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INFLICTED TRAUMATIC BRAIN INJURY/ SHAKEN BABY SYNDROME IN ESTONIA — EPIDEMIOLOGY AND OUTCOME

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To my family and Estonian children

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LIST OF ORIGINAL PUBLICATIONS

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3. Talvik I, Männamaa M, Jüri P, Leito K, Põder H, Hämarik M, Kool P, Talvik T. Outcome of infants with inflicted traumatic brain injury (shaken baby syndrome) in Estonia. Acta Paediatr 2007; 96 (8): 1164–1168.
4. Talvik I, Lintrop M, Metsvaht T, Talvik T. Millal mõelda raputatud lapse sündroomile: kirjanduse ülevaade ning haigusjuhu kirjeldus. Eesti Arst 2007; 6: 420–423.
5. Talvik I, Vibo R, Metsvaht T, Talvik T. Shaken baby syndrome in Estonia. Europ J of Paediatr Neurol 2001; 5 (5): A141 (Abstracts for the 4th International Congress of the European Paediatric Neurology Society).

ABBREVATIONS

AAP	American Academy of Pediatrics
betaAPP	beta-amyloid precursor protein
CP	cerebral palsy
CSF	cerebrospinal fluid
CT	computed tomography
dTAI	diffuse axonal injury
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
ICD	International Classification of Disease
ICNT	inflicted childhood neurotrauma
IQ	intelligence quotient
ITBI	inflicted traumatic brain injury
K-ABC	Kaufmann Assessment Battery for Children
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAHI	non-accidental head injury
nTBI	non-inflicted traumatic brain injury
PICU	paediatric intensive care unit
POPCS	paediatrics overall performance category scale
RH	retinal haemorrhage
RDS	Rankin Disability Scale
SAH	subarachnoid haematoma
SBS	shaken baby syndrome
SDH	subdural haematoma
TBI	traumatic brain injury
US	ultrasound
VAI	vascular axonal injury
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1. INTRODUCTION

Inflicted traumatic brain injury (ITBI) or shaken baby syndrome (SBS) represents a silent epidemic and unique disease entity that has a huge socioeconomic impact - yet it has stimulated relatively little research (Kochanek et al. 2007). More than 1 in 3000 children younger than 1 year of age is a victim of severe or fatal inflicted childhood neurotrauma (ICNT) making SBS/ITBI almost as common as cystic fibrosis and more common than acute lymphocytic leukaemia (Kochanek et al. 2007). The estimated number of mild cases may be over 100 times higher (Keenan et al. 2003, Theodore et al. 2005).

According to Kochanek et al. (2007) ICNT or SBS/ITBI is the leading cause of death from traumatic brain injury (TBI) in children younger than two years of age. The mortality rate for SBS/ITBI varies from 13% to 30% (King et al. 2003, Keenan et al. 2003, Dias et al. 1998, Hadley et al. 1989, Sinal et al. 1987, Zimmerman et al. 1979). Specific evidence of previous brain injuries (old intracranial haematomas from different ages) from shaking episodes is found in about 33% to 40% of all cases (Alexander et al. 1990, Ewing-Cobbs et al. 1998).

In SBS/ITBI brain injury is caused by violent shaking resulting from tension and frustration generated by a baby's crying and/or irritability (Dykes 1986). The act of shaking leading to SBS is so violent that individuals observing it would recognize it as dangerous and likely to kill the child (AAP 2001). The provocative effect of infant' crying on abuse occurs more often in the first six months of life (Barlow et al. 2000, Agran et al. 2003). The results of a study by Reijneveld et al. (2001) provided the link between data on infant crying and infant maltreatment, supported by case studies on fatal abuse that seemed to be induced by infant crying. Clinicians and other health-care providers working with parents of infants should be aware of the risks for babies associated with their crying, especially if parents are complaining of excessive crying and are in a social position that could put pressure on the family situation (van der Wal et al. 1998). The actual duration of crying at a given moment seems to be less relevant than the parents' perception regarding of the crying of their infant over the long term (Reijneveld et al. 2004). Caretakers at risk for abusive behaviour generally have unrealistic expectations for their children and may exhibit a role reversal whereby caretakers expect their needs to be met by the child (Steele et al. 1974, Coody et al. 1994, Carty et al. 1995).

Due to the high mortality and morbidity rate, highlighting the high incidence of repeated injuries the correct diagnoses of these children very important.

2. REVIEW OF THE LITERATURE

Terminology of SBS/ITBI is conflicting. Original term — shaken baby syndrome (SBS) is probably the most accurate describing this specific type of child abuse — violent shaking of the child by the caretaker is causing brain injury of variable severity frequently with simultaneous retinal haemorrhages (RH).

In the literature many synonyms have been used and are still used such as — SBS, whiplash shaken baby syndrome, shaken infant syndrome, inflicted traumatic brain injury, non-accidental head injury (NAHI), battered child, abusive head injury, inflicted childhood neurotrauma and shaken impact syndrome (with additional signs of impact: scalp injury, scull fracture etc). All above mentioned terminology is used to describe only one specific form of physical non-accidental injury to infants characterized by an acute brain injury with intracranial (most frequently subdural) haematoma and RH, occurring in the context of inappropriate or inconsistent history and commonly accompanied by other apparently inflicted injuries and it is caused by shaking the infant violently (Case et al. 2001, AAP 2001). It is proven that shaking by itself can cause serious or fatal injuries (Alexander et al. 1990). In spite of the different terms that have been used throughout the literature, the most commonly used term "shaken baby syndrome" seems appropriate in terms of pointing out the cause — shaking as the only cause of injury to infants in this context.

This form of brain injury has set off several conceptual discussions: in 2004 regarding diagnostic criteria (Geddes et al. 2004) and in 2006 concerning terminology (Richards et al.). Richards et al. (2006) proposed to use the term/ diagnosis brain injury instead of SBS underlining the social impact of the diagnosis of SBS.

In terms of historical background, in 1972, paediatric radiologist John Caffey used the term "whiplash shaken baby syndrome" to describe a constellation of clinical findings in infants that included RH, subdural — (SDH) and/or subarachnoid haematomas (SAH), and little or no evidence of external cranial trauma. A year earlier (1971), Guthkelch had postulated that whiplash forces caused SDH by tearing cortical bridging veins.

In 2003 Mark Donohoe examined the trends in the quality of scientific evidence in SBS/ITBI using the keyword "SBS" and unfortunately several articles with other keywords were missed. He concluded based on papers with SBS as the only keyword that widely used diagnostic criteria in literature for SBS are not evidence based. One striking limitation of the Donohoe paper (2003) was that he used only one keyword. This is again a clear reflection of the confusing situation in the literature and of the need for a terminological/ diagnostic consensus. On the other hand, without widely accepted terminology and diagnostic criteria good quality scientific research on this very important topic is difficult (Reece et al. 2004).

2.1. Clinical symptoms and diagnostic criteria for SBS/ITBI

2.1.1. Clinical symptoms

History is the very important part of the diagnosis of SBS/ITBI. It is generally accepted that certain features of the history, such as a changing history, a history of low–impact trauma, or a history of no trauma suggest abuse (Leventhal et al. 1993). Hettler et al. (2003) showed in their study of 163 children admitted due to TBI that 49 (30%) of the 163 children met the criteria for definite abuse by shaking. The children with brain injury but not having history of trauma had a high specificity (0.97) and a positive predictive value (0.92) for abuse. Furthermore among the subgroup of patients with brain injury and persistent neurological abnormality at hospital discharge (n=34), having no history of trauma or low-impact trauma had a specificity of 1.0 and a positive predictive value of 1.0 for definite abuse (Hettler et al. 2003).

Clinical signs of SBS/ITBI may vary from mild and non-specific to severe and immediately identifiable clinically as brain injury (Jenny et al. 1999). A victim of sublethal shaking may have a history of poor feeding, vomiting, lethargy, and/or irritability occurring for days or weeks. These clinical signs of SBS/ITBI are immediate and identifiable as problematic even to parents who are not medically knowledgeable (Duhaime et al. 1998). However, depending on the severity of clinical signs caretakers may or may not seek medical attention (AAP 2001). These signs are often attributed by physicians to a viral illness, feeding dysfunction or colic (Jenny et al. 1999).

The triad of symptoms — disturbances of consciousness (usually named as an acute encephalopathy), SDH and RH have stood the test of time in diagnosis of SBS/ITBI. Other causes for this combination of injuries are extremely rare (Richards et al. 2006).

