaly and enlarged subarachnoid spaces "represent the extreme of the normal population rather than a distinct clinical entity" (107). The vast number of terms used for this and similar conditions (see Table 1) reflect the different views on etiology, outcome, and clinical importance.

The term external hydrocephalus is used throughout this thesis, and defined as a large head (≥97.5th percentile) or rapidly increasing head circumference (crossing two or more percentiles) in an infant, combined with typical radiological findings of enlarged subarachnoid spaces – especially frontally – and normal or slightly to moderately enlarged lateral ventricles. The term *benign* external hydrocephalus (BEH) was used in the articles that constitutes this thesis.

Based on the presented results, one might question the use of the word 'benign'. Furthermore, as 'hydrocephalus' is commonly used for a condition of increased CSF volume leading to enlarged ventricles and increased ICP (153), a different term should be considered. Extra-axial fluid collection is a description covering the neuroimaging features, while still being broad enough to include several types of fluid (such as blood).

5.2 Epidemiology

We found the incidence of idiopathic external hydrocephalus in our population to be 0.4 per 1000 births. As population-based incidences have not been reported earlier, no comparison is possible. However, due to the structure of the Norwegian health system (with mandatory health center workups), we believe that essentially all patients in our region have been registered. The variation in head circumference charts, and different cutoff values, and the lack of strict radiological criteria are all variables that may influence the number of patients, and hence the incidence of external hydrocephalus. Another important aspect of the study population is our choice not to include infants with bleedings, such as SDH, and premature infants. As these are known risk factors for developing external hydrocephalus, the total incidence in the entire infant population is higher than our figures indicate.

A national study found the incidence of primary hydrocephalus to be 0.75 per 1000 births in Norway (115), thus external hydrocephalus comprises a considerable amount (>50 %) of the hydrocephalic children managed by the health care system.

5.2.1 Sex

The male preponderance in our study is as high as 86.4 %. This overrepresentation of boys is somewhat more marked, although in accordance with earlier publications (32, 89, 109). A male preponderance is also found in pediatric hydrocephalus: 74 % was found in a similar Norwegian cohort (115); and 66 % in a large Danish register study (154). The authors of the latter

suggested that the male preponderance seen in both isolated and syndromic congenital hydrocephalus could be due to X-linked genetic factors. Another aspect is that boys in general have a higher risk of neonatal morbidity and mortality, including SDH (155, 156). It is possible that a larger fetal head circumference, known to be associated with complicated labor (157), could explain some of the sex difference. A higher risk of congenital hydrocephalus is seen in first-born children, which hypothetically could be due to perinatal SDH, again "due to lower mechanical compliance of the birth canal of the primiparous" (154). Interestingly, though, mean head circumference at birth is similar in boys and girls (158), pointing to relevant susceptibility also *after* birth. Whether these factors can explain the sex difference seen in external hydrocephalus remains unknown.

5.2.2 Age

At birth, external hydrocephalus children have head circumferences marginally larger than the normal population. This is found in our study (paper 1) and has been reported before (7, 32, 89, 122). The mean age at which the macrocephaly was discovered was 3.4 months, and no children started to show signs of external hydrocephalus later than 7 months of age. The referral age of 7.3 months corresponds well with the literature (16, 32).

5.3 Pathophysiology – what this study adds

The theory of 'delayed maturation' of the arachnoid granulations, which is often presented, cannot fully explain external hydrocephalus, as the arachnoid granulations develop late during infancy in normal subjects as well (45). In paper 5, we have discussed the theory that perinatal blood might surround the structures in the dural capillary bed, thereby hampering CSF absorption through this alternative route (53). This blood can be the result of the birth process, where small perinatal subdural hemorrhages can be created, a quite common phenomenon as reported by Rooks et al. (152). In their MRI study, they found that 46 % of asymptomatic term neonates had subdural

hemorrhages. In a more recent survey on incidental MRI findings, 115 of 500 (23 %) asymptomatic term neonates had SDH (159), while yet another study reported SDH in 37.8 % of neonates investigated with CT or MRI for various reasons (160). As pointed out in the prior section, infants which later present with external hydrocephalus are born with marginally larger heads than their normal peers. Hypothetically, it is possible that these larger heads can be more prone to perinatal SDH during the birth process, which has been suggested for other forms of hydrocephalus as well (154).

The decrease in absorption capacity will result in a larger CSF volume, which then gives an increased ICP, leading to an increase in head circumference and other symptoms associated with external hydrocephalus. A net increase in the subarachnoid CSF volume could be the neuroimaging result of this process.

Small intradural bleedings can trigger larger subdural hemorrhages through the process of inflammation and neomembrane formation (161). This theory of pathology unifying external hydrocephalus and chronic SDH can explain some of the striking epidemiological similarities. Both conditions have a male preponderance and a similar age of occurrence (around 3.5 months) (156). See Figure 4 for an anatomical overview.

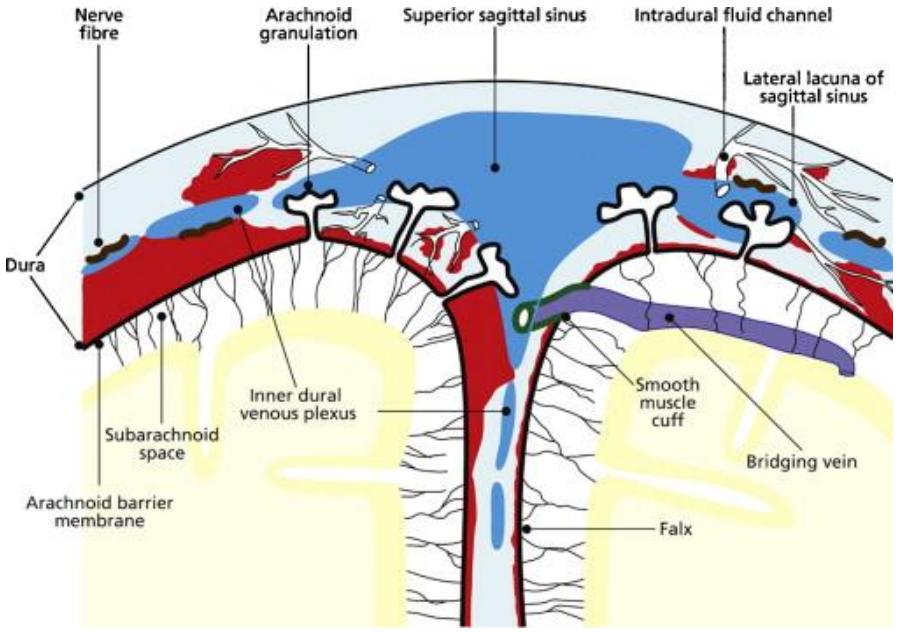

Figure 4: Schematic drawing of a cross-section through the superior sagittal sinus. Examples of intradural bleeding sites are depicted.

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A difficult labor (vacuum extraction, forceps, cesarean section) is known to increase the risk for SDH (162). Could this be the case with external hydrocephalus as well? In our retrospective study, we unfortunately did not systematically register birth related data, and to the knowledge of the author, this has not been systematically investigated. As pointed out by Miller et al., SDH in a macrocephalic child raises the possibility of several medical explanations, not only AHT (163). External hydrocephalus is one of the best-known risk factors for infant SDH (32, 90, 164, 165). The higher incidence of

SDH reported in external hydrocephalus children can be turned upside down: in concordance with the unifying theory presented above, one might hypothesize that external hydrocephalus can be an early or intermediate form of SDH.

Whitehead and colleagues, based on findings of altered subarachnoid diffusion in external hydrocephalus, suggested that capillary hyperpermeability and reduced protein transport in the frontal region could explain the formation of extracerebral fluid (166). This however cannot explain the initial cause of excessive fluid.

Sainz et al. found that 15 out of 17 patients with external hydrocephalus had venous sinus abnormalities (167). They thus interpreted external hydrocephalus findings primarily as a result of cerebral venous hypertension. Some questions could be raised regarding this hypothesis. First, no control group was used, and the amount of normal children with similar venous findings are unknown. Second, the reason for these structural abnormalities, and how they obviously resolve over time, remains unexplained. More recently, Cinalli et al. investigated 97 infants with external hydrocephalus and compared them with 75 healthy controls (168). They found both a higher number and more severe grade of dural sinus anomalies in the external hydrocephalus group compared with the controls, hypothesizing that this could result in an increased venous outflow resistance possible leading to external hydrocephalus.

Given the diversity of findings as mentioned, as well as associated conditions, a unifying pathophysiological explanation for all external hydrocephalus patients seems improbable. More likely, the development of excessive extracerebral fluid could be caused by several factors and mechanisms, probably in various forms of coexistence.

5.4 External hydrocephalus and SDH, and the connection with AHT

If external hydrocephalus, for instance related to birth difficulties (as discussed above) or prematurity, is a form of chronic SDH, or could evolve into chronic SDH, then the risk of falsely assuming AHT in a child with external hydrocephalus is obvious. What would further imply that this could be the case?

1) more children than expected with alleged AHT would have signs of preexisting external hydrocephalus;

2) more children than expected with alleged AHT would have a history of birth difficulties or prematurity; and

3) the age and sex distribution of children with alleged AHT would show a typical occurrence around 3 months of age and a male preponderance, as seen in external hydrocephalus.

As shown in paper 7 and by Andersson et al. (169), all these three implications are seen. First, many infants with suspected AHT due to a finding of chronic SDH have neuroimaging signs of external hydrocephalus (enlarged subarachnoid spaces) and increased head circumference (169). Second, infants with alleged AHT are more likely to have been born prematurely than expected (170). Whether alleged AHT is associated with birth difficulties is not known. Third, the chronic SDH group of alleged AHT infants showed a male preponderance and age distribution (around 3 months of age) quite similar to external hydrocephalus (169).

SDH in infants is often considered a sign of AHT (171). Especially in macrocephalic children, this interpretation is very uncertain, and may lead to false accusations – and verdicts - of abuse. A close monitoring of head circumference, attention to birth problems, and a general awareness of the possibility that a perinatal SDH may develop into external hydrocephalus and chronic SDH, is important. This again should lead to early and rapid neuropediatric evaluation and neuroimaging in susceptible children.

5.5 Neuroimaging

5.5.1 External hydrocephalus characteristics

Although our population-based studies (papers 1-4) were not based on renewed neuroimaging, the condition external hydrocephalus depends on neuroimaging findings. Especially what one would consider an enlarged subarachnoid space is poorly defined. Furthermore, as pointed out by Andersson et al. (169), what is regarded as normal values may differ between ethnic groups.

The majority of patients had some degree of ventricular dilatation at time of diagnosis. This corresponds well with earlier studies, but has not been published at a population level before. On a longer term, it seems from our results that the excessive extracerebral fluid resolves earlier than the intraventricular fluid. In accordance, Maytal et al. reported that ventricular dilatation was a later finding than enlarged subarachnoid spaces (84). One might suspect that the ventricular dilatation could be a sign of a slightly increased ICP in these patients. In our study however, we found no correlation between the degree of ventricular dilatation and clinical findings. Whether ventricular dilatation was associated with head circumference growth rate could not be elicited from our data.

Haws et al. did a large, retrospective study of external hydrocephalus children diagnosed with ultrasound (124). They concluded that further neuroimaging with CT/MRI was unnecessary in patients with no neurologic deficits. However, 30.5 % of their tested children had developmental delay at last clinical follow-up (mean age 3.6 years).

Advanced MRI technology using diffusion tensor imaging technique has shown that external hydrocephalus children have different periventricular white matter diffusion compared with normal children (172). As with other external hydrocephalus findings, this seemed to normalize over time.

As for future research, a study correlating clinical and developmental outcome with neuroimaging development over time, could yield valuable information regarding long-term effects of external hydrocephalus.

5.5.2 Chronic SDH characteristics

In infants with SDH, and hence potential AHT, the possibility of an underlying external hydrocephalus should be kept in mind. In infants with acute SDH and skull fracture, but with no known trauma, AHT could be suspected, although birth trauma may also be the cause (173). In children with neuroimaging findings of CVT, chronic SDH, HII, and stretched bridging veins, other causes than AHT seem just as likely (papers 6 and 7), and investigation should be conducted accordingly. Especially CVT, as thoroughly discussed in paper 6, has wrongfully been regarded as a sign of bridging vein rupture caused by a trauma. The evidence for this, however, is lacking.

5.6 Clinical presentation

5.6.1 Macrocephaly

A large or rapidly increasing head circumference was the leading cause for referral in our cohort. In all patients, this took place during the first seven months of life. This corresponds well with earlier studies (7, 36). For some of the children, this abnormal growth rate continued beyond 12 months of age, signifying a long-lasting increased ICP. Whether this group of infants is more susceptible to long-term sequela remains unknown, but could be a subject for future research. Indeed, the very speed at which the heads grow during the entire infancy is still unexplored. Could a very fast head circumference growth rate predict the need for a shunting procedure? Intuitively, one might expect a rapid rate to be associated with a higher ICP, hence higher risk of neurological damage. The head size in itself, however, did not correlate with motor delay in the long-term follow-up by Yew et al. (38).

2.5 % of infants are macrocephalic (≥ 97.5th percentile). As the annual average of live births in the health regions during the study period was 44,225 (paper 1), we would expect the number of macrocephalic children to be 1106 per year. We thus found that around 1.5 % of macrocephalic children have external hydrocephalus. This is much lower than previously published (see chapter 1.2.3) (16, 30, 39, 40). One reason for this could be that our study is population-based, not based on hospital or department patients with an increased likelihood of pathology. Furthermore, we chose to exclude premature infants and patients with comorbidities. Finally, the inclusion criteria in the mentioned radiological studies are based on strict neuroimaging findings, a dimension lacking in our study.

5.6.2 Other signs and symptoms at presentation

Some of the signs and symptoms found in external hydrocephalus are typically seen as signs of increased ICP, such as vomiting, irritability, sunset gaze, and tense fontanels. Other typical symptoms are seizures and delayed psychomotor development. As presented in chapter 1.7, a delayed psychomotor development is a very common finding in external hydrocephalus throughout the literature. Recently, Maruccia et al. confirmed this using a standardized evaluation tool (Bayley-III) on their patients (174). In four out of 21 (19 %) term infants, a neurodevelopmental (gross motor) delay was found at presentation. Moreover, they found that premature infants with external hydrocephalus had significantly higher risk of neurodevelopmental (fine and gross motor) delay than term infants.

5.7 Long-term consequences

Many children and adolescents with external hydrocephalus during infancy seem to do well. However, subtle neurocognitive difficulties and various social and developmental problems are seen in a non-negligible number of patients. Although our patients were evaluated using standardized tests, some uncertainty remains. The border between normal and delayed will obviously be

difficult to outline in the individual patient, and will probably fluctuate some over time. Furthermore, as a child may be regarded developmentally within normal limits, it is hard to know whether he or she could have developed even "better" under more ideal circumstances.

5.7.1 Cognitive function

Our patients performed poorer than the normative mean on several cognitive domains such as verbal IQ, attention span, executive function, psychomotor speed, and motor speed and coordination. Similarly, Muenchberger et al. found reduced attention span and psychomotor speed in their follow-up of adolescents with prior external hydrocephalus (24). Late emerging verbal problems have also been described earlier. Yew et al. found a late occurring verbal delay in six of their 99 patients on long-term follow-up (38).

Eight of our 142 patients were labeled with 'mental retardation' (paper 4). Laubscher et al. also reported mental retardation in eight of their 74 patients (89). The term mental retardation is quite unspecific, and difficult to compare. As six of our patients with later mental retardation were treated with a shunting procedure during infancy, it could point to a more serious preoperative condition, possibly with a higher ICP.

5.7.2 Quality of life

The children scored themselves above the normative mean on all aspects of health-related quality of life. Yew et al. found a slightly lower quality of life compared with normal children, but better than hydrocephalic patients (38). We found that the parents scored their children lower (worser quality of life) than the normative mean, and significantly so for the domain school functioning. This discrepancy between children/adolescents and parents could reflect variations in interpreting the questions, or reduced self-awareness of the child.