Minns and Busuttil (2004) proposed to identify four types of clinical presentation of SBS/ITBI: hyperacute encephalopathy (cervicomedullary syndrome), acute encephalopathy, subacute non-encephalopathic presentation and chronic extracerebral presentation. A database (Minns and Busuttil 2004) was collected for more than five years of documented Scottish cases of suspected SBS/ITBI diagnosed after a multiagency assessment and including cases with uncoerced confessions of perpetrators and criminal convictions. Minns and Busuttil (2004) suggested using the following classification to describe the variable severity of SBS/ITBI:

1. Hyperacute encephalopathy (6% of all cases) results from extreme “whiplashing” forces, the infant suffering the equivalent of a broken neck or, more correctly, a broken brain stem. These cases, which truly reflect a “whiplash” shaking injury to the stem, are infrequently seen by clinicians because the patients are either dead on admission or die shortly thereafter;

2. Acute encephalopathy (53% of cases) is clinically characterised by a depressed conscious state, seizures, apnoea, changes in muscle tone, anaemia, shock and retinopathy. Neuroimaging verify the raised intracranial pressure due to bilateral SDH, and widespread haemorrhagic lesions. In these patients metaphyseal fractures or other non-accidental injuries coexistent of rib fractures may be found;

3. Non-encephalopathic subacute presentation (19% of cases) the brain injury is less intense, without oedema, diffuse cerebral hypodensities, or clinical encephalopathic features. These children have various combinations of SDH and RH, rib and other skeletal fractures, bruising, etc. This is the most common presentation seen by paediatricians and is referred to as the "classic SBS" (repetitive rotational injury). The outcome in this group is better;

4. Chronic extracerebral presentation (22% of cases) is seen in children of a few months of age who present with an isolated SDH, which is often chronic (>3 weeks) and late in presenting. A rapidly expanding head circumference and signs of raised intracranial tension are common: the child may be irritable, vomiting, failing to thrive, hypotonic and fitting but with little encephalopathy.

In summary, the clinical symptoms of SBS/ITBI are variable from non-specific and mild (poor feeding, vomiting, lethargy, and/or irritability occurring days or weeks) to classical symptoms of severe brain injury often with RH in the context of inappropriate history.

2.1.2. Radiology

Imaging is the main diagnostic tool in the diagnosis of SBS/ITBI to confirm the brain injury. Brain injury in the context of skeletal bone fractures is a major indicator of abuse in babies (Wheeler 2003). All infants and children with suspected intracranial injury must undergo cranial computed tomography (CT) or magnetic resonance imaging (MRI), or both (AAP 2007). According to the latest suggestions MRI has the best modality and a high sensitivity in diagnosing an intracranial injury, including, SAH, SDH, epidural haematomas, intraparenchymal haemorrhages, contusions, shear injuries, and brain oedema (Barlow et al. 1999, AAP 2007, Bechtel et al. 2006). MRI offers the highest sensitivity and specificity for diagnosing subacute and chronic injury and should be considered whenever typical skeletal injuries associated with shaking or impacts are identified (Ball 1989, Sato et al. 1989, Bechtel at al. 2006). CT without intravenous contrast should be performed as a part of the initial evaluation for suspected SBS/ITBI (Demaerel et al. 2002).

A skeletal survey of the hands, feet, long bones, skull, spine, and ribs can demonstrate fractures (Smith 1997, AAP 2001). Skeletal findings, usually metaphyseal long bone and posterolateral rib fractures are reported in 10–30% of children with SBS/ITBI (Kocher et al. 2000). Some studies report skeletal abnormalities being as high as 46–51% and even cervical spine injuries in 4%

(King et al. 2003). Recent rib fractures might not be immediately apparent on radiography, but can be detected by radionuclide scanning (Blumenthal 2002) though the clinical significance of this method is to be established (Bechtel et al. 2006). MRI can also document bone and soft tissue lesions and can be of significant importance in contributing to the diagnoses in suspected child abuse cases (Eltermann et al. 2007).

Blunt thoracoabdominal injury may occur in victims of child abuse (AAP 2007). The evaluation and management of acute problems is the same as for children with accidental injuries (Sivit et al. 1989). Duodenal haematomas, bowel perforations, and thoracoabdominal injury associated with rib fracture heighten a suspicion of child abuse (AAP 2007). The use of ultrasound investigation as diagnostic tool is controversial, as for seriously injured children and those suspected of being abused, CT scanning is the preferred initial diagnostic modality (AAP 2007).

In summary, MRI has the highest sensitivity and specificity for diagnosing acute, subacute and chronic brain injury and should be considered whenever typical skeletal injuries associated with shaking or impacts are identified (Ball 1989, Sato et al. 1989, Bechtel at al. 2006). CT without intravenous contrast should be performed as part of the initial evaluation in children with suspected SBS/ITBI (Demaerel et al. 2002).

2.1.3. Retinal Haemorrhages

Retinal haemorrhages (RH) are pathognomic features of SBS/ITBI, and many authors include these in diagnostic criteria (Geddes et al. 2004). However, Lantz et al. (2004) described the case of a 14 month old boy with an accidental head injury and RH and perimacular retinal folds — the authors concluded that clinical and autopsy studies with appropriately matched controls are needed to determine the causal mechanism of perimacular retinal folds and their specificity for abusive head injury. Lantz et al. (2004) also stressed that professionals should be careful in interpreting eye findings out of context. This careful case study reinforces the need for a meticulous identification of the complexity of the injury and for evaluating the findings against the validity of the explanation offered (Harding et al. 2004). Although research on the subject of SBS/ITBI does not claim that RH are pathognomic for abuse, it does show that RH are, overwhelmingly, more common in SBS/ITBI than in non-inflicted injury (Reece et al. 2004).

RH are unilateral or bilateral and present in 50–100% of cases (AAP 2001, Levin 2000, Kivlin et al. 2000, Morad et al. 2002, King et al. 2003, Gilles et al. 2003, Morad et al. 2004). Haemorrhages may be subretinal, intraretinal, or preretinal and vary enormously in both size and severity from a few small flame-shaped nerve fiber layer haemorrhages to extensive haemorrhages, obscuring underlying retinal structures (Levin 2000).

In 2005 Cirovic et al. developed a finite element computer model of the eye, orbit, and orbital bone and used it to stimulate the effects of single-impact and oscillatory motions inputs. Their results strongly suggested that suction between the eye and its surrounding fat dominates the dynamical stability of the system composed of the eye, its socket, and the components and materials supporting the eye. Computer simulations incorporating this functional anatomical relationship show that deceleration of the head generates pressure gradients inside and outside the eye; these could cause damaging shear stresses in structures such as retina and blood vessels. Simulations also showed that oscillating the bone of the orbit causes the eye to move anteriorly and posteriorly with increasing amplitude, building up the stresses within the eye over time (Cirovic et al. 2005).

Sezen's (1970) work showed that 14% of newborns have RH at birth, with this reducing to 2.6% by day 5 as the haemorrhages fade. More recently, Emerson et al. (2001) looked at RH in newborns and found, in a study of 149 healthy babies, that 34% had RH, though it is important to underline that in 86% of cases, these birth-related RH disappeared 2 weeks after birth. The authors concluded that intraretinal haemorrhaging in an infant of over four weeks of age is unlikely to be related to birth trauma (Emerson et al. 2001).

A recent study by Gnanaraj et al. (2007) concluded after investigating ocular manifestations of crush head injuries in children that intraretinal and preretinal haemorrhages, predominantly in the posterior pole, can occur in a crush injury to a child's head. However, retinal folds and the typical macular retinoschisis associated with SBS/ITBI were not observed (Gnanaraj et al. 2007). The statement that a patient has RH is not sufficient enough to include or exclude SBS/ITBI from differentials. It is imperative to know whether the RH are unilateral or bilateral and where in the retina they are located (Bechtel 2006).

In summary, in spite of some controversies in the literature the presence of RH in co-existence with other symptoms strongly support the diagnosis of SBS/ITBI, therefore an ophthalmological investigation of possible victims is important.

2.1.4. Autopsy

At autopsy infants with SBS/ITBI have severe brain oedema and hypoxic injury but little axonal shearing and only a thin (trivial) SDH. Such presentations could result from a primary injury to the brain stem, induced by hyperflexion and hyperextension or rarely, from traumatic thrombosis of the vertebral arteries in the foramina of the cervical vertebrae (Minns and Busuttil 2004).

Intracranial findings of babies with SBS/ITBI often include subdural and/or subarachnoid blood. SDH commonly arises from torn bridging veins and is often regarded as a marker of severe head injury. The various parenchymal haemorrhages are thought to arise from tensile and/or rotational/torsional forces

along the midline and paramidline structures of the brain. These haemorrhages serve as markers of severe diffuse brain injury (Dolinak et al. 2006).