5.7.3 School

The reported learning disabilities, cognitive problems and social behavioral issues in our cohort (papers 2 and 4) points to a general vulnerability for

school problems in children with external hydrocephalus, as reported by the parents through the quality of life questionnaire. Our results correspond well with Muenchberger et al., who reported rather severe school problems for some of their patients (24).

5.7.4 Autism spectrum disorder

Five patients in our study were diagnosed with autism spectrum disorder. Recently, Shen and colleagues did two surveys where they followed groups of infants with repeated MRI scans (175, 176). The children who later developed autism had significantly greater extracerebral fluid, and an early detection of fluid (around 6 months of age) was associated with a more severe autism. The authors conclude that external hydrocephalus could be an early marker for autism spectrum disorder. Indeed, macrocephaly is known to occur in 15-35 % of autistic children (177), which is well above what is seen in the normal population. Abnormally accelerated head growth during infancy has also been suggested as an early sign of risk of autism spectrum disorder (178).

5.7.5 Why is there a developmental delay?

Can a temporary increased ICP have neurological consequences beyond the immediate symptoms? Indeed, 'critical periods' in brain development have been identified, especially in the visual cortex (179, 180). Development is thought to occur stepwise, as the plasticity of the brain can be seen as a cascade of events where genetical, intrinsic and extrinsic factors have various effects depending on the time of development (181, 182). Learning outside this time window is possible, but probably more difficult.

Furthermore, CSF studies in other types of hydrocephalus have showed signs of tissue damage (possibly due to increased ICP) such as apoptosis (183), altered metabolism (184), inflammation (185), and reduction in neurotransmitters (186).

The head size itself has previously been suggested as a reason for developmental delay, making the infant unable to control its head during movement (33).

5.8 Treatment

The word 'benign' often used alongside external hydrocephalus underline the traditional view that the condition is self-limiting and without negative long-term consequences. Hence, the condition is rarely treated. In our population, quite a few patients have been treated, mainly surgically with a ventriculoperitoneal shunting procedure. The operated children scored lower than the non-operated children on some of the neuropsychological tests. The main problem concerning the evaluation of this finding is the fact that it is a retrospective survey, which gives a high risk of selection bias. It is reasonable to assume that children treated with surgery had a more serious condition initially. In general, children with ventriculoperitoneal shunts report lowered quality of life (187). Especially patients who require revision surgery are prone to this, although this was not found in our study.

A prospective, randomized intervention trial of external hydrocephalus is probably unethical. However, as discussed in the prior section, maybe a detailed subgrouping based on neuroimaging, head circumference and other clinical signs could be helpful in detecting the infants most vulnerable to developmental problems, hence most likely to benefit from treatment.

The recent research into aquaporins responsible for CSF homeostasis could open up new possibilities for targeted regulation of CSF secretion, and hence ICP management (188, 189).

5.9 Strengths and limitations

This project has investigated the condition known as external hydrocephalus in infants. Some strengths of the study are:

- The patient group is larger than previously published, representing around 75 % of Norway's total population, and is based on mandatory infant check-ups.

- The follow-up time is longer than most other external hydrocephalus studies.
- The neuropsychological assessment is thorough and systematic.
- The combination of neuropsychological results, quality of life evaluation, and clinical and psychosocial information gives a more comprehensive picture of the long-term effects of the condition.
- The population-based design for both study populations (papers 1-4 and paper 7) give good predictions of incidence and other epidemiological data.
- These epidemiological data are used to explore the relationship between external hydrocephalus and SDH.
- It gives new insight into head circumference development and radiological change in children with external hydrocephalus.
- The alleged AHT cases were based on a national register, covering 25 consecutive years.

The study has its limitations. Quite many patients/families identified with external hydrocephalus were not included in the neuropsychological testing (around 40 %), partly due to lack of time, and partly due to reluctance to participate. For the 71 that did not answer the quality of life-questionnaires (self-report or parent report), 17 patients were reported by their physicians to have relevant developmental or social problems. Whether or not our study group is biased in some direction for this reason is possible, but difficult to tell.

A classification bias is also possible. First, head circumference registration sheets vary with nations and ethnic groups and are occasionally revised. The macrocephaly cut-off point also varies between earlier studies, from the 90th to the 98th percentiles (14, 16), meaning that a large head in Norway is not necessarily defined as a large head in another country. Second, no strict radiological criteria exist for external hydrocephalus. This applies when comparing our results with others, but it is also a possible internal bias in our study. We have used the original radiological interpretations (made by an

unknown number of different radiologists), without the possibility to secure ‘inner’ consistency.

The comparison of operated and non-operated patients is also susceptible to a selection bias. External hydrocephalus children with more ‘dramatic’ preoperative clinical signs and symptoms (e.g., very large heads, vomiting, sunset gaze, etc.) were probably more often selected for surgery. The distinction between external hydrocephalus and communicating hydrocephalus is difficult in a retrospective study as this. Some clinicians would probably define shunted external hydrocephalus patients in the latter group. However, as shown in paper 1 (Table 2), clinical signs of increased ICP were found in external hydrocephalus patients both with and without enlarged lateral ventricles.

In some of the older cases of alleged AHT in the national registry study, the neuroradiology was lacking. Furthermore, CVT can be difficult to differentiate from subarachnoid blood clots on CT and could thus be underdiagnosed. However, no systematic bias is expected.

6 Conclusions

- External hydrocephalus is a neuropediatric condition with an incidence of about 0.4 per 1000 births, and with a marked male preponderance.
- Mean age at symptom debut (increased head circumference) is 3.4 months.
- Although most children do well, based on neuropsychological tests and quality of life evaluation, a non-negligible number of children report subtle neurocognitive and social problems. Especially school functioning seems problematic in external hydrocephalus children.
- There is no evidence that treating external hydrocephalus with ventriculoperitoneal shunting improves long-term outcome.
- Perinatal SDH could be a common initial cause of both external hydrocephalus and chronic SDH, based on similar neuroimaging, epidemiological and pathophysiological findings. This is important in the managing of infant SDHs, which are often considered to be AHT.
- Existing knowledge does not support the hypothesis that neuroradiological signs of bridging vein thrombosis correlate with rupture of bridging veins, for instance through shaking/abuse.
- A preexisting external hydrocephalus is common in infants with alleged AHT. It should be carefully considered in all such cases as SDH can develop without trauma in external hydrocephalus.

7 Further perspectives

Our study as well as previous ones have shown that especially school functioning is difficult for some external hydrocephalus children. Awareness and if needed early educational intervention from parents and teachers could prove imperative for some of these children. A new, similar study as ours, but done prospectively, would give a more precise picture of long-term outcome as some biases are ruled out.

Larger and longer lasting studies on the significance and development of perinatal SDH is important for further insight into the possible development of external hydrocephalus and chronic SDH.

Larger, radiological studies could yield more information about the association between the amount of extra-axial fluid and long-term outcome.

Hypothetically, a certain craniocortical width cut-off, head circumference growth rate, or other clinical criteria, could separate patients at risk of developmental problems from those who are not.

The association between autism spectrum disorder and external hydrocephalus should be further investigated. An increased awareness about this connection could possibly lead to earlier intervention in high-risk patients.

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Paper 1

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Original Article

Epidemiology of Benign External Hydrocephalus in Norway—A Population-Based Study

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ABSTRACT

BACKGROUND: Benign external hydrocephalus is defined as a rapidly increasing head circumference (occipitofrontal circumference) with characteristic radiological findings of increased subarachnoid cerebrospinal fluid spaces on neuroimaging. The incidence of benign external hydrocephalus has not been previously reported, and there is no available information on the ratio of benign external hydrocephalus in the population of hydrocephalic children. **METHODS:** This study is retrospective and population-based study, geographically covering two health regions in the southern half of Norway with a total mean population of 3.34 million in the ten-year study period, constituting approximately 75% of the Norwegian population. Children with a head circumference crossing two percentiles, or greater than the 97.5th percentile, and with typical imaging findings of enlarged frontal subarachnoid spaces with or without enlarged ventricles were included. Children were excluded if they had a history of head trauma, intracranial hemorrhage, central nervous system infection, other known causes of hydrocephalus, or were born preterm defined as birth before 37 weeks of gestation. **RESULTS:** A total of 176 children fitting the criteria were identified, giving an incidence of 0.4 per 1000 live births. One hundred fifty-two (86.4%) of the patients were male, and mean age at referral was 7.3 months. Increasing head circumference was the main reason for referral in 158 (89.8%) patients and the only finding in 60 (34.1%) patients. Thirty-seven (21%) children had normal ventricles on imaging; the remainder had increased ventricular size. The incidence of pediatric hydrocephalus in Norway is reported to be 0.75 per 1000 live births, thus benign external hydrocephalus accounts for approximately 50% of hydrocephalic conditions in this population. **CONCLUSIONS:** The incidence of benign external hydrocephalus was found to be 0.4 per 1000 live births in this population.

Keywords: benign external hydrocephalus, incidence, hydrocephalus, epidemiology, head circumference, macrocephaly

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Introduction

Hydrocephalus is a relatively common neuropediatric condition; the incidence is reported internationally as 0.36 to 0.75 per 1000 live births. In Norway the incidence has been found to be 0.75 per 1000 live births.[1] The most up-to-date definition of hydrocephalus was agreed upon internationally in 2010 and states that "Hydrocephalus is a condition characterised by a dynamic imbalance between the formation (production) and absorption of spinal fluid that results in an increase in the size of the fluid cavities within the brain and, in some situations, in an expansion of the spaces outside the brain, with or without an increase in the size of the ventricles."[2]

Benign external hydrocephalus (BEH) is a subgroup of hydrocephalus, which mainly occurs during infancy. It is

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defined as a rapid increase in head circumference (HC), measured as occipitofrontal circumference (OFC), combined with enlarged, usually frontal, subarachnoid cerebrospinal fluid spaces on neuroimaging and normal or only moderately enlarged ventricular system.[3,4] For a review of the condition, see Zahl et al.[5] A rapidly increasing HC or a large head a are most commonly what brings the infants to medical attention. Frontal bossing, dilated scalp veins, and a tense fontanel have also been described, as well as irritability, hypotonia, and developmental delay, most commonly gross motor delay; language delay is also seen. The developmental delay and hypotonia have been found to be generally transient, usually normalizing over a period of one to four years.[4-7] Neuroimaging findings generally also normalize over a few years.[8] The disease has been regarded as benign and self-limiting and is rarely treated.[9-12]

The incidence of BEH has not been previously reported, and there is no available information on the ratio of BEH in the population of hydrocephalic children. We aim to determine the incidence of BEH in the general pediatric population. We will also discuss clinical and neuroimaging findings in the BEH population.

Materials and Methods

This study is a retrospective and population-based study, geographically covering two healthcare regions in the southern half of Norway with a total mean population of 3.34 million in the 10-year study period, constituting approximately 75% of Norway's mean population of 4.44 million during the same period. The annual average of live births in the health regions during the study period was 44,225.[13]

Norway is a sparsely populated country with a public three-level hierarchical hospital structure, with local community hospitals as the primary referral centers. Most counties have a central hospital with a pediatric department as a secondary referral center. At the top, there are four university clinics with a neurosurgical department, each serving a geographically well-defined health region consisting of several counties.

Within the Norwegian medicolegal system infants have to be seen at regular intervals at an outpatient mother-and-child health center. Instructions with the legal authority of law are given by the Norwegian health authorities; these regulate the activities of the health centers. Consequently, it is mandatory for the parents to bring the child to the local health center at certain intervals. Norwegian recommendations are that the HC should be measured routinely at each regular visit to the health center during the first year of life. According to these instructions, all children with a rapidly increasing HC should be referred to a specialist; for all practical purposes, all these children end up being referred to and evaluated by the collaborating pediatric and neurosurgical departments in the regional hospital.

Rapidly increasing HC is defined as crossing two percentile curves on the HC registration sheet, which is based on Norwegian reference values.

Diagnosis and treatment of the pediatric population in our two regions were undertaken in the two regional neurosurgical departments, Oslo University Hospital (Rikshospitalet) and Haukeland University Hospital in Bergen. These two departments were responsible for the pediatric neurosurgical service in the South-Eastern and Western regions, respectively. Medical records at the two centers were searched for relevant hydrocephalus diagnoses in the 10-year period from January 1, 1994 to December 31, 2003.

From the medical records information about age, gender, clinical symptoms and signs, HC, and neuroimaging findings were recorded for each patient.

Inclusion criteria included OFC crossing two percentiles or more, or OFC greater than 97.5th percentile in the first year of life, and typical neuroimaging findings. Children diagnosed after one year, but where diagnostic clinical information from primary care existed before age 12 months, were also included in the study population (seven children, 4%). All the included children had been examined with neuroimaging modalities allowing measurement of the subarachnoid/subdural space. For most children who were referred from a lower level institution, the neuroimaging was attached the referral documents and merged with the regional hospital's files.

Children were excluded if any of the following were identified: history of head trauma, intracranial hemorrhage, central nervous system infection, other known causes of hydrocephalus, or prematurity defined as birth before 37 weeks of gestation.

The project was approved by the Regional Ethics Committee, the Norwegian Social Science Data Service, and the Norwegian Directorate of Health.

Results

Overall epidemiological results

A total of 176 children with BEH were identified in the 10-year period in the two regions. This finding gives an incidence of 0.4 per 1000 live births (95% confidence interval, 0.34 to 0.46).[13] The incidence of pediatric hydrocephalus in Norway during the approximate same period was 0.75 per 1000 live births.[1] Thus the incidence of BEH is approximately half that of all primary hydrocephalus in a pediatric setting.

At birth, the patients had a slightly larger HC than in the normal distribution (Figure). At referral, this deviation was naturally much more marked, with most patients having an HC greater than the 97.5th percentile.

There was a marked male preponderance in the BEH population; 152 (86.4%) were boys. The corresponding figure for all hydrocephalic children is 74% in the reasonably matched population of Zahl et al.[1] Approximately 51% of live births in Norway are boys.[13]

Symptoms and clinical findings

The mean age at referral for investigation by specialist care was 7.3 months (range 1.5 to 23 months, median 7 months). There was no difference in referral age between genders. The main reason for contact with the health service was a large and/or rapidly increasing OFC detected during the routine measurements at the public health

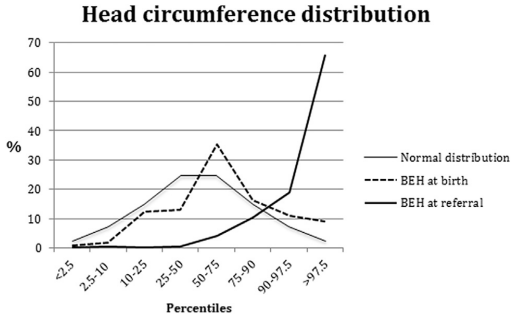

FIGURE.
The graph shows that the head circumference (HC) for the study population did not deviate much from the normal distribution at birth and that the HC increase had occurred between birth and referral (mean age 7.3 months). BEH, benign external hydrocephalus.

clinics (158 patients, 89.8%). Another three patients had increasing OFC listed as an additional finding; thus a total of 91.5% of children were referred with increasing HC as one of the findings. In 68 (38.6%) children a large and/or rapidly increasing HC was the only finding at referral. Other symptoms and clinical findings are listed in Table 1. There was no gender difference with regards to symptoms or signs. Twenty-eight (15.9%) children had one or more findings that could be related to increased intracranial pressure (ICP) (sunset gaze, vomiting, lethargy, irritability, bulging/tense fontanels, and/or splaying of sutures).

Neuroimaging

As increased subarachnoid space was used as a diagnostic criterion, this was present in all patients. There was no grading used by reporting neuroradiologists.