Immunohistochemical staining for beta-amyloid precursor protein (betaAPP) is a well-established marker of traumatic axonal injury in adults. Recent studies have used similar techniques to evaluate nonaccidental brain injury in infants and young children. In a study by Reichard et al. (2003) the authors reported the results of betaAPP immunohistochemistry on the brain and spinal cord in 28 paediatric cases of SBS/ITBI. BetaAPP-immunoreactive axons were present in 27/28 cases. Vascular axonal injury (VAI) due to brain oedema and secondary vascular compromise was the most common pattern of betaAPP immunoreactivity and was detected in 22 of 28 cases. Traumatic axonal injury (TAI) was detected in 19/28 cases, although only 8 of these cases showed brainstem staining, thus fulfilling the criteria for the diagnosis of diffuse TAI (dTAI). TAI and VAI were both present in 16/28 cases. Isolated TAI and VAI occurred in three and five cases, respectively. All children with isolated VAI were < 18 months of age. The authors concluded that betaAPP immunohistochemistry aids in documenting trauma in nonaccidental central nervous system injury in infants and young children and that VAI is a common finding (Reichard et al. 2003).

An evaluation of the cases of central nervous system NAI revealed 17 of 18 (94%) with SDH; 15 of 18 (83%) with SAH; 17 of 18 (94%) with RH; 16 of 18 (88%) with perioptic nerve haemorrhage; and 6 of 18 (33%) with optic nerve betaAPP immunoreactive axonal swellings. These findings confirm the presence of optic nerve axonal injury in some cases of fatal paediatric SBS/ITBI (Reichard et al. 2004).

Paediatric spine and spinal cord injuries are rare squeal of intentional trauma (Ghatan et al. 2002). They may easily be overlooked, however, and probably represent an underreported phenomenon. Autopsy data analyzed in conjunction with prior case series indicate that injury to the upper cervical spine and brainstem may significantly contribute to major morbidity, mortality, and neuropathology in SBS/ITBI. The findings illustrate several important points regarding spine and spinal cord injury after intentional trauma. First, the very young are susceptible to a severe, higher cervical injury of both the spine and spinal cord. Second, spine and spinal cord injuries were initially overlooked because of masked neurological findings with the concomitant head injury and multiple other systemic injuries. Finally, a child's outcome with significant cognitive delay due to global brain injury in conjunction with a focal high cervical cord injury may support the hypothesis that hypoxic damage could have occurred secondary to a brainstem and high cervical cord injury (Ghatan et al. 2002).

In summary, a pathological diagnosis of SBS/ITBI requires a careful evaluation of the character and extent of all components of the injury and should not rest merely on the presence or absence of one or more of the constituent lesions (Harding et al. 2004).

2.2. Incidence of SBS/ITBI

The incidence of SBS/ITBI is not precisely known and is mostly estimated from the incidence of SDH in infancy (Barlow et al. 2000). The American Academy of Pediatrics (AAP 2001) proposed that estimated numbers of children with SBS/ITBI represent the "tip of the iceberg". Apparently a much larger group of injured children exist because many children with less severe forms of injury may not be identified or brought to medical attention (AAP 2001, King et al. 2003). In these relatively mild cases acute signs may resolve without the true cause being discovered (AAP 2001). In southwest England and south Wales, the incidence of SDH was 21.0 per 100 000 children under the age of 1 year (95% Cl 7.5–34.4) and it was estimated that SBS/ITBI accounted for 82% of these cases (Jayawant et al. 1998).

There are only three population based studies concerning the incidence of SBS/ITBI available: one from Scotland (Barlow et al. 1998, 2000), one from North Carolina (Keenan et al. 2003) and one from Canada (King et al. 2003). A 15-year retrospective study in Scotland suggested an SBS/ITBI incidence of 11.2 per 100 000 children younger than 1 year. The authors concluded that it was most likely an underestimate because shaken impact syndrome is not a single coding entity in the International Classification of Disease (ICD) (Barlow et al. 1998). During an 18 month prospective study the annual incidence of SBS/ITBI in Scotland was two times higher — 24.6 per 100 000 (95% Cl 14.9–38.5) (Barlow et al. 2000). The second population based study was carried out in North Carolina and published in 2003. The study demonstrated similarly high incidence of SBS/ITBI — 29.7 per 100 000 children less than one year of age, with 62% of children being boys (Keenan et al. 2003). These results are consistent with other reports suggesting that male infants are at a higher risk for SBS/ITBI (Barlow et al. 2000, Jayawant et al. 1998, Feldman et al. 2001, Morad et al. 2002). A 10 year (from 1988 to 1998) Canadian retrospective study (King et al. 2003) based on 11 tertiary care paediatric hospitals (representing an estimated 85% of tertiary care paediatric beds), collected 364 children with SBS/ITBI and suggested that a minimum of 40 cases of SBS/ITBI occur annually in Canada. The mean age for children with SBS/ITBI was 4.6 months (range 7 days to 58 months) (King et al. 2003), 5.9 months (0.5 years IQR: 0.2–0.5) (Keenan et al. 2003, Keenan et al. 2006), but in a series by Morad et al. (2002) the babies were older — 10.6 months (range 2–48 months).

In summary, there are few prospective population based epidemiological studies on incidence of SBS/ITBI and the results vary from 11.2–29.7 per 100 000 children under 1 year of age. The variability depends significantly on used methods (retrospective, prospective, hospital-based, population based). Population based prospective studies show consistently higher incidence of SBS/ITBI than retrospective studies.

2.3 Outcome of SBS/ITBI

Child maltreatment exacts a significant toll on society, causing immense childhood suffering, and poor health and psychological outcomes in adulthood. In spite of the advances in the recognition of the clinical, radiographic, and pathological findings of SBS/ITBI, less is known about the long term outcomes of survivors (Makaroff et al. 2003). Surprisingly, the literature regarding the outcome of SBS/ITBI specifically is scarce, although the outcome is generally assumed to be poor (Barlow et al. 2004, Makaroff et al. 2003, Keenan et al. 2004, Duhaime et al. 1996, Jayawant et al. 2007). Slowly, progress is being made in our understanding of the complex phenomenon of child abuse and data continue to accumulate regarding the long-term deleterious effects (Newton et al. 2007). Relatively early literature reports neurological abnormalities in children who had suffered maltreatment (Barlow et al. 2004). Up to 50% of these children were either "mentally retarded" or had other neurological squeal (Elmer et al. 1967, Birrell et al. 1968, Johnson et al. 1968, Martin et al. 1974).

Most of the outcome studies have been retrospective with different sources of involved children — chart reviews (Ludwig et al. 1984, Holloway et al. 1994, Haviland et al. 1997, Kivlin et al. 2000, Fung et al. 2002, Barlow et al. 2000), telephone interviews (Fischer et al. 1994, Duhaime et al. 1996). There are prospective studies (Goldstein et al. 1993, Bonnier et al. 1995, Cho et al. 1995, Ewing-Cobbs et al. 1999, Barlow et al. 2004) and some cross-sectional studies (Fischer et al. 1994, Duhaime et al. 1996, Gilles et al. 1998, Bonnier et al. 2003, Barlow et al. 2004). Some authors report the outcome of children who had been admitted to a PICU. It is reasonable to assume that these children were more severely injured and were more likely to have bad prognosis and outcome (Goldstein et al. 1993, Cho et al. 1995, Haviland et al. 1997). The outcome of this group of children seems to be invariably serious — good outcome has been documented from 7% (1 patient) (Goldstein et al. 1993, Haviland et al. 1997) to 17% of children (4 patients) (Cho et al. 1995).

Several articles address the outcome of SBS/ITBI children at discharge (Goldstein et al. 1993, Holloway et al. 1993, Keenan et al. 2004). Some studies do not specify the duration of the follow-up period (Ludwig et al. 1984, Goldstein et al. 1993, Fung et al. 2002). Other studies describe the outcome 1–5 years after the acute event (Cho et al. 1995, Haviland et al. 1997, Gilles et al. 1998, Kivlin et al. 2000, Barlow et al. 2000, Barlow et al. 2004, Karandikar et al. 2004, Barlow et al. 2005).

Only few studies describe the outcome 5–10 years after the acute event (Fischer et al. 1994, Bonnier et al. 1995, Duhaime et al. 1996, Bonnier et al. 2003).