A total of 37 (21%) children had normal ventricles according to reporting neuroradiologists; the remainder had some degree of ventricular enlargement. The degree of ventricular enlargement was subjectively graded as mild (39.6%) or moderate (11.5%), or was simply stated to be increased without any attempts at grading (48.9%). There was no statistically significant difference when clinical findings were compared with ventricular enlargement (Table 2).

Treatment of BEH

In total, 49 (27.8%) of the children with BEH were treated surgically. Ventriculoperitoneal shunting was the most common surgical procedure in 44 (89.8%) patients. Other treatment options were endoscopic third ventriculocisternostomy in three patients, whereas one patient each was treated with subduroperitoneal or lumboperitoneal shunts. Of the 28 children who had one or more signs or symptoms that could be related to increased ICP, 14 children were surgically treated. This group of surgically treated patients constitute 28.6% of the 49 treated patients; thus 71.4% of the treated patients had no symptoms or signs of raised ICP. A slightly lower proportion of the surgically treated children had normal ventricular size (18.4%); however, this is not statistically significant ($P = 0.69$).

TABLE 1.
Symptoms and Signs at Referral

Symptoms and signs*	Number (176)	%
Increased occipitofrontal circumferenc†	161	91.5
Frontal bossing	37	21
Delayed development	31	17.6
Distended veins	29	16.5
Large head†	20	11.4
Abnormal/asymmetric head shape	19	10.8
Large/bulging fontanel/suture diastasis	16	9.1
Hypotonia/head lag	13	7.4
Sunset gaze	10	5.7
Vomiting/retching	7	4
Other eye signs‡	6	3.4
Crying	5	2.8
Hypertonia/hyperreflexia	4	2.3
Seizures/seizure-like activity	3	1.7
Torticollis	2	1.1
Lethargy	2	1.1
Irritability	2	1.1
Reflux	1	0.6
Poor weight gain	1	0.6
Dysmorphic facial features	1	0.6

* More than one per child.
† Subjective term from patient records.
‡ Includes poor vision, nystagmus, strabismus, not fixing and following.

TABLE 2.
Ventricular Size and Clinical Findings at Referral

Ventricle Size	Increased intracranial pressure*	Other	None†	Sum
Normal	6 (16.2%)	18 (48.6%)	13 (35.1%)	37
Enlarged	22 (15.8%)	62 (44.6%)	55 (39.6%)	139
All patients	28 (15.9%)	80 (45.5%)	68 (38.6%)	176

* Includes sunset gaze, vomiting, lethargy, irritability, bulging/tense fontanels, and splaying of sutures.
† Increased occipitofrontal circumference and/or large head only.

Discussion

In this population-based study, we found the incidence of BEH to be 0.4 per 1000 live births, constituting approximately 50% of all children diagnosed with hydrocephalus. The incidence of BEH in a population has not been previously reported. There are therefore no numbers for direct comparison with our findings. As will be discussed subsequently, establishing an exact, generally valid BEH incidence is hampered by several factors: methods for detecting infants at risk, as well as the differing clinical and radiological criteria from one study to another.

The patients in our study were identified through medical record searches in the two regional hospitals where children fitting the criteria of BEH should all be referred to following the national guidelines at local health centers. Thus we cannot be certain that some children may not have been identified or referred appropriately. However, with Norway having mandatory health center visits in infancy and firm guidelines for the referral of children fitting the criteria, we believe the numbers of missed children to be low, well within the range of the 95% confidence interval.

Previous attempts at establishing BEH incidence

Hamza et al.[10] found BEH in 13 of 81 patients (16%) with macrocrania in a group of children diagnosed with low-density fluid collections on computed tomography (CT). Kendall and Holland[14] also investigated CT images and found enlarged cerebrospinal fluid spaces of no known etiology in 14 of 500 CT image sets (2.8%). One retrospective review of incidental magnetic resonance imaging findings in a tertiary pediatric center found external hydrocephalus in 0.6% of imaged children.[15] This study and other studies[16-20] also include infants born prematurely (12% to 52%); in these studies, however, the definition of prematurity differs with a cutoff point of between 35 and 38 weeks of gestation. One study[21] excluded premature children, as we have done, but they did not include epidemiological data. Many publications do not mention whether preterm infants are included.[6,11,17,22-24]

One article[16] included only children with normal or only mildly dilated ventricles. Infants with signs of raised ICP,[11,16,19] abnormal neurological examination,[25] or developmental delay[10,19] are also sometimes excluded, which implies that the authors must have regarded BEH as a condition that cannot yield such symptoms. It also means that the studies cannot be easily and soundly compared.

Clinical criteria for the BEH detection and diagnosis

Mean referral age in our study is 7.3 months (range 1.5 to 23 months). This study compares well with other studies where referral age or age at diagnosis ranges from 6.5 to 8.9 months.[6,16,18,20] The age at which infants are diagnosed is determined by several factors. One such factor is the onset of clinical symptoms and signs. Many children present with an increase in HC, often with few, if any, other clinical findings. Early detection because of increased HC is probably facilitated by routine measurements. Thus one may expect such routines to influence the detection of the condition. The most commonly reported symptoms and signs apart from increased head OFC that lead to investigations and ultimately the diagnosis of BEH are seizures,[26-28] delayed psychomotor development,[27,28] and signs of increased ICP such as tense or large fontanels.[27]

Pediatric hydrocephalus is more common in the male population; this is even more so for the subgroup of hydrocephalic children with BEH. In various studies, the male preponderance ranges from 52% to 80%.[4,6,12,18-21] In our study, the gender distribution is even more skewed, with 86.4% boys. Study populations are, however, generally small compared with our study, some have less than 10 patients included, making direct comparison difficult.[6,7,29]

From our results, we find that for those where OFC at birth was registered (153), the OFC was slightly higher than in the normal population at birth, with 71.9% having an HC greater than fiftieth percentile, 20.3% greater than the ninetieth percentile, and 9.2% greater than the 97.5th percentile. This finding compares well with Halevy et al.[16] who found an average at birth at the fifty-eighth percentile and the results of Hellbusch[17] who found that most had OFC between the fiftieth and the ninety-eighth percentiles. Laubscher et al.[18] found that 12 of 21 patients (57%) of their group with dilated pericerebral subarachnoid space had an HC of greater than the ninetieth percentile at birth. Thus there is a trend toward larger OFC at birth in children who later develop BEH, but still most of the children with BEH had HCs within the normal range at birth. At diagnosis the HC distribution had become much more skewered in the BEH population. In our study, 65.9% of children had an OFC greater than the 97.5th percentile (mean age 7.3 months). This finding compares well with 50% greater than the ninety-eighth percentile at a mean age seven months in Hellbusch's study and mean OFC at the 79.5th percentile at a mean age 5.8 months (Halevy et al.).[16] The present study is the largest to date showing this relatively dramatic increase in HC from birth to diagnosis.

BEH can also be diagnosed due to excessive head growth alone, even if the OFC still is within the normal range. In Norway, rapidly increasing HC is defined as crossing at least two percentile curves on the national HC registration charts.[1] There have also been published examples of BEH in microcephalic children.[30]

Throughout the world there are different percentile charts in use, our Norwegian population was studied using the growth charts that were introduced in the 1980s.[31,32] Many use the World Health Organization charts, which are based on data from Norway, Brazil, Ghana, India, Oman, and the United States. However, they have been shown to be at variance compared with national or regional OFC growth references.[33-36] As these studies have shown, the use of standard OFC charts that are not based on regional/national populations may cause variations in the registered incidence of hydrocephalus, including BEH.

In the studies of BEH, the cutoff value used in the diagnosis of macrocephaly varies from the ninetieth to the ninety-eighth percentile[4,10,14,17,18,25,37]; in our study, we have used the 97.5th percentile as the cutoff point. As discussed previously, the use of different percentile charts and differing cutoff values will certainly have impact on the incidence of BEH in a population.

Radiological criteria for the BEH diagnosis

In this study, the children were examined with ultrasound, CT, or magnetic resonance imaging. Many were investigated with more than one imaging modality. In most instances, the subarachnoid space is simply reported as increased by the neuroradiologist, with no exact measurements given. Several studies on the different imaging modalities have been done to evaluate what the normal range of subarachnoid space is in infants. The three most common measurements evaluated are sinocortical width (SCW), craniocortical width (CCW), and interhemispheric distance (IHD). SCW was introduced by Govaert et al.[38] and is defined as the shortest distance between the lateral wall of the triangular superior sagittal sinus and the surface of the adjacent cerebral cortex. The CCW is the shortest vertical distance between the calvarium and the surface of the cerebral cortex, whereas the IHD is defined as the widest horizontal IHD. Measurements are taken on coronal views, at the level of the foramen of Monro.[39,40] These distances vary with the infant's age with an increase in normal subarachnoid space during the first year of life, peaking at approximately seven months, with a gradual decrease thereafter.[40,41] Depending on the imaging modality chosen, the age of the child and the selection of study population with regards to OFC, the upper limit above which the CCW is likely to be abnormal, ranges from 4 mm to 10 mm.[4,23,39,41,42] The corresponding ranges for SCW are 2 mm to 10 mm and for IHD 6 mm to 8.5 mm. However, no validated normal values exist and thus the cutoff values may differ between radiologists. As the increased subarachnoid space is one of the diagnostic criteria for the diagnosis of BEH, this has implications for whether a child is diagnosed with BEH; thus the incidence in a population depends to some degree on the cutoff value used by radiologists. This lack of uniformity also applies to the present study, as the definitions of abnormal distances most probably varied between the describing radiologists.

Lateral ventricle size is generally defined as normal or only moderately enlarged in BEH. However, this definition, which is stated in many publications, does not seem to be

supported by findings in those same publications where reported ventricle size ranges from normal to gross dilatation. The degree of dilatation of lateral ventricles has been found to be roughly proportional to the width of the frontal subarachnoid space.[21] Ventricular dilatation, when it occurs, also seems to be a later finding than enlarged subarachnoid spaces.[43]

BEH versus idiopathic communicating hydrocephalus

BEH and other forms of idiopathic communicating hydrocephalus may very well be part of a spectrum of hydrocephalus,[3,27] and a clear distinction between the two is difficult to make in a retrospective study such as this one. One clear limitation of this study is that we cannot, at least in our group of treated children, be certain of this distinction between BEH and communicating hydrocephalus, as a proportion of the patients had signs and symptoms of raised ICP and/or enlarged ventricles. However, patients with communicating hydrocephalus are generally believed to be in need of surgical treatment, and most patients in our study with signs or symptoms of raised ICP and/or ventricular dilatation did not receive any surgical treatment.

The present study is the first to describe the incidence of BEH in a relatively large and well-defined population, with the limitations discussed previously. As most of the included children were detected by a mandatory regime of repeated routine HC measurements, we believe the figures reported here to be fairly representative.

Conclusions

BEH is the most common hydrocephalic condition in young children; it is also one of the least studied, which might be attributed to its assumed benign course. Our findings suggest that the incidence of BEH is approximately half the incidence of primary pediatric hydrocephalus in reasonably comparable populations. Because of the lack of studies of this condition, there is also no clear knowledge of diagnostic criteria or the correct treatment, if any. We suggest that the routine well-child clinic may help identify this group of patients. Any child found on routine follow-up to have a rapidly increasing OFC, or macrocephaly, should be referred on to the nearest pediatric department for clinical examination and imaging.

Data from other populations, and data including subgroups such as premature infants, would be helpful to validate our epidemiological findings in BEH.

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Paper 3

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Original Article

Clinical, Radiological, and Demographic Details of Benign External Hydrocephalus: A Population-Based Study

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ABSTRACT

Background: Benign external hydrocephalus has an incidence of about 0.4 per 1000 live births. It affects infants and is characterized by an increasing head circumference and typical neuroimaging findings. Previously published studies on benign external hydrocephalus often contain groups of few and selected patients.
Methods: This is a follow-up of a recently published article reporting the incidence of benign external hydrocephalus. This retrospective and population-based study covers two large health regions in Norway, over a 10-year period (1994 to 2003). Infants with increasing head circumference, combined with typical radiological findings of enlarged subarachnoid spaces, were included. Information about head circumference development, neuroimaging findings, and birth delivery methods, as well as demographic details, was retrieved from the hospital medical records.
Results: A total of 176 children with benign external hydrocephalus were included, 86.4% being boys. At birth, the head circumference was close to normal. Mean age for when the head circumference reached abnormal values, i.e., crossing two percentiles or reaching the 97.5 percentile, was 3.4 months; none was older than seven months. Around four of five children had dilated lateral ventricles in addition to enlarged subarachnoid spaces. The neuroimaging findings tended to normalize after age 12 months. About half of the patients ended up with head circumferences at or above the 97.5 percentile.
Conclusions: Most infants with benign external hydrocephalus are born with a normal head circumference that increases too fast and reaches abnormally high values before age six months. This age and gender distribution is very similar to that described for infant subdural hemorrhage.

Background

Benign external hydrocephalus (BEH) is a relatively common pediatric condition with an estimated incidence of about 0.4 per 1000 live births and with a marked male preponderance.[1] This condition occurs during infancy and is characterized by a rapidly increasing head circumference (HC) combined with typical neuroimaging findings of increased subarachnoid cerebrospinal fluid spaces—especially overlying the frontal lobes—and normal or enlarged ventricles.[2-7] For an extensive review of the condition, see Zahl et al.[2]

Many other terms have been used for this or similar conditions, such as "subdural effusion,"[8] "subdural hygroma,"[9] "extraventricular obstructive hydrocephalus,"[10] "benign subdural collections,"[11] "benign enlargement of the subarachnoid spaces,"[12,13] "primitive megalencephaly,"[14] and macrocephaly.[15] The condition is referred to as BEH in the following discussion.

The main sign leading to medical attention is increasing HC, although other symptoms and signs have been reported, such as a tense anterior fontanel,[16,17] dilated scalp veins,[3] irritability,[6,18] gross motor delay,[12,19] and seizures.[20,21]

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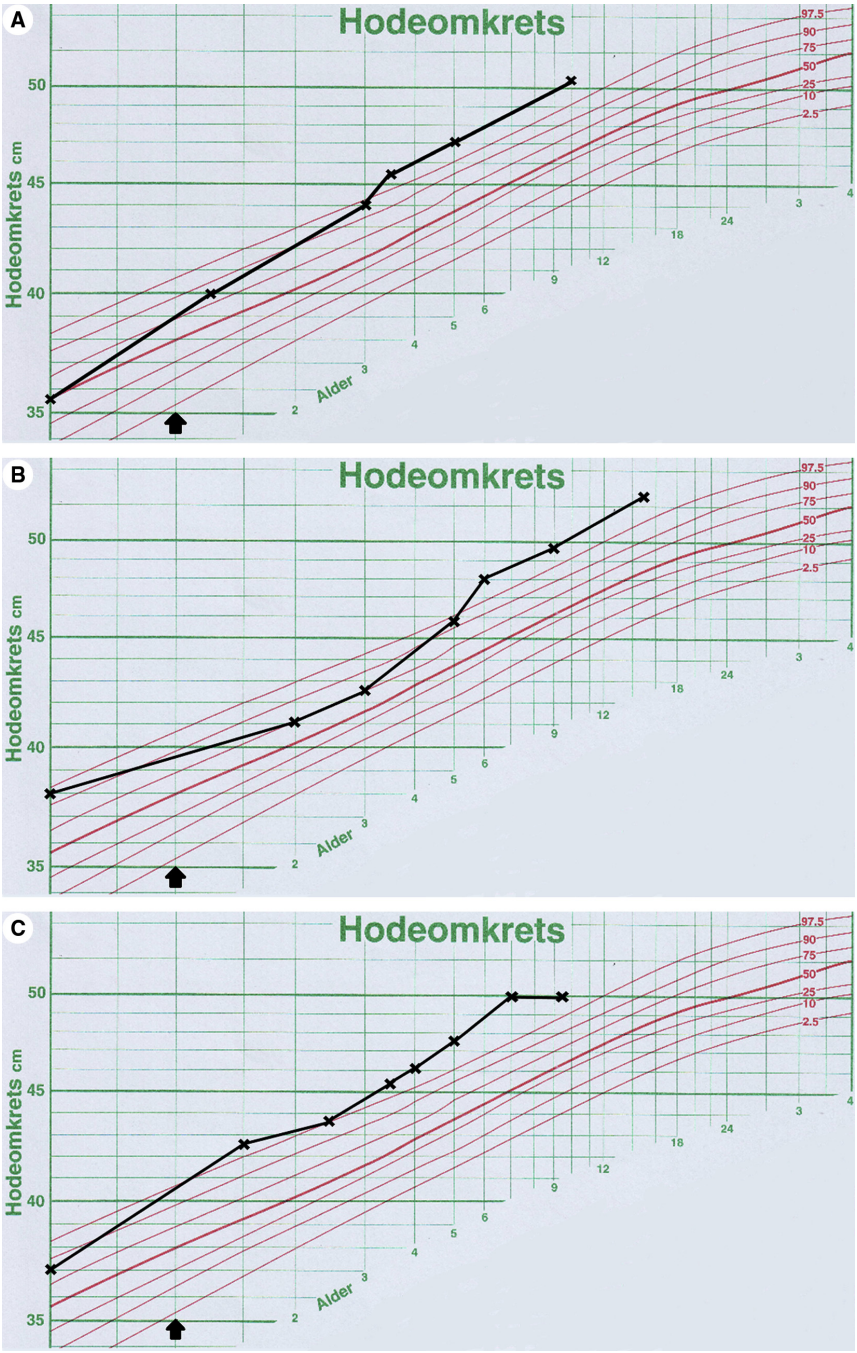

FIGURE 1. Norwegian head circumference registration sheets used at the time of the study. *Hodeomkrets* = head circumference, shown in centimeters along the *Y* axis. The *X* axis shows the age in months. Black arrows mark the age one month. (A) An infant boy with gradually increasing HC after birth, with rapid growth around age three months, thereafter stabilizing at a high percentile. (B) This boy had a fairly late HC growth spurt, most rapidly around the age five to six months. Of notice is also a significant decrease in HC in the first two months, possibly due to a temporary head swelling after birth. (C) Infant boy referred at age 5.5 months. The HC chart shows rapid growth even at an early age (before two months). The color version of this figure is available in the online edition.

In addition to reporting the incidence of BEH, our previous population-based study showed that the HC was close to normal at birth and that increased or enlarging HC was the main cause for referral.[1] We also found that approximately one-fifth of the children had normal ventricles on neuroimaging, whereas the remainder had increased ventricular size at diagnosis.

The aim of this study is to explore in detail when the head growth becomes abnormal, by collecting information from medical journals and HC growth charts. In addition, we report some information about radiological outcome.

Methods

This is a retrospective and population-based study, covering two well-defined health care regions in Norway with a mean total population of 3.34 million during the 10-year study period from 1994 to 2003; this constitutes about 75% of Norway's mean population during this period. Norway has a regionalized public health care system; within this system only two regional neurosurgical departments (in Oslo and Bergen) dealt with all pediatric neurosurgical conditions in these two regions. Medical records at these centers were searched for relevant hydrocephalus diagnoses. Information about age, gender, symptoms, clinical signs, neuroimaging, and HC development were collected for each patient. The radiological data are based on the radiologists' original reports; hence this is not a retrospective imaging study.

Inclusion criteria included HC above the 97.5th percentile or an HC crossing two or more percentiles during the first year of life, together with neuroimaging findings typical of BEH. Children with histories of head trauma, intracranial hemorrhage, central nervous system infection, other known causes of hydrocephalus, or prematurity (born before 37 weeks' gestation) were all excluded.

For further information about the study and selection methods, see Wiig et al.[1]

The study was approved by the Regional Committee for Medical Research Ethics.

Results

A total of 176 children (152 boys and 24 girls) matched the inclusion criteria for BEH during the study period; 44 (25 %) of the children required a ventriculoperitoneal shunt.[1]

Onset of sign was defined as the age at which the infant's HC curve crossed two percentiles or exceeded the 97.5 percentile. Detailed data for HC development were available for 107 children. Figure 1 shows the HC registration sheets for three infants.

Mean age of sign onset was 3.4 months (median 3.0 months, range 0 to 7.0 months). Mean age of onset for girls was 2.9 months ($n = 14$), and for boys, 3.5 months ($n = 93$). None of the 107 infants had sign debut after age seven months (Fig 2). The mean age for referral to our hospitals was 7.3 months, and the main reason for health service contact was a large or increasing HC.[1]

Twenty-one children (11.9 %) were delivered by Caesarean section, and two children had assisted deliveries (forceps and vacuum extraction). Thirteen children (7.4 %) were twins, but in no cases did the other twin develop BEH. Most of the twins (i.e., 11 of 13) were boys; unfortunately, we do not know the gender of the sibling twins.

For 28 of the 176 patients we had no information regarding the development of HC or radiology apart from what was found at the first hospital consultation. For the remaining children follow-up information existed to a varying degree.

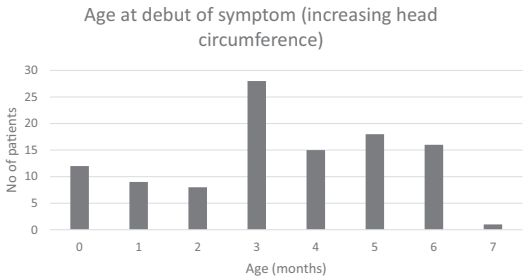

FIGURE 2. Bar graph showing sign onset, i.e., when the infants' HC became abnormally large. Onset was defined as the age at which the infant's HC crossed two percentiles or exceeded the 97.5 percentile. No patient had sign onset after age seven months. Please note that a small fraction of the infants showed an increased HC at birth or shortly thereafter. Detailed information about HC development was available for 107 of the patients ($n = 107$).

Neuroimaging: follow-up

Detailed information about radiology findings before age 12 months existed for 123 of the patients. They were all found to have excessive extracerebral fluid; 100 of these also had dilated ventricles (exact size not described). Figure 3 shows the magnetic resonance imaging of one of our patients with BEH.

For 77 infants we found reports on neuroimaging follow-up beyond age 12 months. In 57 of these, increased subarachnoid cerebrospinal fluid spaces were persisting, and 47 also had dilated lateral ventricles. Eight children had dilated lateral ventricles only, and in 12 patients the intracranial radiological findings were described as normal. Mean age at the final radiological examination for those who were followed-up beyond age 12 months was 21.7 months (median 18 months, range 12 to 104 months).

For 66 children we had information about neuroimaging both before and after age 12 months. Figure 4 gives a flow chart showing the development of radiological findings in these patients. As we

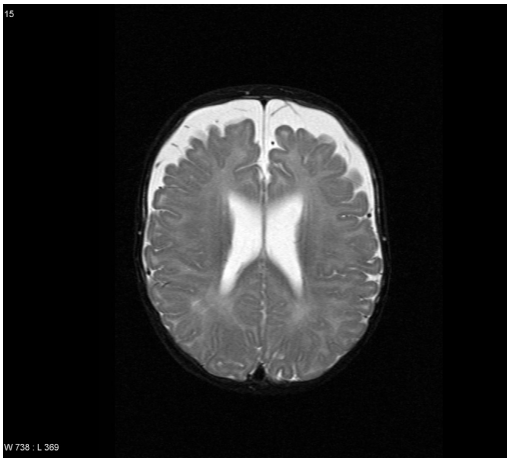

FIGURE 3. Magnetic resonance image of a 6.5-month-old boy (the same as in Fig 1A), referred because of increasing head circumference. The image shows enlarged frontal subarachnoid spaces, moderately increased lateral ventricles, and a widened frontal interhemispheric fissure.

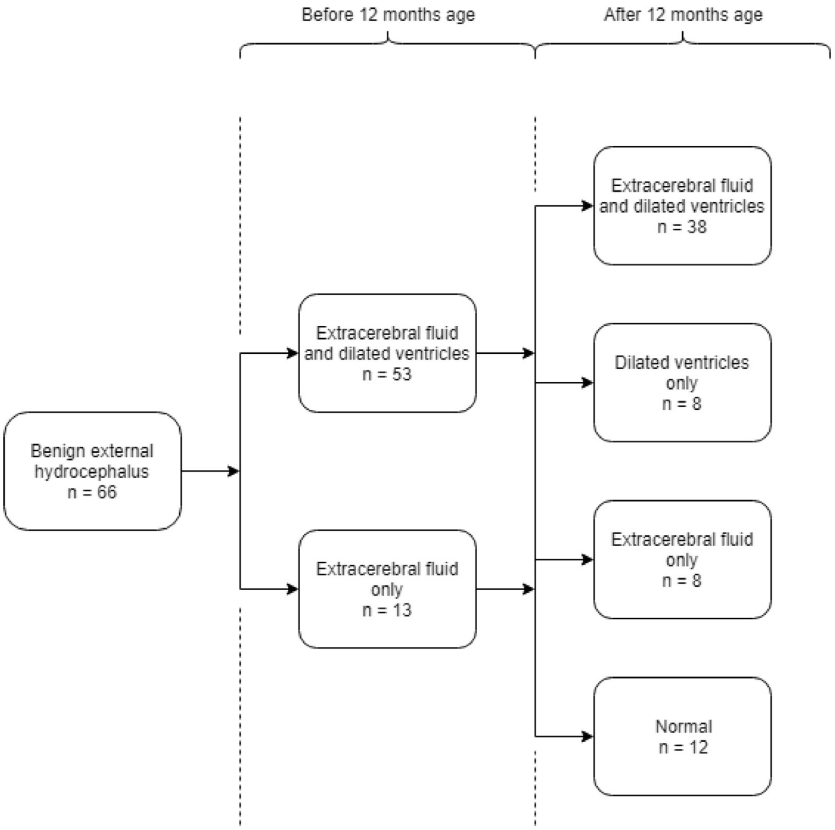

FIGURE 4. Flowchart that groups infants with neuroimaging both before and after age 12 months, according to the original radiologist's analysis. Number of patients mentioned below the description.

did not have access to the actual images—only the radiologists' interpretations—no exact numbers of size changes are available.

Head circumference: follow-up

For 106 children we had information about the HC development after age 12 months. Mean age at the final HC measurement for these children was 28 months. Of these children, 55 (52%) had a final HC at or above the 97.5 percentile. The mean age for the final measurement for these infants was 26 months. For the majority of these 55 children, the HC percentile stayed the same or decreased, whereas for 13 (24 %) the HC percentile continued to increase after age 12 months.

Discussion

This study is a follow-up and extension of our article from 2017,[1] based on the same population and study group.

The majority of patients had dilated lateral ventricles in addition to excessive extracerebral fluid on neuroimaging. This corresponds with earlier publications. Although we do not know when the excessive fluid begins to accumulate in each patient, it appears reasonable to assume that this coincides with the HC increase, i.e., sometime before age six months. For the long-term radiology, our results suggest that the excessive extracerebral fluid disappears earlier than the excessive intraventricular fluid.

In our selection of patients, we chose to exclude patients born prematurely or with a diagnosis of intracranial hemorrhage. We believe this was a mistake, as prematurity has been showed to be associated with BEH[22] and BEH is known to be complicated by subdural hematoma (SDH).[23,24] Thus these exclusions probably deprived us of valuable information about BEH in these groups of infants. Exact numbers for the excluded patients are not available.

Our results show that at least half of the patients will end up with large heads beyond infancy. We know from our previous study that HC at birth was close to normal.[1] As shown in Fig 2, the increase in HC typically occurs during the first six months of life, with a mean age of 3.4 months for sign onset. The mean age at referral for investigation by specialist was 7.3 months.[1] Thus the mean interval from sign debut to specialized medical evaluation was about four months.

This age distribution of BEH is strikingly similar to the distribution of infant SDH, which has a peak incidence during the first few months of life.[25–27] This also seems to be the case with the male preponderance (86.4% boys), a gender distribution similar to that of infant SDH.[25–28] These similarities in age and gender distribution may not be coincidental, as BEH is a known risk factor for developing SDH.[13,29,30] It is also somewhat intriguing that infants

diagnosed with abusive head trauma show an almost identical age and gender distribution to the one found for BEH.[31,32]

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Paper 4

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ORIGINAL PAPER

Quality of life and physician-reported developmental, cognitive, and social problems in children with benign external hydrocephalus—long-term follow-up

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Abstract

Introduction Benign external hydrocephalus (BEH) is characterized by too rapidly increasing head circumference in infants, combined with typical neuroimaging findings. Psychomotor developmental delay is typically seen during the first few years of life; after that, the children's development assumedly normalizes. However, little is known about the long-term effects of BEH.

Methods In this retrospective population-based study, children diagnosed with BEH during the years 1994–2003 in Southern Norway were asked to participate. Included patients (age 8–18 years old) and their parents answered the PedsQL questionnaire. The patient's family physicians contributed by giving information from medical records, with special emphasis on developmental, cognitive, and social function.

Results One hundred seventy-six children were identified with BEH. One hundred three patients and 86 parents completed the PedsQL questionnaire. Supplemental medical information for 142 of the patients was received, mainly from their family physicians. Children and adolescents with BEH score themselves better than the normative mean on health-related quality of life, while the parents score their BEH children within the normative mean, except for the school functioning subgroup, where they score significantly lower. Various developmental, physical, and social problems are reported, like mental retardation, speech problems, epilepsy, motor impairment, psychiatric disorders, and cognitive difficulties. Among these patients, there is a discrepancy in some areas between the child-reported and parent-reported quality of life.

Conclusions Children and adolescents who were diagnosed with BEH during infancy generally do well. However, for some patients, there appear to be various developmental, social, and cognitive problems, and they seem to struggle more in school than their healthy peers.

Keywords Benign external hydrocephalus (BEH) · Quality of life · Neuropsychology · Psychosocial function · Macrocephaly · Outcome studies

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Introduction

Benign external hydrocephalus (BEH) is a condition in infants with an incidence of about 0.4 per 1000 live births [30]. It is defined as a rapid increase in the head circumference, typically around the age of 6 months [32]. Radiologically, three neuroimaging features characterize the condition: enlarged subarachnoid spaces—especially overlying the frontal lobes, normal or moderately enlarged ventricles, and a typical widened frontal interhemispheric fissure [2, 13]. Many other symptoms are described, all shared with "ordinary hydrocephalus," e.g., frontal bossing, dilated scalp veins, hypotonia, and developmental delay. However, these symptoms have been regarded as transient, together with neuroimaging findings. Hence, the condition has been described as being benign, and therefore rarely treated.

Many other terms have been used for the same and similar conditions, such as subdural hygroma/effusion/collection [4, 10, 22], primitive megalencephaly [11], or benign enlargement of the subarachnoid spaces—BESS [15, 27]. For simplicity, the condition will be referred to as BEH in this article.

Few articles have been published on long-term effects of BEH [11, 16, 17]. Only one of these included children who were shunted [16]. Generally, children and adolescents with BEH show subtle neurocognitive difficulties, but the results do vary. Muenchberger et al. reported problems for some patients, especially in school [17]. Laubscher et al. found one patient with mental retardation and several children who were clumsy or delayed in language at school age follow-up [11]. One study found that children with BEH report slightly reduced quality of life [31].

This article is a follow-up and extension of our study from 2017 [16]. We present follow-up information from the patient's family physicians regarding different problems and diagnoses considered relevant, together with self-reported, and parent-reported health-related quality of life.