The morbidity rate in different studies among survivors has varied from 38–45% (Barlow et al. 1999, Kivlin et al. 2000, Swenson et al. 1997, Karandikar et al. 2004) to 58–70% (Johnson et al. 1995, Wilkerson et al. 1989, Fischer

et al. 1994, Ludwig et al. 1984, Barlow et al. 2005). Some studies report the morbidity rate being as high as 80–100% among survivors (Ewing-Cobbs et al. 1998, Ewing-Cobbs et al. 1999, Gilles et al. 1998, Duhaime et al. 1996, Bonnier et al. 2003). The differences in morbidity rate among survivors are influenced by different follow-up time (from at discharge to 10 years later), different sizes of the study groups (10–56 patients) and severity of initial trauma. One of problems of follow-up studies is constantly low number of patients who agree to participate — approximately 50%–10/21 (Fischer et al. 1994), 14/61 (Duhaime et al. 1996), 56/87 (Kivlin et al. 2000) and 25/49 (Barlow et al. 2004). The number of healthy children seems to be higher in studies with longer follow-up period being around 30% (Duhaime et al. 1996, Fischer et al. 1994), and in a larger study groups (56 patients) – 39% (Kivlin et al. 2000). The differences are partially explained by the fact that no common outcome scores were used (Barlow et al. 2004).

There is anecdotal data proposing that in some children undiagnosed SBS/ITBI will result in severe mental and physical disability interpreted as cerebral palsy (CP). This is demonstrated in a study by Gill et al. (2007) in New York City, in which they reviewed the records of 5 delayed fatalities (with survival intervals from 2.5 to 17 years) due to non-accidental infant brain injury, all initially diagnosed as CP or developmental delay. Their autopsies showed typical signs of SBS/ITBI.

In summary, generally the outcome of children with SBS/ITBI is poor, but variable depending on the number of children in study group, duration of follow-up period and the severity of initial trauma. Some differences in results can be explained the absence of standards in measuring outcome.

2.3.1. Outcome measures

Outcome measures used vary significantly. The problems are related to the lack of consensus on a suitable outcome scores for brain injury in children and also differences in follow-up time (Barlow et al. 2004). The absence of a “gold standard” battery of outcome measures and the subsequent use of non-standardised and variable outcome measures has led to difficulties in the comparability of outcome data following SBS/ITBI (Jayawant et al. 2007). Outcome measures used have included the Glasgow Outcome Scale (GOS) (Duhaime et al. 1996, Ewing-Cobbs et al. 1998, Ewing-Cobbs et al. 1999, Barlow et al. 2005), Seshia’s global outcome score (Barlow et al. 2000, Barlow et al. 2005), King’s Outcome Scale for Childhood Head injury (Karandikar et al. 2004) and the Paediatric Overall Performance Category (POPC) (Keenan et al. 2004, Keenan et al. 2006). GOS (Jennett et al. 1975) and its modifications has been the most widely used for measuring long-term outcome. However GOS may not identify subtle cognitive and fine motor deficits (Koelfen et al. 1997). The common

problem with different outcome scales is that they categorise individuals within a rather narrow scale results in a categorization rather than a dimensionalisation of outcome (Jayawant et al. 2007).

Ewing-Cobbs et al. (1999) in their prospective study of 28 children reported that 16% had a severe outcome, 61% had a moderate outcome, and 25% had a good outcome according to GOS at mean follow-up of 3 months. In an earlier study by the same authors (Ewing-Cobbs et al. 1998), for which the authors conducted the developmental measures of children after SBS/ITBI at an average of 1.3 months after injury: 45% of the patients scored in the mentally deficient range for cognitive testing and 25% scored in the mentally deficient range for motor testing. The overall morbidity in reports on a total of 292 survivors is 74% (range: 59–100%), with only 25% being "normal" on follow-up (Barlow et al. 2004).

In their follow-up study, with mean length of follow-up 59 months, Barlow et al. (2005) showed a high morbidity rate among the survivors. On follow-up a total of 68% of survivors in this study were disabled, 36% had severe difficulties and were totally dependant, 16% had moderate difficulties, and 16% had mild difficulties. In the same study wide ranges of neurological squeal were seen, including motor deficits (60%), visual deficits (48%), epilepsy (20%), being often intractable (Barlow et al. 2000), speech and language abnormalities (64%), and behavioural problems (52%). There was a wide range of cognitive abilities: for the mean psychomotor index, 69.9 (SD: ±25.73); and for the mean mental development index, 74.53 (SD: ±28.55). Adaptive functioning showed a wide range of difficulties across all domains: the communication domain (mean: 76.1; SD: ±25.4), the daily living skills domain (mean: 76.9; SD: ±24.3), and the socialization domain (mean: 79.1; SD: ±23.1). Outcome was found to correlate with the Paediatric Trauma Score and the Glasgow Coma Score (GCS) but did not correlate with age at injury or mechanism of injury (Barlow et al. 2005). Many of these children had complex disabilities with varying combinations of cognitive, motor, language and behavioural abnormalities (Barlow et al. 2005). The authors concluded that SBS/ITBI has a very poor prognosis and correlates with the severity of injury and stressed that extended follow-up is necessary not to underestimate problems such as specific learning difficulties and attention deficit and memory problems that may become apparent only once a child is in school. Barlow et al. (2005) highlighted the behavioural problems, the consequence of frontal lobe injury, found in 52% of children and can manifest clinically between the second and third years of life, not diagnosed in case the follow-up period is shorter (Barlow et al. 2005). The behavioural abnormalities included self-injurious and self-stimulating behaviours, hyperactivity, impulsivity, temper tantrums, and rage reactions. Behavioural problems are likely to be attributed to varying combinations of frontal lobe injury, speech and language abnormalities, and genetic and environmental factors (Barlow et al. 2005). In their research Eslinger et al. (2004) proposed that as consequences of damage to the frontal lobe may not manifest until

puberty or even later, it is possible that substantially more than 50% will have problems when follow-up is extended into adolescence and early adulthood. The study by Barlow et al. (2005) highlighted that in addition to behavioural problems sleep abnormalities (24%) are often seen in this population of children.

Kivlin et al. (2000) reported that 25% of children in their study group of 56 children with SBS/ITBI had some degree of visual impairment, largely the result of cerebral visual impairment. Barlow et al. (2005) found that 40% of patients have a significant visual deficit. However, they stressed that visual assessments were not done by a paediatric ophthalmologist, and they assumed that the number of abnormalities may be underestimated. The types of visual impairment were variable, including cortical blindness (16%), visual deficits, visual agnosia, and decreased visual acuity (Barlow et al. 2005).

Barlow et al. (2005) evaluated cognitive functions in 25 children by testing using the Bailey Scales of Infant Development, the British Ability Scales, and the Vinel and Adaptive Behaviour Scales. According to this study the cognitive performance fell below the 1st percentile for 10 children, and 3 were in the borderline intelligence range. Three patient in this study group attended mainstream schools without learning support, but two of these children were found to have significant memory deficits.

Most of the studies still only address short term outcomes (King et al. 2003), even these are very alarming: of the 295 survivors, only 65 (22%) were felt to be "well" (absence of health or developmental impairment) at the time of discharge, with 162 (55%) having a persistent neurological deficit and 192 (65%) having visual impairment. Of survivors, 251/295 (85%) required ongoing multidisciplinary care (King et al. 2003).

However, Bonnier et al. (1995) described a "sign free interval" in 6 of 13 cases of SBS/ITBI between 6 months and 5 years. In her study, two children were thought to be normal at three years of age, and of these two children, one was found to have learning disability at five years of age. Five of the 11 children demonstrated a falling DQ in speech and language, and 4 of these also changed outcome categories. In a more recent study Bonnier et al. (2003) conducted a retrospective medical record review of 23 children with confirmed SBS/ITBI, for whom an extended follow-up of 2.5 to 13 years (mean: 6 years) was contemplated. The authors compared GCS, severity of retinal haemorrhages, presence of skull fractures, cranial growth deceleration, and sequential neuroimaging data (CT and/or MRI) with patterns of clinical evolution assessed by the GOS. Clinical outcome showed that 14 (61%) children had severe disabilities, 8 (35%) had moderate disabilities, and 1 (4%) was normal. A low initial GCS, severe retinal haemorrhages, presence of skull fracture, and cranial growth deceleration were significantly associated with a poor developmental outcome. Eighteen of the 23 patients had abnormal MRI scans. This examination disclosed atrophy when performed beyond 15 days of injury. Atrophy seemingly resulted from various brain lesions, namely, contusions,

infarcts, and other lesions within the white matter. The presence of intraparenchymal brain lesions within the first three months was significantly associated with neurodevelopmental impairment. The severity of motor and cognitive dysfunctions was related to the extent of intraparenchymal lesions (Bonnier et al. 2003).