Methods

This is a population-based retrospective study of children diagnosed with BEH during infancy. Medical records of all children referred to two Norwegian university hospitals during the study period (1994–2003) were reviewed and considered for inclusion. These hospitals are the only referral centers for neurosurgery for about 3.34 million people (75% of Norway's population). For a thorough and relevant description of Norway's health system, see Wiig et al. [30]. Only children with BEH (increased or increasing head circumference and typical neuroimaging findings) were included. Inclusion criteria were head circumference greater than the 97.5th percentile or crossing two percentiles during the first year of life, and typical neuroimaging findings. From the medical records, information about age, gender, clinical symptoms and signs, neuroimaging, treatment, and follow-up were collected. The patients and their families were invited by a letter to join the study.

Exclusion criteria: a history of head trauma, intracranial hemorrhage, CNS infection, prematurity (birth before 37 weeks of gestation), and other known causes of hydrocephalus.

Consenting patients and parents filled out the Pediatric Quality of Life Inventory (PedsQL) questionnaire. PedsQL is a health-related quality of life measurement tool with good reliability and validity [28], translated and validated for use also in Norway [21]. It generates a total score and further consists of four subscales: physical function, emotional function, social function, and school function. We present raw scores as means and compare them with the normative mean [21]. To be clinically significant, scale score is 70 or lower [9]. Results are presented as raw scores and compared with normative data when available.

In Norway, all inhabitants have been registered with a family physician that provides primary health care and receives reports from medical specialists involved with their patients. We contacted the family physician of every included patient and received medical records. Information from the records about the patient's health, with an emphasis on developmental, cognitive, and social status, was collected and categorized.

The study was approved by the Regional Committee for Medical Research Ethics.

Results

One hundred seventy-six children were identified with BEH during the 10-year period. One hundred fifty-two (86.4%) were boys. For further demographic details, see Wiig et al. [30]. Forty-nine (27.8%) of the children received surgical treatment for their hydrocephalus, but information about specific surgical indication was not available for each individual patient. For further information about differences in outcome for treated versus untreated patients, see Mikkelsen et al. [16].

Eighty-eight teenagers (age 13–18 years) and 15 children (age 8–12 years) answered the PedsQL questionnaire. Eighty-six parents completed the corresponding parent version of PedsQL. Table 1 shows the PedsQL scores from the parent (proxy) and self-report questionnaires. They are compared with the normative means [21] using a one-sample *t* test. For the parent reports, only the school score was significantly lower than the normative mean, while the other subscores and total score were lower but not significantly so. The self-reported total scores and all subscores were significantly higher than the normative mean.

When differing between children and teenager PedsQL scores and their respective parents, the results were no different from those reported in Table 1. This applies to both total score and subscores.

For a total of 142 (81%) of the patients, we received medical information from their family physicians. We also received follow-up hospital records for some of the patients. For 38 of these 142 patients, clinically relevant problems were reported. Table 2 summarizes this and shows the corresponding parent- and self-reported PedsQL with mean total scores for those patients where these were available. The number of patients is small, but in general, the parent scores are lower than the self-reported scores, and some scores are also lower than the clinical cutoff score. For the remaining 104 patients (of 142), the physicians/hospitals reported no relevant problems.

Information regarding the 71 patients who did not answer the quality of life questionnaire (self-report nor parent-report)

Table 1 Self- and parent-reported health-related quality of life using the PedsQL questionnaire. Means are compared with normative means using a one-sample *t* test (level of significance $p < 0.05$). For the parent reports, school score is significantly lower than the normative mean. For the self-reports, both total score and all subscores are significantly higher than the normative mean

				One-sample *t* test		
PedsQL parent report	N	Mean (SD)	Min-max	*t* (df)	*p*	Normative mean [21]
Total score	86	83.39 (17.31)	33.70–100	−1.45 (85)	0.150	86.10
Physical health	86	88.83 (16.45)	31.25–100	0.00 (85)	0.998	88.83
Emotions	86	79.83 (20.62)	15.00–100	−0.07 (85)	0.945	79.98
Social	86	83.97 (23.56)	0.00–100	−1.61 (85)	0.112	88.05
School	84	78.27 (20.11)	30.00–100	−4.87 (83)	0.000	88.97
PedsQL self-report	N	Mean (SD)	Min-max	*t* (df)	*p*	Normative mean [21]
Total score	103	89.85 (9.20)	57.61–100	5.04 (102)	0.000	85.29
Physical health	103	93.60 (8.46)	56.25–100	2.98 (102)	0.004	91.12
Emotions	103	85.70 (14.66)	40–100	5.92 (102)	0.000	77.15
Social	103	93.98 (9.27)	60–100	6.42 (102)	0.000	88.12
School	102	83.70 (14.47)	40–100	3.96 (101)	0.000	78.02

was also explored. Thirty-seven were reported by physicians and hospitals to have no relevant problems. For 17 patients, no supplemental information existed. For the rest (17 patients), various problems were described, as reported in Table 2.

Discussion

The purpose of this study was to investigate the long-term effects of BEH. Mikkelsen et al. reported that children with BEH show subtle neurocognitive difficulties [16]. Our study population includes some of the same patients. Most children with BEH seem to do quite well during late childhood and adolescence, yet some children report difficulties.

As shown in Table 1, BEH children score within the normative values on the total score on health-related quality of life. Only school-functioning scores were significantly lower than the normative mean, but only by parent reports. In general, the children and adolescents score themselves above the normative mean, and the parents score their children slightly below the normative mean. The results were not different when children (8–12 years) and adolescents (13–18 years) were analyzed separately. It seems that the parent scores better reflect the clinical conditions.

Table 2 For 142 patients, we received medical information from physicians and hospitals. Thirty-eight of these reported problems/conditions (often more than one) are shown in this table. The table also shows the corresponding PedsQL scores for those patients where we had this information and the amount of shunted patients

Reported problems	No. of patients	Percent of reported patients	No. of shunted patients	Mean PedsQL self-report score (*N*)	Mean PedsQL parent report score (*N*)
Delayed speech	13	9.2%	6/13	84.1 (5)	75.4 (5)
Social behavioral problems	12	8.5%	7/12	85.1 (6)	57.6 (8)
Motor impairment	11	7.7%	5/11	81.0 (6)	75.4 (5)
Mental retardation*	8	5.6%	6/8	94.0 (2)	40.6 (3)
Concentration problems	8	5.6%	2/8	81.5 (7)	75.4 (5)
Cognitive deficits	7	4.9%	4/7	83.4 (4)	48.4 (2)
Epilepsy	7	4.9%	3/7	81.0 (4)	67.6 (5)
ADHD/ADD	6	4.2%	2/6	72.8 (2)	53.3 (3)
Autism spectrum disorders	5	3.5%	1/5	57.6 (1)	57.4 (4)
Anxiety and depression	5	3.5%	0/5	83.7 (3)	68.1 (3)
Dyslexia	4	2.8%	3/4	90.2 (3)	79.9 (2)

*The eight patients with mental retardation are also contained in other groups: speech problems (four of the eight mentally retarded patients); motor impairment (four patients); epilepsy (two patients); autism spectrum disorders (two patients); cognitive deficits (two patients); social behavioral problems (three patients)

As found in our previous study [16], the only functional area BEH patients seem to struggle on a long-term basis is in school although they do not seem to perceive that themselves. Whether this discrepancy is due to a deficient self-knowledge in children or parental bias towards "expected" problems remains uncertain. There was no difference in PedsQL scores when differing between children and adolescents, and the corresponding parent scores. This observation shows that increasing age not necessarily implies a more "realistic" view on the quality of life.

The divergence in the PedsQL score for school functioning should be the target for future research, for instance with a prospective longitudinal study of this patient group.

Physician-reported problems are shown in Table 2. Some report rather serious conditions, often more than one per child. These patients have no other known causes for their problems. We have no established control group; hence, it is difficult to draw conclusions.

Mental retardation

The overall prevalence of mental retardation in a Norwegian population study was 6.2/1000 [24]. One previous study describes mental retardation in eight out of 74 patients with BEH and/or megalencephaly [11]. Six of the eight patients with mental retardation in our material had been treated with a shunt. This could reflect a slightly different clinical condition, with more pronounced symptoms leading to shunt surgery, possibly due to a higher ICP, and hence, a larger risk of serious brain damage (mental retardation). Mental retardation is a serious condition that brings about several symptoms. For that reason, some of these patients will also be reported in other groups: speech problems (four of the eight mentally retarded patients); motor impairment (four patients); epilepsy (two patients); autism spectrum disorders (two patients); cognitive deficits (two patients); social behavioral problems (three patients).

Speech problems

The delayed speech was reported in quite a few of our patients, this has been described in earlier studies, but usually in one or very few patients [3, 8, 19]. Yew et al. reported that six of their 72 patients had verbal deficits detected late during follow-up and not at diagnosis [31]. Unfortunately, we have insufficient information about the degree or duration of speech problems in our study group.

Motor impairment

Motor impairment/clumsiness was seen in around 6% of patients where we had reliable health information. Additionally, we found that 14 out of the 133 children (10.5%), who later had normal motor development, showed a temporary delay in motor skills typically before 3 years of age. This corresponds well with earlier studies [2, 17, 31]. Delayed gross motor function is described also on a long-term follow-up [8, 18, 19]. For the patients where we also had the quality of life reports, the PedsQL physical subscores did not differ significantly from total score, or between patients and their parents.

Epilepsy

Epilepsy is reported in some patients. Both seizures during childhood and abnormal electroencephalograms have been reported in infants with BEH [5, 20]. To our knowledge, no earlier studies have reported this as a permanent long-term finding in older children. We do not know the severity of epilepsy in our patients, but the incidence seems higher than in the general population [26].

Autism spectrum disorders

Autism spectrum disorder was found in five of our patients (all boys). This seems to be a higher incidence than in the general Norwegian pediatric population [25]. The authors of a recent study, using repeated magnetic resonance imaging scans, propose that extra-axial fluid that persists from infancy and beyond 12–24 months of age could be a possible biomarker for the early detection of an autism spectrum disorder risk [23]. Our results may support this possibility.

Psychiatric disorders

Psychiatric disorders like ADHD (six patients) and anxiety and depression (five patients) have rarely been reported before, probably because very few studies have a long enough follow-up for such symptoms to appear. Muenchberger et al. describe one patient with depression and two with panic attacks, one of them is also diagnosed with hyperactivity [17]. The overall prevalence of mental disorder for this age group in Norway is about 7% [7]. Whether or not our patients were formally diagnosed by specialists are unknown. Based on this and our limited number of patients, we have no reason to suspect that BEH is an important risk factor for developing psychiatric disorders.

Learning disabilities

Some patients display various learning/cognitive problems (Table 2). To our knowledge, only two studies have reported school functioning in children with BEH. Muenchberger et al. found that eight of 15 patients had to repeat grades or attend special classes [17]. Laubscher et al. found that 11 of 12 children had a normal school outcome [11]. The PedsQL results presented earlier support the belief that BEH is associated with a higher risk of problems in school.

Social behavioral problems

Social behavioral problems are commonly reported (Table 2). Although unspecific, it seems to have a significant impact on the quality of life, as reported by parents. When looking at the five patients with reported social behavioral problems where we have PedsQL scores from both patients and parents, four of five parents report significantly lower values on the PedsQL social subscores than their children (difference range 15–55). It seems that children with social behavioral problems have reduced self-awareness regarding this. As mentioned earlier, three of these patients were found to be mentally retarded.

When looking at patients with reported PedsQL scores of less than 70, i.e., indicating clinically significant problems for whom supplemental information exists, the medical reports confirm various developmental, cognitive, and social problems.

This study has its limitations. A high number of patients (41%) and parents (51%) did not answer the quality of life questionnaire. This was explored by looking at patients where we did not receive PedsQL answers but did receive supplemental information from family physicians or hospital medical records, and we found quite a few patients with various problems (as reported in Table 2). This shows that our reported PedsQL scores probably are unnaturally high, as conditions like these most likely will cause lower quality of life scores. It is possible that some parents with concern about their child's development and well-being have preferred not to answer the quality of life questionnaire, and children with difficulties and problems find it too painful. The reason for the difference between child self-reports and parent proxy-reports is debated. It has been demonstrated that levels of agreement can be affected by child age and development, domains investigated, and the parent's own quality of life [6].

Another limitation is our decision to exclude prematurely born infants and children with subdural hematomas. Prematurity is a risk factor for developing BEH [1, 8]. Subdural hematoma is a known complication to BEH, even without a head trauma [12, 14, 29]. In retrospect, we believe this deprived us of patients who could have enlightened our knowledge about long-term effects.

Conclusions

Patients with BEH generally seem to do well as they grow up. They report a normal quality of life except for school functioning were some of the children seem to struggle more than their peers do. In addition, various medical, social, and cognitive problems are reported for some of the patients.

Compliance with ethical standards

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

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Paper 5

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REVIEW ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Examining perinatal subdural haematoma as an aetiology of extra-axial hygroma and chronic subdural haematoma

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Abstract

Aim: Benign external hydrocephalus (BEH), hygroma and chronic subdural haematoma are extra-axial fluid collections in infants. MRI studies have shown that almost half of all new-borns have perinatal subdural blood, generally referred to as subdural haematoma (SDH) or perinatal SDH. Epidemiologically there are striking similarities between chronic SDH and BEH in infants.

Methods: Discussion of pathophysiological mechanisms for BEH and chronic SDH, based on existing literature.

Results: Perinatal SDH is common, and we hypothesise that this condition in some infants develop into extra-axial fluid collections, known as hygroma, BEH or chronic subdural haematoma. The mechanism seems to be an intradural bleeding that creates an obstructive layer preventing normal CSF absorption. The site where the bleeding originates from and those areas enveloped in blood from the primary damaged area are prone to later rebleeds, seen as 'acute on chronic' haematomas. With steady production of CSF and the blockage, increased intracranial pressure drives the accelerated skull growth seen in many of these children.

Conclusion: Perinatal SDH hampers CSF absorption, possibly leading to BEH and chronic SDH, with a high risk of false accusations of abuse. Close monitoring of head circumference could prove vital in detecting children with this condition.

KEYWORDS

subdural haematoma, infants, hygroma, child abuse, head circumference, false accusations of abuse

1 | BACKGROUND

Benign external hydrocephalus (BEH) is the term widely used for a neuropaediatric condition with intracranial, extra-axial fluid collections. Most often the condition is defined as a combination of a clinical macrocephaly that is increased or rapidly increasing head circumference, and typical neuroimaging findings of enlarged subarachnoid or subdural spaces, especially over the frontal lobes, prominent interhemispheric fissure, and normal or slightly enlarged lateral ventricles.[1] The distinction between subarachnoid and subdural spaces may be difficult, especially on CT imaging, but often also on MRI.

Given the criterion of a clinically detected large head and/or pathologically accelerated growth, together with the neuroimaging

Abbreviations: BEH, benign external hydrocephalus; SDH, subdural haematoma; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

findings, the only population-based epidemiological study indicates an incidence of extra-axial collections of about 0.4 per 1000 live births.[2] Such extra-axial fluid collections are probably more frequent in infants than that, especially during the first months of life [3]; however, if their head circumference does not reach defined abnormal values, these infants will not fit the strict criteria above and will probably remain undetected in spite of potential evolving pathology. Thus, epidemiological studies with a clinically detected large head as a prerequisite will only reveal the tip of the iceberg. Many children whose head circumference has grown more than two standard deviations of percentile growth may have significant hygroma that is never studied. If the head circumference does not reach values qualifying for macrocephaly, their condition will not even be noted as potentially pathologic. Since the era of advanced neuroimaging began (CT and MRI), several articles about this condition have been published, as reviewed elsewhere.[4] Quite different names have been used in the literature; a collection of the most common terms is found in Table 1.

The word 'benign' reflects the traditional and possibly misleading opinion that the condition is self-limiting and produces only temporary, mild or no symptoms and is without long-lasting problems. Recently published long-term follow-up studies, however, show that some patients have various developmental, social and cognitive problems,[5-7] including psychomotor delay.[8] Additionally, much more severe conditions have been reported in association with such subdural fluid collections, above all, epileptic seizures,[9-18] subdural haematoma (SDH),[8,10,12-14,16,19-28] increased intracranial pressure [29] and in others apparent life-threatening events (ALTE).[30] Seizures and SDH are quite often described in the same patients. In addition, MRI diffusion shows white matter changes in BEH infants,[31] and an association between BEH and later development of autism spectrum disorder has also been suggested.[32] Thus, the term 'benign' appears to be misleading.