Keenan et al. (2006a) in their prospective cohort study assessed outcomes one year after severe traumatic brain injury (TBI) among young children and compared outcomes between children with inflicted (SBS/ITBI) versus noninflicted injuries (nTBI). During the study period all North Carolina resident children who were hospitalized in any of the state's nine PICUs and who had survived a severe TBI that occurred on or before their second birthday were included to the study. Child health status, child use of ancillary medical resources, and family characteristics were determined through maternal caregiver interviews approximately one year after injury. Comparisons were made between family characteristics and child outcomes according to injury type. The authors found that 72 interviews of maternal caregivers were completed among 112 survivors (64.3%). Children with SBS/ITBI (n=41) had worse outcomes than did children with nTBI (n=31), as measured using the Paediatric Outcome Performance Category (POPC) and Stein-Jessup Functional Status II (Revised) tools. However, approximately 50% of the children with SBS/ITBI had only mild deficits. Children with inflicted injuries had a higher use of ancillary medical resources. Families caring for the children did not differ substantively, with a large proportion of single, working, minority mothers. The authors concluded that children with SBS/ITBI had worse outcomes than did children with other nTBIs one year after injury. However, outcomes for these children were better than those reported previously. Many families caring for children after severe TBI are socially disadvantaged. Interventions to improve child outcomes may include enhanced family support (Keenan et al. 2006a).

However follow-up study by Keenan et al. (2006b) showed the results of a 2-year study period evaluation of 112 children who had survived a TBI. Fifty-seven (79%) of the 72 maternal caretakers who had completed an interview 1 year after the child injury participated in the year 2 interview. Most children (67%) had an outcome of mild disability or better at year 2, with 45% functioning at an age-appropriate level. Children's outcomes did not differ significantly at year 2 according to the mechanism of injury. The majority (67%) of children retained their POPC scores from year 1 to year 2. Children who changed were as likely to show improvement as deterioration. Families tended to have multiple environmental factors that could put their children at risk for poor developmental outcomes, including living below the poverty level (22%) and low social capital (39%). This study concluded that the children in this cohort had relatively stable functional outcomes from year 1 to year 2 after injury. This population of children remains very vulnerable to poor developmental outcomes secondary to the effects of their TBI and environmental factors (Keenan et al. 2006b).

In summary, the outcome of children with SBS/ITBI is poor: these children can have behavioural, sleep and cognitive problems. Unfortunately long-term follow-up studies to detect all problems of these children are largely missing and needed. It is important to develop standards for outcome of these children to be able to identify and quantify gross and more subtle problems. Different outcome scales, developmental scales and neuropsychological tests in combination are desirable (Jayawant et al. 2007).

2.3.2. Prognostic factors

The prediction of outcome of SBS/ITBI is a challenge. Makoroff et al. (2005) recently evaluated children with SBS/ITBI using magnetic resonance spectroscopy (MRS). They postulated that children with hypoxic-ischemic injury indicated by elevated lactate in the acute phase of injury will have worse early neurological status and short-term clinical outcomes than those without lactate upon MRS. This prospective study employed proton MRS to sample bilaterally the frontal lobes and the parasagital cortex within the parietal and occipital lobes of 11 patients with SBS/ITBI who were undergoing a clinical MRI examination. The patients' measured clinical course while hospitalized included initial neurological evaluation, the presence of seizure activity, need for admission to the PICU, number of hospital days, the presence of retinal haemorrhages and bone fractures. Measurement of outcome was determined using the POPCS (1=good performance; 6=death). The authors found that four children demonstrated elevated lactate and diminished N-acetyl aspartate (a neuronal marker) within several regions, indicating global ischemic injury (lactate-positive global group). These four children all had seizure activity and abnormal initial neurological examinations and required admission to the PICU. The mean POPCS for this group was 3.25. In four other children, lactate was detected within at least one region, indicating a focal ischemic injury (lactate-positive focal group); two of these children had seizure activity, and two had an abnormal initial neurological examination. The mean POPCS score was 1.5 for this group. The remaining three children had no evidence of lactate upon MRS (lactate-negative group). These children did not have seizure activity, did not require admission to the PICU, nor did they have initial abnormal neurological examinations. The mean POPCS score was 1.3 for this group. Makoroff et al. (2005) concluded that patients with SBS/ITBI and evidence of hypoxic-ischemic injury as indicated by elevated lactate on MRS tend to have worse early neurological status and early outcome scores. Lactate levels as sampled by MRS might predict early clinical outcome in SBS/ITBI (Makoroff et al. 2005).

Even more recently an interest in biomarkers has been shown in the context of outcome. Beers et al. (2007) studied the outcome and serum concentrations of NSE (neuron-specific enolase), S100B, and MBP (myelin-basic protein). The limitation of these studies is still small number of children.

Children with SBS/ITBI tend to be symptomatic on presentation as compared to those with nTBI and tend to have a higher frequency of cerebral oedema, anoxic/ischaemic damage (Keenan et al. 2004). These findings would support the hypothesis that children with SBS/ITBI have delayed presentation for medical care compared with nTBI, which may be partially explanatory of their worse outcomes (Keenan et al. 2004, Jayawant et al. 2007). However, because of the difficulty in knowing the exact timing of a shaking event and because nearly 1/3 of the children with SBS/ITBI have a documented previous injury this cannot be stated with certainty (Keenan et al. 2004). Another difference between nTBI and SBS/ITBI in reports to date is that accidentally injured children have tended to be older than non-accidentally injured children (Keenan et al. 2004).

An interesting study concerning executive functions was done by Landry et al. (2004); in this study they examined social and cognitive competence in 25 infants aged 3 to 23 months who sustained moderate to severe TBI secondary to physical abuse (SBS/ITBI) and in comparison to 22 healthy community children. Children with TBI were evaluated an average of 1.6 months after the injury. The SBS/ITBI group showed significant reduction in both social and cognitive domains relative to the comparison group. Canonical correlation analyses disclosed that SBS/ITBI was associated with a reduction in (a) the initiation of social interactions, (b) responsiveness to interactions initiated by the examiner, (c) positive affect, and (d) compliance. The groups performed comparably on indexes of gestural and verbal communication and on the occurrence of negative affect. Joint attention was an area of vulnerability for the TBI group in both social initiation and response contexts. Although general cognitive and motor scores were lower in the SBS/ITBI group, the complexity of independent toy play did not differ across groups. Early brain injury causes significant disruption in behaviours regulating initiation and responsiveness in social contexts (Landry et al. 2004).

It is important to stress that it is not only direct brain injury affects the development of children. In 2005 Prasad et al. studied a sample of 19 children, aged 14–77 months, who had been hospitalized for physical abuse with no evidence of neurological injury with a comparison group of 19 children matched for age and socioeconomic status. The children underwent cognitive, language, and motor testing within three months of their discharge from the hospital. The caregivers of the injured children were interviewed and were asked to complete questionnaires to characterize the child's developmental level and behaviour just prior to the hospitalization. This study found that children who had been physically abused scored significantly lower than the comparison group on measures of cognitive functioning, motor skills, and language skills. The groups did not differ in child behaviour ratings completed by the caregivers. MRI of the brain was performed in 15 children in the physical abuse group; in 2/15 significant cerebral atrophy was found. The authors concluded that children who have been physically abused are at a high risk for delays in

cognitive, motor, and language development. The standard of care for these children should include developmental testing as well as neuroimaging of the brain to detect occult brain injury (Prasad et al. 2005).

In summary, neither good prognostic markers nor MRS in these children are available in everyday practice but can be helpful in the future. There are limitations for evaluating prognostic factors in this group of children due to small number of children in studies.

3. THE AIMS OF THE STUDY

The aims of the study were:

- to estimate the incidence of SBS/ITBI in Estonia
- to characterize the clinical symptoms of SBS/ITBI
- to identify the outcome of these children
  - neurological outcome
  - cognitive functioning

4. PATIENTS AND METHODS

The Bioethical Committee of the University of Tartu approved the study. Parents gave their informed consent for participation in the study.

4.1. Pilot study (Paper I, Paper V)

The very first case of SBS/ITBI in Estonia was diagnosed in December 1999 and afterwards the pilot study was initiated in order to control the hypothesis that children with SBS/ITBI were present earlier but were misdiagnosed. Also, as no children were diagnosed as having SBS/ITBI before 1999 we hypothesized that SBS/ITBI is rare in Estonia.

The pilot study was a hospital based retro- and prospective study based on the paediatric intensive care unit (PICU) of the Tartu University Hospital from 1 January 1991 until 31 December 2001. All medical records of children admitted to PICU due to brain injury (52 children) during the period from 1991 till 1999 were reviewed retrospectively to identify possible undiagnosed children with SBS/ITBI.

From 1 January 2000 to 31 June 2001 the prospective study was initiated. Only patients with at least two of the following criteria were included in the study group: 1) no apparent/consistent history of trauma; 2) radiological features of brain injury (SDH, contusion, SAH, diffuse brain oedema) on CT/ultrasonography/MRI; and /or 3) skeletal fractures; and /or 4) RH and 5) no history or clinical and laboratory signs of haemorrhagic or metabolic disorder. During retrospective period of the pilot study (1991–1999) six children admitted to PICU because of TBI and during prospective period (2000–2001) three children were identified (Table 1).