TABLE 1 These different names have been used in the literature for the same or similar conditions

Benign/idiopathic external hydrocephalus[1,78]
Benign familial macrocephaly[79]
Benign infantile hydrocephalus[80]
Benign subdural collections[62]
Benign extra-axial fluid/collections[40,81]
Benign extracerebral fluid collections[82]
Benign communicating hydrocephalus[83]
Benign enlargement of the subarachnoid spaces[84]
Subarachnoid fluid collections[85]
Chronic subdural hygromas[86]
Pericerebral fluid collection[87]
Idiopathic macrocephaly[7]
Chronic subdural haematomas[88]
Subdural effusion[89]

Key notes

- A perinatal haemorrhage is very common, especially if birth is complicated.
- We hypothesise that some infants with perinatal subdural haematoma (SDH) will develop benign external hydrocephalus (BEH) or chronic SDH.
- Lack of attention to this development will likely result in false accusations of abusive head trauma.

BEH is already considered to be a risk factor for developing SDH [10,20,23]; the larger the subdural fluid collections, the more likely it is that it will be associated with or even cause an SDH.[33] BEH and SDH have both been considered a form of subdural collection, and as shown in Table 1, the terms have sometimes been used interchangeably. When apparent prior BEH is complicated with acute haemorrhage into the collections, this complex of findings is in radiology reports often referred to as 'acute on chronic SDH'; a term that may more accurately reflect the aetiology of the hygroma as related to chronic SDH.

A subdural collection containing blood elements in an infant is in itself enough to raise suspicion of child abuse, especially if the carers cannot provide what is regarded an acceptable and plausible trauma history.[34] If the subdural blood is caused by a spontaneous leakage of blood, see below, there is no trauma history to tell. Several authors have pointed to the risk of a spontaneously occurring SDH in an infant with BEH being misdiagnosed as abusive head trauma (AHT).[12,16,35] A recent article describes the legal and social consequences of such diagnostic mistakes in detail.[36]

SDH in infants without an acceptable history of trauma is likely to be associated with AHT/NAT (nonaccidental trauma, formerly known as shaken baby syndrome—SBS). However, without a valid scientific basis for assuming such a causal relation,[37] other possible causes and associations are important to explore. The aim of this article is to examine more closely the possible connection between birth-related SDH (perinatal SDH) during infancy and the development of extra-axial fluid collections, not as 'benign' collections, but as chronic SDH, as discussed by Gabaeff,[38] on the basis of several observations.[39,40] In the following, different aspects of this will be presented.

2 | SDH AT BIRTH—PERINATAL SDH

SDH following difficult births have been recognised for a long time.[41-43] For the last decade, it has been known that subdural blood is common in about half of 'normal' vaginally delivered or unscheduled caesarean sections, preceded by labour, in new-borns.[39]

The first hint of birth-related SDH or perinatal SDH came from Looney et al in 2007 using early MRI technology.[44] A follow-up MRI study in 2008 by Rooks et al,[39] using more up to date MRI

technology, unpredictably, astonishingly and reliably showed that 46% of 101 asymptomatic term neonates had a perinatal SDH after 'normal' deliveries. In 18% of the 101 infants, a follow-up MRI was performed at 3 months of age. All but one showed resolution of the haematomas. One of these infants had a large rebleed after 26 days in a nonabuse context, with another MRI at 5 months showing resolution of the SDH, however, with a remaining prominent subarachnoid space.[39] While this case cannot predict the frequency of perinatal SDH leading to chronic SDH, it does refute what we believe is the false assumption: that all birth-related bleeding (at least 1 million in 4 million births annually in the United States) resolves without complications.

Abnormal or complicated labour increases the risk of intracranial haemorrhage,[45,46] with SDH being the most common type of bleeding.[47,48] Many new-borns with subdural haemorrhages are asymptomatic [49] or insufficiently symptomatic to arouse medical attention.

Supporting data in another study showed 53 cases of nontraumatic death in children with mean age 9 weeks, 70% had blood or hemosiderin in orbit tissues and subdural compartments; according to the authors, it was '…likely a consequence of the birth process'.[50] Vinchon et al reported 16 infants with spontaneous SDH, 9 of them had a history of complicated labour and 12 children had macrocrania.[35] In still another report, intradural haemorrhage and SDH were found in nontraumatic cases of child death, most commonly in infants under 1 month of corrected age.[51] In a large, population-based study of infants with SDH, perinatal SDH (diagnosed the first week of life) was associated with obstructed labour, emergency caesarean section, assisted vaginal delivery, asphyxia, and preterm birth, amongst others.[52]

Even if perinatal SDH seems to resolve in some cases, the restoring rate and grade is unknown. Evidently, in many infants a haematoma will persist for weeks and months, and some, if large enough, may become permanent retracted clots infused with scar tissue and fragile with respect to rebleeding. We believe that extra-axial blood in these subdural collections and the dural capillary bed can obstruct CSF reabsorption, thereby maintaining the subdural collections. Once obstructed, the fluid exerts a pressure on the skull, resulting in an increasing head circumference. Both the origin of the intradural bleeding and, in extreme cases, the stretching of bridging veins beyond their tensile capacities, caused by the chronic SDH, can result in rebleeds into this persistent subdural collection (see below).

3 | EPIDEMIOLOGY OF SDH AND BEH

In a population-based study, the incidence of BEH was around 0.4 per 1000 live births, with a male preponderance of 86.4%.[2] Median age at symptom debut (usually increasing head circumference) was 3.4 months.[53]

Another study had similar findings with an incidence of SDH during infancy of around 0.17 per 1000 live births, and a male preponderance of 64.7%.[52] Median age in this Swedish register study was 3.5 months for infants older than 1 week.

Yet another study found a similar annual incidence of 0.24 for SDH.[54] The gender distribution for this whole study group (0-2-year-olds) was 65% boys, and the average age at diagnosis was 17 weeks (approx. 4 months). Zaben et al performed a review of infants diagnosed with SDH following forceps-assisted delivery in that study; where gender was specified, 11 out of 14 patients were boys.[46]

It is clear that there is a discrepancy in incidences of SDH and BEH, compared with for example Rooks et al.[39] We believe it may be explained by Rooks et al describing only asymptomatic subdural blood in new-borns, whereas the other studies look at only symptomatic infants that come to medical attention because they have developed a clinical condition.

According to these population-based studies of BEH and SDH, there are striking similarities between these two conditions, both in age and gender distribution. The male preponderance was evident even in the earliest publications on SDH, as was the age distribution with a peak incidence during the first 6 months of life.[43,55] The similar gender distribution of BEH and SDH with a marked male preponderance has been noted before.[36,56] In general, boys, presumably with larger heads than girls, have a higher risk of neonatal morbidity and mortality.[57] A large foetal head circumference in itself is associated with complicated labour.[58] Historically, a thorough article by Ingraham and Matson from 1944 also contains other interesting observations, for example that SDH should be suspected in infants with an earlier 'triad', totally different from the content of the present version of the term: failure to thrive, increasing head circumference and a history of difficult labour.[43]

4 | NEUROIMAGING AND FLUID CHARACTERISTICS

As shown in Table 1, the terms BEH and SDH are sometimes used interchangeably, also in recent publications.[59] Some articles include fluid analyses from these subdural collections, reporting both CSF-like fluid and 'mixed density' fluid with variable protein concentration (Table 2).

With mixed density fluid, the neuroimaging appearance is often described as BEH initially. However, with similar findings in the context of acute blood, the space is then referred to as chronic SDH. In these cases, the term 'acute on chronic' appears to replace BEH and is common in radiology reports.

Furthermore, the presence of hygroma, mixed density fluid and inflammatory membranes (neomembranes) is diagnostic criteria for chronic SDH. The layering of blood and the appearance of blood on CT and during drainage can be used to estimate the frequency of rebleeding and the age of blood. This remains an ongoing issue, with researchers still trying to find a common terminology, as these age estimates remain important due to the legal aspects of suspected AHT.[60]

TABLE 2 Published subdural fluid analyses. The list is not necessarily exhaustive

Authors	No of patients	Fluid appearance/characteristics
Kasinathan et al[59]	1	Haemorrhagic fluid with elevated proteins (2.6 g/dL) and predominant lymphocytic pleocytosis (200 cells/dL)
Briner & Bodensteiner[90]	2	Patient 1: Dark yellow fluid with a protein content of 2 g/dL. RBC count 7000/cu mm. Patient 2: Straw-coloured fluid, with protein content 0.4 g/dL. RBC count 700/cu mm
Chazal et al[29]	2	Patient 1: Protein concentration 1.2 g/dL. Markedly decreased prealbumin level (0.9%). Patient 2: Protein 1.0 g/dL
Alvarez et al[1]	1	Normal CSF values
Kumar[91]	4	Resembled CSF on biochemical and cytological examination except for cell counts. The cell counts on tap ranged from 2 to 15 per mm^3
Nogueira & Zaglul[92]	4	1 negative. Normal CSF in small amount in 2 patients. Xanthochromic fluid in small amount in 1
Neveling & Truex[93]	4	Results were 'negative', probably considered similar to CSF
Roshan et al [94]	4	CSF was normal (whether this was spinal CSF or from the enlarged SAS is unknown)
Wilms et al[95]	6	Mean protein content was 1.4 ± 0.8 g/dL
Barlow[61]	1	'Subdural tap through the fontanelle was dry'
Ment et al [84]	3	'No subdural fluid was demonstrated in any of the three patients in whom the subdural space was examined'
Palmer & Albert[96]	6	1 patient with 'motor oil' appearance 5 patients with xanthochromic and/or CSF-like fluid
Zouros et al[97]	5	'Haemorrhagic fluid' was found in all patients
Aoki et al[98]	3	Protein concentrations of 984 mg/dL; 2800 mg/dL; and 2610 mg/dL

5 | PATHOPHYSIOLOGY

The pathophysiology behind BEH might roughly be summarised in the following assorted hypotheses.

The most common hypothesis is that the accumulation of fluid is caused by immature arachnoid granulations during the first months of life not being able to absorb CSF.[61] Why the arachnoid granulations mature so late remains unknown, but this seems to be a normal biological event.

Another hypothesis, presented by Robertson and colleagues in 1979, is that subdural fluid somehow obstructs CSF reabsorption.[62] They suggested that the subdural fluid, although primarily CSF, often with particulate matter seen in the fluid, acts like a mechanical block, preventing CSF from reaching the arachnoid granulations. This condition subsequently dilates the adjacent subarachnoid channels, which would be seen on CT as wide cerebral sulci and prominent interhemispheric fissures.

Prior to the maturation of the arachnoid granulations, the intradural capillary bed appears to carry the load of reabsorbing CSF.[63-65] Channels pass through the dural border layer and conduct CSF to venules they are in contact with in the capillary bed. As arachnoid granulations mature late, the dura appears to be more important in CSF absorption during this period, as discussed by Oi et al.[66]

A common hypothesis on the association between BEH and SDH is that bridging veins traversing the subdural/subarachnoid space/hygroma are stretched with enlarged extra-axial collections, increasing the risk of venous rupture, either spontaneously or following minor trauma.[27] Images of actual bridging veins in autopsy photos, however, call this into question (Figure 1). The phenomenon of blood oozing from the veins' entry points is commonly observed during any craniotomy (eg by the second author); just manipulating the bridging veins at their dural entry points with a blunt instrument is enough to cause oozing of blood without the vein being torn. This blood could be leaking from the adjacent dural capillary bed.

With perinatal SDH, blood envelopes the structures within the dural capillary bed, obstructing its absorption capability. The reabsorption, which is constant and must occur to complete the CSF 'circulation', then has to operate at higher pressure. This increased pressure causes the skull bones to be pushed out and the hygroma forms as the virtually noncompressible brain continues to grow at a normal, steady rate. When the arachnoid granulations mature at 8-12 months of age, the dural capillary bed no longer performs this function, ICP decreases and accelerated head circumference growth stops. Thereafter, brain growth drives skull growth.[67]

Recent research further indicates that SDH can be initiated by a minor intradural bleeding, possibly originating from venous plexuses in the capillary bed. This creates a thin film of blood in the subdural space,[68] which, if sufficient, then overflows internally through the dural border cell layer and separates the arachnoid from the dura forming SDH between them.

Neomembranes are often seen on imaging and autopsies as a result of an inflammatory response from leaked blood.[68] These neomembranes are loose collections of scar tissue and capillaries that encase the prior haematoma. The SDH complications are then more susceptible to rebleeding either episodically or in small amounts, as Ito et al showed.[69] Clinically, we have noticed anaemia to be present, months after birth, during abuse workups and this raises suspicion about daily rebleeds of 1-2 mL/d. This may support

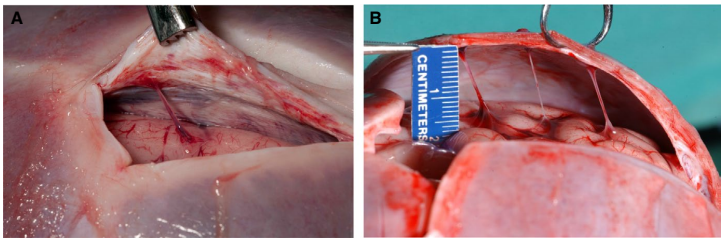

FIGURE 1 Two autopsy photos showing bridging veins. In A there is some visible blood at the dural entrance. In B one may observe three bridging veins stretched extensively

perinatal SDH as the primary bleeding event, especially without a prior history or evidence of major postnatal trauma.

A unifying pathophysiologic theory may in our opinion be a birth-related bleeding that disrupts the CSF absorption in the dural capillary bed by hampering absorption of the continuously produced CSF, and that together with blood products and inflammatory debris in the hygroma, creates a subdural collection, prone to cause rebleeding. There are growth factors in old haematomas that have been shown to induce neovascularisation in the parietal haematoma membrane; these pathological vessels bleed easily,[70-73] and there are other factors that disturb normal coagulation or cause fibrinolysis in subdural haematomas.[69,74-76]

This dysfunction exists as long as the subdural capillary bed is the main absorbing route. As the arachnoid granulations gradually mature during the latter half of the first year, subdural collections and hence the head circumference gradually normalise. There is reason to believe that infants prone to a particularly difficult labour and/or instrumentation are susceptible to larger perinatal SDHs, and probably also a more complicated perinatal period. In a study of macrocephalic neonatal care survivors, hygroma evolved in about 40%, and presence of extra-axial fluid was associated with an increased risk of developmental delay.[40]

6 | SUMMARY

Perinatal SDH is a common condition in new-borns, creating a temporary dysfunction in CSF absorption in the dural capillary bed during infancy. The five main consequences of this are as follows: (a) an obstructing layer of fluid/blood creating a subdural collection; (b) neovascularisation and rebleeds from the original bleeding site intradurally and subdurally in the previously damaged area; (c) in extreme cases with wide hygromas, stretching of bridging veins that may bleed spontaneously or after minor trauma; (d) a subtle increase in ICP resulting in increased HC and temporary developmental delay; (e) a variety of apparent life-threatening events that precipitate medical intervention.

This theory on the formation of subdural collections, combined with the similar demographics of BEH/hygroma and SDH, leads us to theorise that these conditions in fact are the same. Perinatal SDH creates a subdural collection with or without visible blood (hence the terms BEH, hygroma, chronic SDH, or with acute blood, 'acute on chronic', etc). A complicated labour clearly increases the risk of this development. Rebleeds from damaged areas that are neovascularised or new bleeds from bridging veins insertion points create acute SDHs, often seen as acute blood or mixed density collections within the hygroma.