4.2. Nationwide study (Paper II and III)

4.2.1. General information

The nationwide study consisted of epidemiological study and the outcome study of the survivors.

A nationwide epidemiological study had two parts: retrospective and prospective part of the study. The study was conducted, from 1 January 1997 until 31 December 2003. In this nationwide study we focused on children with SBS/ITBI admitted to two tertiary centres for paediatric intensive care with the only neurosurgical and paediatric neurology units in Estonia.

Study area. Estonia is the northernmost of the Baltic States, with a population of 1.3 million and area of 45 227 square km and 15 counties. The number of child-

ren in the population during the study period was 11911–12981 per year in the age group less than one year of age (www.stat.ee). There are two tertiary hospitals for children in Estonia — the Tallinn Children's Hospital for the northern part and the Children's Clinic of Tartu University Hospitals for the southern part. According to the consensus documents in Estonia all critically or severely ill children with brain damage are hospitalized at these tertiary centres where PICU, units of imaging, neurosurgery and paediatric neurology are located. All children with developmental problems according to the consensus document in Estonia should be referred as early as possible to these two hospitals for diagnostic work-up.

For this study both tertiary children's hospitals agreed to the criteria for inclusion/exclusion to the study group. Before the nationwide study started several lectures and training courses were held to introduce the syndrome and diagnostic criteria to the specialists involved in the study.

Study periods. The retrospective study included all children admitted during the period of 1 January 1997 until 31 December 1999. The prospective study period was from 1 January 2000 to 31 December 2003. According to the results of the pilot study the same inclusion criteria were used. MRI complemented sonography in the nation-wide study. The outcome of children of the epidemiological study was evaluated during the years 2005–2006.

4.2.2. Patients

The incidence study had two parts: retrospective and prospective part of the study. For the retrospective study the case reports of all patients with intracranial, intraocular and/or skeletal injuries admitted to the two tertiary centres from 1 January 1997 until 31 December 1999 were identified and reanalyzed.

The prospective part of the study started from 1 January 2000 until 31 December 2003. During the prospective part of the study period all children admitted due to brain injury were very carefully examined and evaluated by a multidisciplinary team (intensive care doctor, paediatric neurologist, paediatrician, ophthalmologist and neurosurgeon).

During the study period (from January 1997 until December 2003) 26 children with SBS/ITBI were identified; 5 children during the retrospective part of the study and 21 during the prospective part of the study. Four children died. One child died on admission, one during first 24 hours (being brain dead on admission) and two children were identified from forensic databases.

Outcome study. Despite some difficulties, we were able to locate all survivors (22) of the epidemiological study and evaluate the outcome of these children.

All 22 children who survived the acute event were evaluated by the members of the study team: paediatric neurologist, experienced ophthalmologist and clinical psychologist and by child psychiatrist if necessary. Description of patients is in Table 2.

Table 2. Description of patients during the first admission (2) and on follow-up.

Pt	sex	Age on admission months	Seizures / Disturbances of consciousness	GCS	Fundus hemorr	CT*/ MRT	Age Year/ month	Epil	Neurol	Cognition	Visual acuity	Final fundus	GOS	RDS
1	M	2	Y/Y	10	L	SDH AC L	7/2	No	Hemip D	F 83	D=S=1,0	N	1	2
2	M	4	Y/Y	7	BIL	SDH AC et CR L	6/5	Y	Clumsy	F83	D=0,2S=1,0	N	1	2
3	M	6	No/Y	8	BIL	SDH R	5/6	Y	Clumsy	F83	Fix	R fibrous changes	1	2
4	M	2	No/N*	14	R	SDH CR BIL	4/4	Y	Clumsy	F83	Fix	N	1	2
5	M	7	Y/Y*	14	L	SDH BIL CR	5/1	No	Clumsy	F83	ND	ND	1	2
6	F	4	Y/Y*	8	BIL	SDH BIL CR	5/5	No	Norm	Norm	D=S=0,7	N	1	1
7	M	11	Y/Y	13	BIL	SDH CR	5/3	No	Clumsy	F83	ND	ND	1	2
8	M	2	Y/No	14	R	SDH BIL CR	6/6	Y	Clumsy	F83	D=S=0,5	N	1	2
9	M	6	No/No**	13	No	SDH BIL CR	4/11	No	Clumsy	F83	D=S=0,63	N	1	2
10	M	3	No/Y	10	BIL	SDH CR L	2/8	Y	Tetra-paresis	F79	No fix	Optic atrophy	3	5
11	M	4	No/No**	14	No	SDH BIL CR	2/8	No	Clumsy	R62.0	Good fix	N	1	2
12	M	4	No/No**	14	No	SDH BIL CR	2/8	No	Clumsy	R62.0	Good fix	N	1	2
13	F	1	Y/Y	4	R	SDH, IVH	2/4	Y	Tetra-paresis	F79	No fix	RL — optic atrophy	3	5
14	M	1	Y/Y	8	R	SAH	4/0	Y	Spastic diplegia	F79	ND	RL optic atrophy	3	5
15	M	2	Y/Y	7	R	SDH CR R	4/2	No	Norm	Norm	Fix	N	1	1
16	M	2	Y/Y	11	No	SDH CR BIL	4/1	No	Clumsy	F83	D=0,4 S=0,6	N	1	2
17	M	3	Y/Y	8	ND	SDH BIL	5/1	No	Clumsy	F83	D=S=1,0	N	1	2
18	M	2	Y/Y	12	No	SDH BIL	5/8	No	Norm	Norm	D=S=1,0	N	1	0
19	F	6	No/No*	13	No	SAH	6/6	No	Norm	Norm	D=S=1,0	N	1	1
20	M	2	No/Y	5	BIL	SDH R	5/7	No	Hemip sin	F83	ND	ND	1	2
21	F	5	No/Y	14	BIL	SDH, ICH	9/0	No	Clumsy	F81.3	ND	ND	1	2

Pt	sex	Age on admission months	Seizures / Disturbances of consciousness	GCS	Fundus hemorr	CT*/ MRT	Age Year/ month	Epil	Neurol	Cognition	Visual acuity	Final fundus	GOS	RDS
22	M	3	No/Y	14	ND	SDH CR BIL	8/8	No	Norm	Norm	ND	ND	1	0
23	M	4 days	N/Y	ND	ND	NS	ND							
24	M	1,5	N/Y	ND	ND	NS	ND							
25	F	2	N/Y	ND	ND	NS	ND							
26	F	12	Y/Y	BIL	Oedema cerebri SAH	NS	ND							

Abbreviations in table 3

F — female; M — male, Y — yes; No — no; GCS — Glasgow Coma Score; L — left sided; BIL — bilateral; R — right sided; ND — not done; SDH — subdural haemorrhage; CR — chronic; SAH — subarachnoidal haemorrhage; ICH — intracranial haemorrhage; IVH — intraventricular haemorrhage; AC — acute; et — and; fix- fixation; D — right sided; S — left sided; N — normal; GOS — Glasgow Outcome Score; NS — nonsurvivor; RDS — Rankin Disability Score

* Vomiting

** developmental delay

4.2.3 Methods

4.2.3.1. Epidemiological study

During the retrospective study the case reports were reinvestigated as described on page 28. In prospective part of the epidemiological study all children admitted due to brain injury were very carefully examined and evaluated by a multidisciplinary team (intensive care doctor, paediatric neurologist, paediatrician, ophthalmologist and neurosurgeon).

All children were investigated with CT or MRI, in case of seizures EEG was performed.

Laboratory investigations for screening for coagulopathies included: protrombin, APTT and fibrinogen. Some patients with developmental problems or suspected developmental problems prior to the acute admission were also investigated for possible metabolic disorders (re: amino acids, organic acids).

Only since 2000–2001 have skeletal surveys for the evaluation of any fractures been compulsory in suspected cases. As a skeletal survey was not done on all of the children we did not study this at this point.

An eye examination was performed by an ophthalmologist on all of the children as soon as possible after admission to the hospital. The experienced ophthalmologist obtained a dilated examination to reduce the possibility of missing RH.

All children were scored according to the Modified GCS for Infants on admission (Appendix 1).

4.2.3.2. Outcome study

During outcome study the children were investigated by multidisciplinary team (child neurologist — I.T., clinical psychologist — M.M., ophthalmologist — P.J., psychiatrist).

CT/MRI investigation was performed during the follow-up period in 20/22. In all children with epilepsy (7/22) EEG investigation was performed.

Cognitive functions of children in the outcome study were evaluated with Kaufman-ABC test battery (K-ABC; Kaufman et al. 1983).

The K-ABC test has not been standardized for Estonian language and there are no national norms. For the purpose of this study a control group was set up. The control group for the follow-up/outcome study consisted of 95 healthy children with normal development matched by age, sex and native language to the 22 survivors.

Children of study and the control group were tested individually in a separate room with K-ABC. The testing time varied from 75 to 100 minutes, according to the child's age, behaviour and skills. All tests were performed by one skilled clinical psychologist (M.M).

The K-ABC is an individually administered measure of intelligence and achievement. Intelligence in the K-ABC is defined as problem-solving ability, while achievement level is connected the knowledge of facts.

The test measures a wide range of cognitive abilities and can be used to assess children across an age range of 2.5 to 12.5 years. Two kinds of information processing styles, sequential and simultaneous, can be used during problem solving. A simultaneous processing style demands gestalt-like or spatial integration of information for task completion, while a sequential processing style demands serial or temporal order of stimuli to complete a task (Kaufman et al. 1983). The K-ABC as a multi-subtest battery is suitable for assessing normal and exceptional children (Lichtenberger et al. 2001, Sabbadini et al. 2001, Sattler 2001, Lücke et al. 2005, Schermann et al. 2004); for the K-ABC, verbal abilities are of relatively low significance (if compared to other intelligence tests, e.g. the Wechsler scales — Wechsler Intelligence scale for Children (WISC) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Wechsler 1991, Wechsler 1989)), which is done intentionally in trying to avoid a cultural bias.

We administered the eight K-ABC subtests applicable for all age groups: three simultaneous, three sequential and two achievement scales subtests (Appendix 2) (Kaufman et al. 1983). Some children needed a consultation with a psychiatrist and for diagnostic purposes the ICD-10 Classification of Mental and Behavioural Disorders was used.

If the parents gave their consent, an ophthalmologic examination was performed by an experienced ophthalmologist.

All of the children were scored according to GOS and Rankin Disability Scores (RDS) by two specialists independently who had both examined all of the children (I.T, M.M) (Appendix 3, 4).

4.3. Statistics

Statistical analysis was performed using STATISTICA 6.0 and the statistical package SAS Version 8.02 (Copyright (c) 1999–2001 by SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as mean values with 95% confidence intervals (CI), while qualitative variables are presented as absolute and relative frequencies. The Kolmogorov-Smirnov criterion was used for the assessment of normality. Differences between SBS and control groups were studied with the nonparametric Mann-Whitney U test, because the sample size is small. To compare proportions (qualitative variables) the Chi-square test or the Fisher's Exact test (when expected values were <5%) were used. To examine the association between the variables, the Spearman's correlation test was used. All p values were two sided and differences were considered statistically significant if the p values were less than 0.05.

5. RESULTS

5.1. Pilot study (Paper I, Paper V)

Altogether — 9 children, 3 girls and 6 boys, aged from 1 to 10 months (mean 4.056 months 95%Cl: 1.964–6.147) satisfied the inclusion criteria of the pilot study. Eight children needed admission to the PICU (range 1–14 days). The mean length of stay at PICU was 8 days and for all in-patient care 19 days (range 14–31 days). The main characteristics of these children are shown in Table 1 as well as the characteristics of the brain injury.

Table 1. The main symptoms at admission of patients in the pilot study

	No of patients	%
Seizures	8/9	89%
Focal neurological focal signs	7/9	78%
Disturbances of consciousness	6/9	66%
RH	5/5	100% (all who were examined)
External signs of trauma	2/9	22%
Neuroimaging		
SDH	5/9	56%
SAH	2/9	22%
Multifocal haemorrhagic contusion	2/9	22%

From 9 survivors there were 3 girls (33.5%) and 6 boys (66.5%). The children were aged 1–10 months (mean 4.056 months; 95%Cl: 1.964–6.147). The most important clinical features included seizures, disturbances of consciousness and focal neurological signs. Eight of the nine children were admitted to the hospital due to seizures and six patients had disturbances of consciousness. In two children external injuries were noted: bruises on the thighs and forearms on one child and bruises and on the head and orbital area on the other with skull fractures. Seven of the nine children had neurological focal signs (hemiparesis, spastic diplegia). In all of the children a CT scan and brain ultrasound (US) were the methods of attaining a visualisation of the brain All children demonstrated typical radiological features of brain injury for SBS/ITBI. All of them were originally diagnosed with SDH or SAH with unknown aetiology due to lack of appropriate history and knowledge.

SDH was diagnosed in five cases (surgery was needed in four children); SAH was diagnosed in one case and brain contusion in three cases.

RH in acute period was found in all 5 investigated children, 4 children were not investigated.

Three patients (3/9) were screened for coagulopathies, but all tests were normal.

The main finding of this study was a surprisingly high number of victims of SBS/ITBI confirming a need for appropriate nationwide study of this tragic and previously neglected subject.

5.2 Incidence of SBS/ITBI (Paper II)

During the epidemiological study (from January 1997 until December 2003), 26 children with SBS/ITBI was identified (Figure 2, Table 2). The population at risk during the study period used in calculation of incidence was 89002 (www.stat.ee). There were 5/26 children in the retrospective study group and 21/26 in the prospective study group (Figure 3). All of the children were younger than one year of age (Figure 4).

The incidence of SBS/ITBI was 28.7 (95%CI: 18.72–40.68) per 100 000 children under one year of age during the whole study period. Incidence rate was 40.5 (95%CI: 25.74–61.15) in the prospective study and 13.5 (95%CI: 4.36–27.52) per 100 000 children under 1 year of age in the retrospective study period. The incidence rate was 3.5 times higher in the prospective study (p=0.018).

There are 15 counties in Estonia, according to our data we have children with SBS/ITBI from 9 counties during the study period. Distribution of children with SBS/ITBI is in Figure 2, Figure 3 and Table 3.

Figure 2. Distribution of patients of our study group in Estonia according to the place of residence.

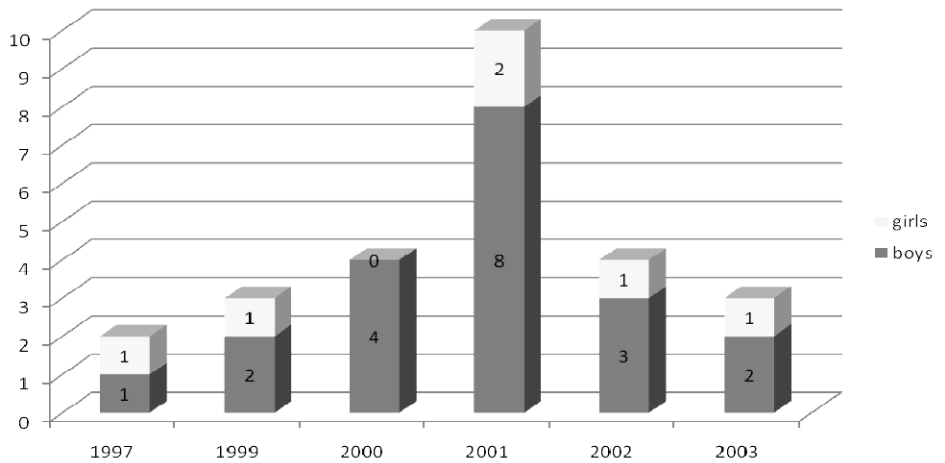


Figure 3. Distribution of patients according to the years of admission during the study period

Table 3. Distribution of children with SBS/ITBI in 15 counties of Estonia.

	SBS/ITBI	Number of children at risk	IR per 100 000
Estonia	26	89002	28.7
Harju county	6	32216	18.6
Hiiu county	0	706	0
Ida-Viru county	4	10829	36.9
Jõgeva county	1	2708	36.9
Järva county	0	2708	0
Lääne county	0	1893	0
Lääne-Viru county	1	4869	20.5
Põlva county	0	2072	0
Pärnu county	1	6059	16.5
Rapla county	0	2508	0
Saare county	0	2309	0
Tartu county	4	10974	36.5
Valga county	3	2482	120.9
Viljandi county	1	3958	25.3
Võru county	5	2614	191.3

The incidence rate of SBS/ITBI in different counties of Estonia is very variable, being remarkably high in Valga (121:100 000 for children under one year of age) and Võru counties (191:100 000 for children under one year of age). It is very interesting result but it has to be analyzed in the context of relatively small

numbers. There are some counties (Hiiu, Järva, Lääne, Põlva, Rapla, Saare counties) where not a single case of SBS/ITBI was diagnosed during the study period.

Among 26 patients there was 1 pair of twin boys with symptoms of TBI and one girl from the pair of twin girls and one boy from the pair of twin boys. All together 4 children were from pair of twins 15.4% versus to the number of twins in the Estonian population 2.12% (p=0.002; 95%CL: 2.1–24.8).