Firstly, we propose that BEH is a form of chronic SDH. Secondly, the cascade of events following the perinatal SDH can lead to both chronic and recurrent acute SDH (often both). In infants, the finding of acute SDH leads to suspicion and accusation of child abuse. The implications of our theory may have huge legal consequences. We fear that many cases of infant SDH, with any amount of acute blood, in the context of extra-axial dural collections or not, have been misdiagnosed as abuse.

A possible first step in avoiding this could be to follow otherwise healthy children with rapidly/exceedingly increasing head circumference closely. Both incremental increases in head circumference that surpass two standard deviations after birth, and/or an absolute head circumference above the 95th percentile should be used to identify this form of neuropathology.[77] Especially, infants with a history of birth problems including meconium staining, latching problems, positional discomfort, instrumented deliveries, prematurity, multiple births or a significant decrease in head circumference in the week after birth followed by accelerated growth should be imaged and monitored closely by a paediatric neurologist. Clinically, vomiting, transient change in feeding or sleeping patterns, intermittent fussiness and changes in behaviour are neurologic symptoms in infants that are often misdiagnosed as gastrointestinal problems. The identification of potentially problematic, and progressive, perinatal SDH involves a high index of suspicion, facilitating early neurosurgical intervention when necessary.

Most importantly, an increased awareness about the magnitude of babies with perinatal SDH and the high risk of false accusations of abuse is the essential first step.

CONFLICT OF INTEREST

SMZ declares no conflict of interest. KW has served as expert witness in AHT/SBS cases. SG has provided consultation in cases involving accusations of child abuse, including AHT/SBS cases and testimony, if appropriate, in other cases with medical issues relating to arguable accusations of abuse.

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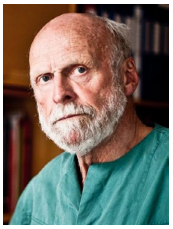

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Paper 6

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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

Thrombosis is not a marker of bridging vein rupture in infants with alleged abusive head trauma

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Abstract

Aim: Thrombosis of bridging veins has been suggested to be a marker of bridging vein rupture, and thus AHT, in infants with subdural haematoma.

Methods: This is a non-systematic review based on Pubmed search, secondary reference tracking and authors' own article collections.

Results: Radiological studies asserting that imaging signs of cortical vein thrombosis were indicative of traumatic bridging vein rupture were unreliable as they lacked pathological verification of either thrombosis or rupture, and paid little regard to medical conditions other than trauma. Autopsy attempts at confirmation of ruptured bridging veins as the origin of SDH were fraught with difficulty. Moreover, microscopic anatomy demonstrated alternative non-traumatic sources of a clot in or around bridging veins. Objective pathological observations did not support the hypothesis that a radiological finding of bridging vein thrombosis was the result of traumatic rupture by AHT. No biomechanical models have produced reliable and reproducible data to demonstrate that shaking alone can be a cause of bridging vein rupture.

Conclusion: There is no conclusive evidence supporting the hypothesis that diagnostic imaging showing thrombosed bridging veins in infants correlates with bridging vein rupture. Hence, there is no literature support for the use of thrombosis as a marker for AHT.

KEYWORDS
abusive head trauma, bridging veins, cerebral venous thrombosis, child abuse, subdural haematoma

1 | INTRODUCTION

Diagnosis of bridging vein thrombosis in infants has become more common in recent years. Controversy has arisen as to whether the diagnosis of thrombosis can be used as a marker for traumatic bridging vein rupture. Specifically, the radiological diagnosis of thrombosis has been suggested as a marker of abusive head trauma (AHT), the so-called lollipop or tadpole signs on magnetic resonance imaging

Abbreviations: AHT, abusive head trauma; BEH, benign external hydrocephalus; CT, computed tomography; ICP, intracranial pressure; ICU, intensive care unit; MRI, magnetic resonance imaging; SDH, subdural haematoma; SSS, superior sagittal sinus; SWI, susceptibility-weighted imaging.

(MRI) or computed tomography (CT).[1–3] Bridging veins are part of the superficial cerebral venous system, draining blood from the cerebral cortex into the large intradural venous sinuses. The cortical veins traverse the subarachnoid and dural compartments and act as the 'bridge' between the intracranial venous circulation and the systemic circulation of the dura.[4] When haemorrhage into the subdural compartment is found, damage to the bridging veins is often assumed to be the cause, and therefore, inspection of the veins on imaging has played an increasingly important role in the diagnosis of suspected AHT.

In this review paper, we will briefly study the embryology, anatomy and clinical significance of bridging veins, then critically appraise the existing literature on pathology, radiology and biomechanics regarding thrombosis as a marker of ruptured bridging veins.

Key Notes

- This is a non-systematic review of the literature regarding the hypothesis that thrombosis of bridging veins is a marker of abusive head trauma.
- The hypothesis lacks pathological verification, has not been verified biomechanically and does not consider other aetiologies of bridging vein thrombosis.
- There is no evidence for the claim that radiologically detected thrombosis is a marker for bridging vein rupture, and hence, abusive head trauma.

2 | METHODS

This was a non-systematic review of literature regarding the various aspects of bridging veins, especially concerning AHT. The review was based on non-structured search in PubMed, secondary reference tracking and the authors' own article collections. No publication date limit was chosen, but search ended on 20 November 2020. Articles in English, German and French were considered. Important search terms were as follows: abusive head trauma; shaken baby syndrome; cortical vein thrombosis; bridging veins; and/or subdural hematoma, among others.

3 | RESULTS

3.1 | Bridging veins

3.1.1 | Embryology

The early connective tissue which later forms the meninges contains a vascular meshwork that evolves into a more distinct vasculature as the brain and skull grow. Initially, the plexus of embryonic vessels divides into deep and superficial layers; the superficial layer becomes the dural vessels while the deeper layers invest the brain to become the leptomeningeal vessels. This primitive network of vessels separates into a distinct venous drainage pattern through the gradual process of venous cleavage. During this process, the number of brain-to-dural venous connections is reduced: many of the veins connecting these early layers are resorbed while a few grow in length and width to become the bridging veins which are more or less fully developed by the end of the first trimester.[5]

While the bridging veins are formed early, the venous structures of the dura undergo modifications throughout gestation and early life. These adjustments in the intradural network are necessary to accommodate the rapid cerebral growth during this period. The configuration of the intradural blood vessels and dural venous sinuses continues to evolve throughout the first year of life, and the major dural sinuses do not attain their adult configuration until well after birth.[6,7]

3.1.2 | Anatomy

As reviewed by Mortazavi et al.[8] the bridging veins are typically found in three anatomical regions: cerebellar, temporal and anterior frontal cortical bridging veins. From a surgical point of view, the bridging veins pose a risk for venous infarction if disrupted or damaged. As personally experienced by the senior author [KW] during craniotomy, any manipulation of the bridging veins easily causes oozing of blood from the dura, at the entry points of the veins.[9,10] As the bridging veins appear unharmed, this bleeding likely comes from the dural capillary bed.

In a post-mortem radiological study, Ehrlich et al.[11] found an average of 17 bridging veins (range 9–31) on the brain, reportedly either few of wide diameter or many smaller ones. Cases were all ages ranging from two months to 96 years, with a mean age of around 50 years old. However, a thorough autopsy study of infants found a mean of 54.1 bridging veins per case.[12] Why the reported numbers vary so much remains unknown, but method of investigation (dissection), age and cohort sizes could play a role.[12] In infants, the mean bridging vein diameter in a series was 0.93 mm (range 0.05–3.07 mm).[12]

The wall of the bridging vein consists of collagen bundles arranged circumferentially, elastin fibres and smooth muscle cells.[13,14] The bridging veins enter the superior sagittal sinus (SSS) in various ways; some, typically found posteriorly, enter at retrograde angles,[15] meaning the blood flows in an anterior direction before entering the SSS. Han et al.[16] found that most bridging veins (97%) entered the SSS in this direction, so one would expect that forces in the postero-anterior direction would be particularly likely to cause stretching tension on these bridging veins. Vignes et al.[17] found that the lumen of the bridging veins narrowed at the junction with SSS, with abundant smooth muscle cells in the vein wall, resembling a sphincter. Physiological narrowing of this sphincter when intracranial pressure (ICP) is increased has been demonstrated in human and animal studies.[18,19]

The dural portions of the bridging veins are thought to be particularly fragile compared with the subarachnoid portion, giving rise to the belief that a bridging vein would rupture preferentially into the dural compartment rather than into the subarachnoid space.[2] Though Yamashima and Friede describe very variable wall thickness in the subdural part of the bridging veins (10–600 μm, vs. 50–200 μm in the subarachnoid part), their data are drawn from frontal bridging veins from only four adult patients aged 53–85 years. Moreover, the authors did not directly address the precise dural anatomy; there is no true subdural space in which to measure the wall thickness of bridging veins; rather the subdural compartment is a dissection phenomenon created after disruption of the 8-micron thick tissue layer (dural border cell layer) between the fibrous dura and the arachnoid barrier membrane.

3.2 | Ruptured bridging veins

Ruptured bridging veins are often assumed to be the cause of SDH in infants.[14,20] In AHT, the presumed tear is believed to be caused by blunt trauma to the head, shaking or a combination of the two.[20,21] Indeed, presumed rupture of bridging veins has become an important criterion of AHT.[2,22,23] Rupture of bridging veins can be investigated from different perspectives by neuroimaging, by autopsy and by biomechanical studies:

3.2.1 | Neuroimaging

A case report of two infants with suspected AHT-related SDH reported the use of susceptibility-weighted imaging (SWI) in MRI.[24] Signal loss was found on SWI, thought to represent clot formation on bridging veins. No signs of venous infarction were found. Whether these findings were verified, by surgery or autopsy, was not reported.

Choudhary et al.[25] used MR venography to study 45 children with assumed AHT based on a retrospective chart review. In 31 (69%) of the children, they found a mass effect on venous sinuses and cortical veins from the nearby hematoma or swollen brain. They also coined the term 'lollipop sign', to describe an imaging finding which they thought was due to a disrupted vein with an associated blood clot. The lollipop sign was found in 20 (44%) of the children in their study. Based on the pre-existing assumption of abuse, the authors concluded that the finding of susceptibility artefact associated with the veins on MRI in the setting of a subdural fluid collection could be viewed as 'evidence of direct trauma to the veins'. They found it unlikely that the venous susceptibility could have been a thrombosis unrelated to trauma. Known causes of cerebral venous thrombosis in children are many, including infections, perinatal complications, haematological disorders and dehydration.[26,27] Trauma is reported as a rare etiological factor.[28]

Hahnemann et al.[1] investigated 29 cases of SDH or subdural hygroma in infants with assumed AHT, using CT and MRI. In 11 cases (40%), they found radiological signs of bridging vein thromboses. In eight of these patients, neuroimaging showed a structure thought to represent a thrombus partly outside of and partly inside a torn bridging vein. It had an oval to round body and a bent tail; hence, the 'tadpole sign' was described.

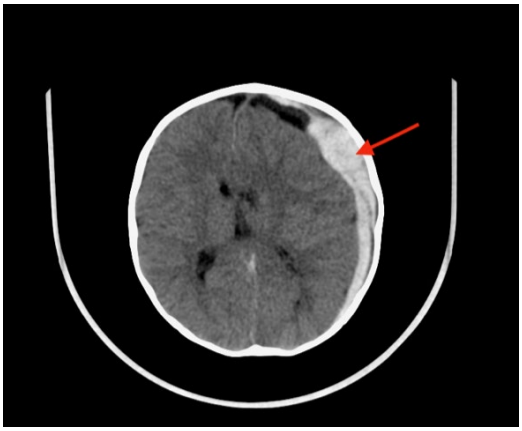

FIGURE 1 Left-sided subdural haematoma (arrow) in a 7-month-old child as seen on computed tomography. Surgery confirmed rupture of an ipsilateral frontal bridging vein

A more recent MRI study reported a remarkable mismatch between primary MRI diagnoses of bridging vein thrombosis, the tadpole sign, on the axial images compared with coronal high-resolution SWI.[29] The authors concluded that the tadpole sign on axial images did not reliably predict thrombosed veins. Instead, they proposed that the signal alteration indicated a traumatic deformation of the vessel, basing their conclusion on 'vessel wall irregularities' detected on the coronal SWI. The limitations of their study included small sample size, lack of pathologic correlation, possible artefacts induced by volume averaging effects and the fact that altered SWI signal cannot differentiate between slow flow and thrombosis.

Adamsbaum and Rambaud reported several cases of allegedly confessed AHT with subdural haematomas and thrombosed bridging veins visible on both CT and MRI.[2] The authors state that thrombosed bridging veins as seen on neuroimaging are evidence of ruptured bridging veins, which in turn must be caused by a head trauma, in itself suggestive of AHT. The images in that article showed hypodense fluid collections within the subdural compartment. Whether or not the confessions of abuse were consistent with the presence of chronic SDH or correlated with the ages of the SDH on scan was not reported. None of the images in their paper show large volume acute SDH, hyperdense on CT, and the authors did not attempt to explain why no significant acute bleeding was present despite the assumption that recent trauma had caused an acute rupture of multiple macroscopic bridging veins. Our Figure 1 shows what an SDH following acute bridging vein rupture can look like, as confirmed by surgery.

Similar doubts arise regarding an article from Ronning et al.[3] They reported 99 infants with SDH, most of them with assumed AHT, fewer with accidental head trauma. The authors found that most children with AHT had parasagittal vertex clots on CT, thought to represent thrombosis, whereas very few of the children with accidental trauma had this CT sign. The images presented in the article, however, do not show SDHs, but rather subdural fluid/hygroma. Furthermore, no pathological investigation or explanation is presented, and evidence on which the diagnosis of abuse rests is not given.

A survey on diffusion-weighted MRI found four patients with venous infarction in relation to assumed ruptured bridging veins in 33 children with alleged AHT.[30] The authors did not consider the possibility that the thrombosis and venous infarction may have been unrelated to trauma.

Orman et al.[31] published MRI findings of an infant (Figure 7 in their article) with typical neuroimaging findings compatible with benign external hydrocephalus (BEH). These figures purportedly show 'hypointense bridging vein thromboses' without discussion of the chronicity of the findings or whether a predisposing condition increased the risk of damage to the vein resulting in thrombosis without significant trauma.

To summarise, several neuroimaging studies report signs of apparent thrombosis which are presumed to reflect traumatic damage to the bridging veins. Three problems, however, emerge from these studies: first, as the findings are based solely on radiological investigations, the physiological/pathological correlates remain obscure. Even if imaging does show thrombosis, bridging vein rupture is not proven, and the studies do not discuss how a ruptured vein would result in a large subdural fluid collection (rather than a large collection of acute blood). Second, the fundamental assumption in AHT cases, that the presence of SDH in children reliably indicates that they were shaken or beaten, is controversial. As reviewed by Lynøe et al.[32] the scientific evidence behind the shaken baby syndrome/AHT theory is very limited. Third, statements such as thrombosis is 'evidence of direct trauma' create an impression of certainty implying high-quality evidence behind these findings. None of the studies describe how they have excluded other conditions or diseases, which are more common than trauma as aetiology of bridging vein thrombosis (Figure 2).

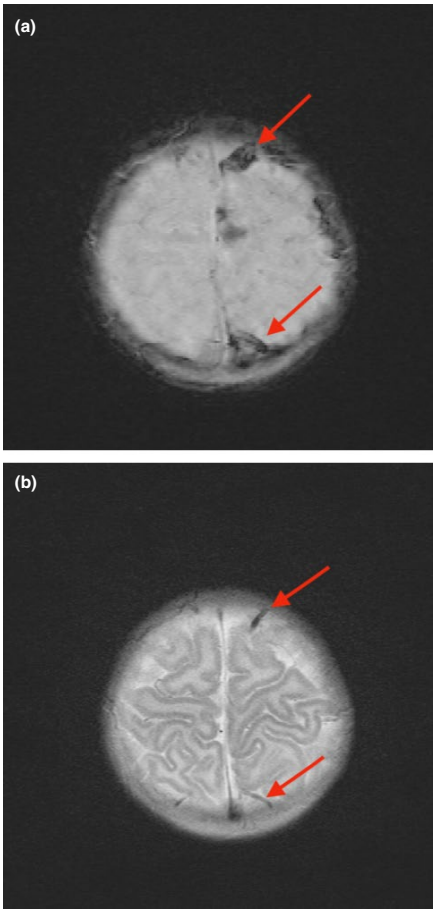

FIGURE 2 (A and B)Magnetic resonance imaging (MRI) of a 26-day-old infant with small volume subdural haematoma and fluid. Seizures developed in the hospital and MRI showed clotted cortical veins (arrows) and evolving non-haemorrhagic infarction. Abuse was initially suggested, but after full evaluation, the charges were dismissed and the child returned to the parents

3.2.2 | Pathology

Several surveys have investigated deaths of infants with SDH. Identification of the source of subdural bleeding at autopsy is commonly recognised as technically difficult, as the bridging veins are easily damaged during the procedure of opening the skull and dura.[12,33]

Cheshire et al.[12] reported 48 autopsies of small children (<2 years of age) where the bridging veins were studied. Of these children, three were classified as AHT cases where the bridging veins seemed engorged with congested blood, and when they were pressed from the outside, they did not blanch. The significance of this observation is not discussed. These veins were not examined microscopically, hence, thrombosis could not be confirmed, nor were the dural sinuses examined to explain the cause of congestion. The authors also found fewer bridging veins in autopsies of children with assumed AHT than in children with no known head trauma. Whether this was due to elastic recoil of small calibre broken veins or veins being obscured from view by the presence of SDH could not be determined.

When comparing microscopic appearances of dura from 50 infants without head trauma with three infants with suspected AHT, Geddes et al.[34] found intradural haemorrhage in 72% of the non-trauma cases. They hypothesised, based on the findings of both intradural and subdural haemorrhage in the suspected AHT cases, that

this could be caused by a cascade reaction of hypoxia, plus brain oedema, increased intracranial and central venous pressure, finally leading to bleeding from intradural and bridging veins because of immaturity and hypoxia-related vascular fragility. Although intriguing, this theory primarily shows that several experts in the field have realised that the origin of bleeding into the subdural compartment is uncertain. Indeed, the publication of this hypothesis ignited a rather intense debate, demonstrating the profound disagreement.[35–37] The striking finding of intradural haemorrhage in 72% of infants without head trauma is important to keep in mind.[34] Subsequent studies have confirmed that intradural bleeding is a common finding in very young infants who undergo autopsy and is associated with hypoxic-ischaemic insult.[38]

When a cerebral vein is thrombosed from any cause, it is distended by a clot and the vessel upstream/proximal of the clot becomes dilated, tortuous and varicose. The cellular reactive changes in the vein wall include proliferation of endothelial lining cells which grow into the clot within the lumen and begin to form new vessels as part of the process of recanalisation. Also, in the early stages, the vein wall becomes leaky, and it is possible to identify red blood cells passing between the cells of the vein wall (diapedesis) leading to haemorrhage into the surrounding tissues, which in the case of cortical veins leads to subarachnoid bleeding (Figure 3). Diapedesis from thrombosed dural veins can lead to intradural bleeding. This small volume haemorrhage may explain the radiological observation of tadpoles and lollipops and does not depend on traumatic tearing of the vein wall, but is the result of venous congestion.

In her review of bridging veins in AHT, Rambaud described histological investigation of ruptured bridging veins.[39] She found surrounding inflammation, siderophages indicating bleeding, partial or total thrombosis, and neovascularisation. According to her, dating of the trauma should be possible by examining the thromboses, although she did not explain how this timing could be done. Again, a statement such as 'bilateral bridging vein rupture confirms violent shaking' is unsupported by evidence. No clear aetiology for trauma is presented in the cases described in the article, and she did not consider natural causes of venous thrombosis.

Radiological autopsy

Some authors have reported results of post-mortem radiological investigation of bridging veins.[11,23,40] Maxeiner[23] used a method where he injected contrast into the SSS in an attempt to produce retrograde filling of the cerebral bridging veins. If contrast appeared on X-ray outside bridging veins, an assumption of premortem traumatic tearing of the veins was made. In his study of infant bridging vein rupture, he found 'typically no significant subdural bleeding despite multiple bridging vein ruptures in the majority of these cases'.[41]

Stein et al.[40] described a technique using direct injection into the SSS through the posterior fontanel in infants who died non-traumatic deaths. Using this method, the authors successfully injected contrast into the sagittal sinus in 8 of 11 infants and determined that it may provide useful information regarding potential bridging vein ruptures. Neither Maxeiner nor Stein et al controlled for injection pressures, addressed post-mortem autolysis as a

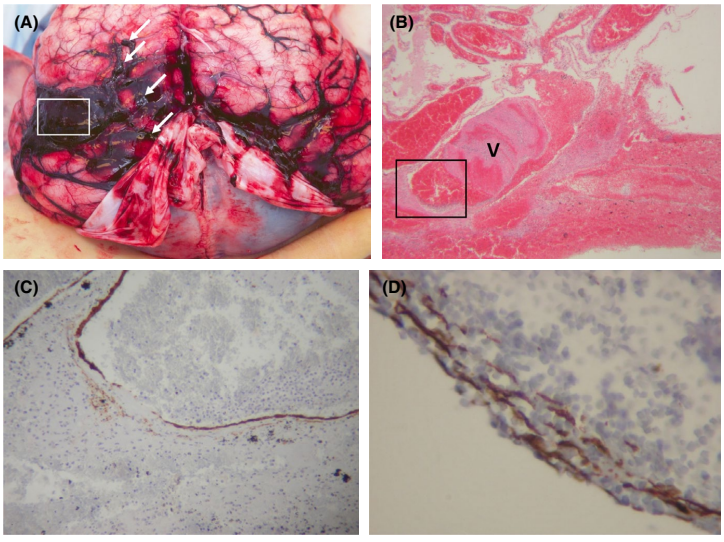

FIGURE 3 (A) Macroscopic view of a large mass of varicose/dilated veins with surrounding subarachnoid blood and local bridging vein thrombosis (white arrows). A section from the area marked with a white box is shown in 3B). (B)Thrombosed vein (V) in the subarachnoid space with surrounding subarachnoid haemorrhage (haematoxylin and eosin stain). (C)Same vein as in B). A defect in the vein wall is seen in the lower left (smooth muscle actin stain, counterstained with haematoxylin and eosin). (D)Higher magnification of vein wall stained with smooth muscle actin (muscle cells are brown, red blood cells are blue). Red blood cells are seen passing between the muscle cells of the vein wall (diapedesis) (smooth muscle actin stain, counterstained with haematoxylin and eosin)

potential contributor to bridging vein disruption after injection or accounted for the presence of the intradural plexus, which would fill with retrograde injection of the sinus. Filling of the plexus would give the impression of contrast outside the sinus and bridging veins which could consequently be mistaken for rupture of the veins.

Neither method has been widely adopted.

3.2.3 | Biomechanics

Through the years, several researchers have tried to investigate the physical properties of bridging veins and their role in SDH formation. Animal studies, finite element studies and cadaveric studies have all been published.

Ommaya et al found that bridging veins ruptured in rhesus monkeys subjected to angular acceleration (shaking), but later stated that these forces were too strong to be achieved by manual shake.[42,43] In a classical study, Duhaime et al.[44] used infant-like dolls with attached accelerometers and subjected them to various shaking and impact episodes. Based on tolerance limits from primates, they found that shaking alone would not create enough force to cause SDH, suggesting that blunt impact to the head was necessary to generate such damage. Their technique was later refined in a study with similar results,[45] but was critically reviewed and questioned by others.[46] As stated by Jones et al in 2015, 'no study has to date demonstrated that shaking alone, without an associated impact, exceeds the injury thresholds associated with SDH'.[47] A recent physics calculation found that a low-level fall yielded greater angular acceleration to a 6-month-old infant than shaking.[48] Similarly, one article, using a doll model, found that the head movements during normal play in an infant were similar to previously published studies on violent shaking in a model, and that shaking movements could not reach angular accelerations regarded as necessary for SDH.[49]

Roth et al.[50] created a finite element head model and found that the bridging veins underwent equal maximum strain for shaking and impact, concluding that both inflictions could cause SDH. However, this study has several limitations: it is not a validated model, the parameters are not from infants, bridging veins are modelled as linear springs which lack viscoelastic properties and the modelled impact can be compared with a short fall of half a metre.

In several studies, human cadaver heads have been subjected to occipital impacts creating various rotational strains.[51–53] Based on post-test findings, the authors suggested threshold levels of rotational accelerations and velocities causing bridging vein rupture. Similar studies have also been performed in adult rhesus monkeys,[54] although the reliability of extrapolating such findings to human infants has been challenged.[55] The main finding in these studies is that quite substantial acceleration forces are required to damage the bridging veins, forces that are reliably created by an impact, but not by shaking alone.

Recent reviews have concluded that thresholds, based on experiments or models, used to assess shaking trauma are of low quality and questionable use.[56,57]

Zhu et al.[58] conducted a combined autopsy and modelling study of 137 bridging veins from six adults. Based on bridging vein diameters and angles relative to the SSS, they calculated that venous thrombosis would occur more easily in wider bridging veins >1.2 mm, and when angles at the entry points were small (<65°).

One model found that the junction between the bridging veins and the SSS is stiffer than the bridging veins themselves, making this part particularly fragile and prone to rupture.[59] This is questionable, considering the previously mentioned finding of a reinforced, sphincter-like junction.[17] Monea et al.[60] did mechanical testing (stress-strain) of this junction and found quite variable results, both between individuals and within the same individual.

Although biomechanical models may seem useful, the multitude of models and the variable results make it difficult to form any definitive conclusions on the role and behaviour of bridging veins in SDH formation in general, and in trauma cases specifically. Results from cadaver studies are problematic due to the use of non-vital tissue already undergoing autolysis and simplistic experiment setups. Finite element studies can provide results from various traumas, but depend on very accurate values of for instance anatomy, geometry and tissue characteristics.[61] Even the intriguing use of cadavers to confirm the biomechanical predictions from a finite element model[62] carries the risk of creating a model based on properties not found in real-life vital tissues. Biomechanical properties of different tissues are largely unknown, and the reported values differ. However, biomechanical studies are still useful as they allow us to compare different situations and traumas, for instance shaking versus a short fall.

3.2.4 | Neurosurgical considerations

Some surgical approaches to the brain involve sacrificing bridging veins. A study of 63 paediatric patients showed no signs of venous infarction on MRI following interhemispheric transcallosal surgical procedures that involved ligature of bridging veins.[63] A recent study, however, found changes in ICP, motor and sensory function, and histological changes, for instance haemorrhage, in mice following venous infarction induced by cutting bridging veins.[64] The changes peaked at around 12 h after surgery and seemed to resolve within 48 h.

In another animal study, an artificial increase in ICP led to dilatation and decreased blood flow velocity in cerebral bridging veins, suggesting a compensatory increase in resistance to outflow.[18]

4 | DISCUSSION

The tearing of bridging veins is considered an important criterion for the diagnosis of AHT. Furthermore, thrombosis of bridging veins has

been suggested as a surrogate for traumatic rupture and a certain diagnostic sign of shaking.[1,2,22]

When reviewing the existing literature in this field, there are some overarching issues that need to be addressed.

First, many studies, both biomechanical and from autopsy, are based on adult patients, not young infants. Considering the rapidly developing cerebral venous system in foetuses and neonates, the direct comparison between adult and infant bridging veins should be done with caution.

Second, studies on infants with SDH and alleged AHT are most often based on assumed or suspected head trauma, not witnessed or proven. The true mechanism behind each case is therefore obscure, and reliance on the presumption of abuse gives rise to circularity and an inherent unreliability in the subsequent conclusions drawn from that data.

Third, there is a growing understanding of the birth process as an important contributor to intracranial haemorrhages in newborns. A difficult birth is a known risk factor for developing SDH,[65,66] but even in normal deliveries and with asymptomatic term neonates, an MRI study found that almost half of the infants had SDH.[67] Bridging vein rupture, as seen on neuroimaging, is very rarely identified in these babies and dural bleeding from the vast intradural venous plexus is a more likely source. The degree to which birth-related SDH may affect later findings and symptoms is still unknown.

Indeed, an important part of diagnostic evaluation of any patient is to consider all possible differential diagnoses. This becomes even more important in cases of suspected AHT, where allegation of abuse and legal proceedings has significant consequences for the infants and their families. Many conditions are recognised as causes of SDH in infants, such as infections, malformations, and metabolic and coagulation disorders.[68]

Benign external hydrocephalus (BEH) is also a known risk factor for developing SDH.[69–74] It has been assumed that the widened subarachnoid space in BEH would stretch the bridging veins, making them more vulnerable to rupture, even with minimal trauma. Surprisingly, a finite element study showed a dampening effect of the enlarged subarachnoid space, claiming that BEH would not be a risk factor for developing SDH.[75] The article, however, has one major limitation, namely that the bridging veins were not assumed to be stretched in the case of widened subarachnoid spaces. Disagreement still exists as to whether BEH is a risk factor or not.[76,77] A recent review investigated the similarities between SDH and BEH, and presented a unifying theory of pathophysiology behind these subdural collections[78]

Few neuroimaging studies have reported findings of ruptured bridging veins, except the ones reviewed above. Findings such as the tadpole or lollipop signs lack pathologic verification of bridging vein injuries. Nevertheless, the authors of the article describing the tadpole sign claim that bridging vein thrombosis is an excellent indicator of AHT in SDH cases.[1] Similarly, it is stated that parasagittal vertex clots may be a novel predictor of AHT.[3] A neuroimaging sign of bridging vein thrombosis may simply reflect either slowed flow or venous thrombosis from natural disease unrelated to trauma and cannot be considered pathognomonic for venous injury or trauma.

A limitation of our review is that no systematic literature search was undertaken. However, there are only limited numbers of articles relevant to our specific question: is bridging vein thrombosis a marker of AHT? We believe that our study of the field has allowed us to make a thorough, albeit not systematic, review.

5 | CONCLUSION

As for neuroimaging, whether a venous injury can be identified, if it really exists, and whether it is caused by a trauma, remains uncertain. As for pathology, neither autopsy nor other examinations can prove that bridging vein ruptures or thromboses are caused by AHT only. As for biomechanics, the multitude of models is not able to show how and which traumas may lead to bridging vein rupture.

The subject of SDH and AHT in infants is a sensitive matter with strong feelings and opinions. This makes it even more important to maintain a high degree of accuracy and verifiability in the field. This review points to an alarming lack of evidence behind the investigation and interpretation of thrombosed bridge veins.

CONFLICTS OF INTEREST

Julie A. Mack has served as an unpaid expert witness in cases of alleged abuse. Cyrille Rossant is the current president of a French non-profit organisation (Adikia) providing moral support to parents facing false allegations of child abuse (unpaid activity). Waney Squier has acted as an expert witness, sometimes paid, in cases of suspected child abuse both for the prosecution and for the defence. She was reported to the General Medical Council (the governing body for the doctors in the UK) on the basis of her evidence in shaken baby cases and got her licence suspended, but restored on appeal. Knut Wester has served as a mostly unpaid expert witness for the court and the defence in a few cases of suspected abusive head injury in Norwegian courts. Sverre Morten Zahl declares no conflicts of interest.

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Errata for
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Oct 31, 2022. Sverre Morten Zahl
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Errata

Page 11 Full stop missing: "…infants with suspected abusive head trauma (AHT)" – corrected to "…infants with suspected abusive head trauma (AHT)."

Page 50 Sentence unnecessary: "Copies of approvals, patient information and consent form are found in the *Appendix* section." The whole sentence is removed, since the Appendix section was removed from the thesis prior to submission.

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