Boys were affected much more often than girls. Of the 26 affected children only 6 were girls (23%) and 20/26 were boys (77%). Male female ratio was 3.3:1.

The mean age on admission was 3.9 months (95%CI: 2.7–5.2). Boys were admitted at an earlier age, with the mean ages at admission for boys and girls being 3.4 (95%CI: 2.2–4.6) and 5.8 (95%CI: 1.5–10.2) months respectively, though this difference was not statistically significant (p =0.2275) (Figure 4)

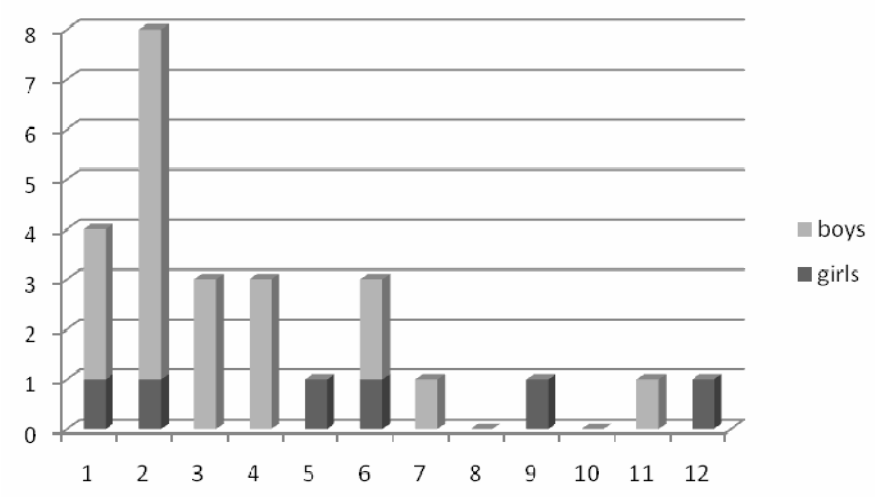


Figure 4. Distribution of children of study group according to age in months on admission

The possible relationship between of babies crying curve (by Hunziker et al. 1986) and the age on admission in weeks of our babies are demonstrated in Figure 5.

According to the outpatients records almost all parents (88.5%) of our study group (23/26) had contacted their family physicians and other specialists because of excessive crying of the baby prior to the admission to the hospital with SBS/ITBI (Figure 5) or death. The age on admission is in good correlation with the crying curve.

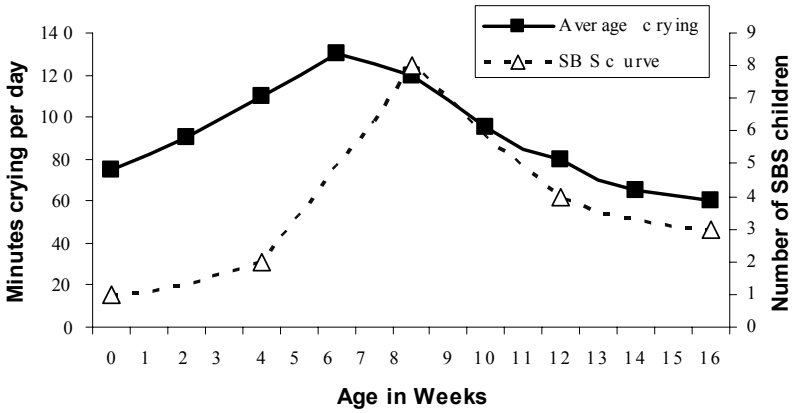


Figure 5. Average crying curve (Hunziker et al. 1986) and the age in weeks of study group on admission

According to the Figure 5 minutes of crying per day are highest from 4 to 10/12 weeks of age and mean age our study group at admission was 3.4 Mo (~14 weeks) for boys and 5.8 Mo (~24 weeks) for girls. It is important that 88.5% of parents of children involved in this study had complained about the excessive crying of their babies before the admission to hospital to medical professionals.

5.3 Clinical symptoms (Paper II, Paper IV)

The most frequent clinical signs (Table 2) in acute period were disturbances of consciousness in 20/26 (77%) of children, and seizures in 13/26 (50%) of all patients. Four children had vomiting as an additional clinical sign at admission.

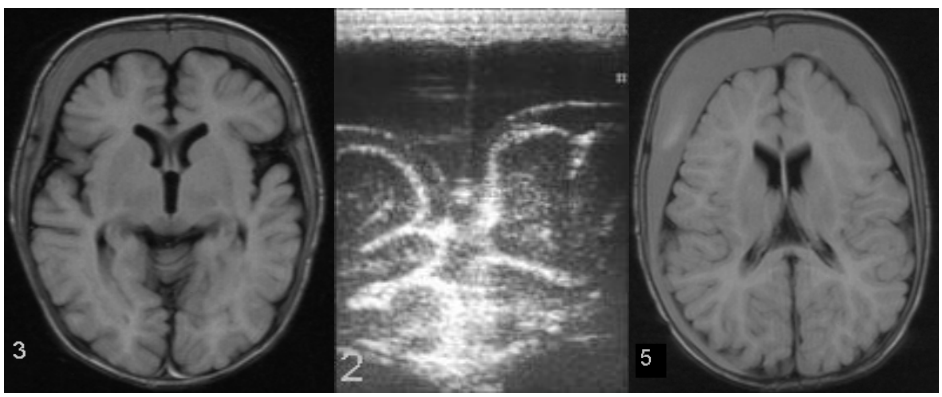
Seven (7/26) (26.9%) of these children had a GCS of 14. Children were either slightly irritated or less active than usual. In 3 children the GCS was 13 and in 10/26 children the GCS was 13−14 (38.5%). Only 8/26 (30.8%) were in critical condition with a GCS of <=8 with remaining 4/26 (15.4%) being in moderately severe condition (GCS of 9−12) Furthermore 3/26 (11.5%) had only developmental delay on admission to the hospital. A GCS is not available in four children who died (15.4%).

According to the proposed classification by Minns and Busuttil (2004) our patients were classified as follows: hyperacute encephalopathy 4 cases (15.4%) — all died and acute encephalopathy in 19 children (73.1%). Three patients were originally admitted because of developmental delay. Therefore it is impossible to guess their condition during acute stage.

Most of the children (22/26) had changes of muscle tone with brisk reflexes and positive Babinski signs, either bilateral or unilateral.

In case of seizures the EEG was performed (13/26).

Neuroradiology. 23/26 children were investigated with CT/MRI (Table 2); one of 23 died and had also autopsy. SDH were confirmed in 20/26 children (76.9%) (example on Figure 6), SAH in 3/26 cases (11.5%), intracerebral haemorrhages in 2/26 infants (7.7%) and epidural haemorrhage in 1 child (3.9%). In 9/20 cases the SDH were chronic and in 8/20 (40%) infants bilateral. In 9/26 (34.6%) there we signs of repeated injuries: SDH of different ages, old fractures (prior extracranial abuse). All children were consulted with neurosurgeons, surgery was performed in 9/26 (34.6%) of babies.



1. MRI 2. US 3. MRI

1. MRI — axial FLAIR (9000/105/2500) one day after admission to the hospital
2. US — coronal US at admission shows large, echo-free, bilateral subdural fluid collections. Note the arachnoid membrane and superficial veins within the subarachnoid space.
3. MRI — axial FLAIR two months later show growing of subdural collections RH-s were found in 57.7% (15/26) of children, of which 53% (8/15) damage was bilateral.

Figure 6. Bilateral chronic subdural haematoma in a 3-month-old boy with apnoea, stupor and mildly bulging fontanelle

Laboratory investigations for screening for coagulopathies included: protrombin, APTT and fibrinogen. Some patients with developmental problems or suspected developmental problems prior to the acute admission were also investigated for possible metabolic disorders (re: amino acids, organic acids). All screening tests for coagulopathies of these children (22/26) were within normal range, 5/22 children were screened for metabolic disorders (amino and organic acids) and no abnormalities were found.

Case report (Paper IV).

In order to highlight the continuing problems of recognising and diagnosing SBS/ITBI in time we described a three month old child diagnosed after this study was finished. The child was admitted to the PICU of Tartu University

Hospital due to disturbances of consciousness and seizures. CT scan revealed chronic subdural haemorrhages (one and two weeks old), brain oedema and skull fractures in the temporal and parietal regions. Three weeks before the parents were consulted at the county hospital because "something was wrong with child's leg". The X-ray was performed but fracture of the left femur was misdiagnosed. Analysis of history demonstrates that during following weeks the child developed two SDH in two consecutive weeks due to repeated shakings confirmed during hospital investigation at Tartu University Hospital.

At the age of 18 months on follow-up the right-sided hemiparesis, focal epilesy and developmental delay was diagnosed.

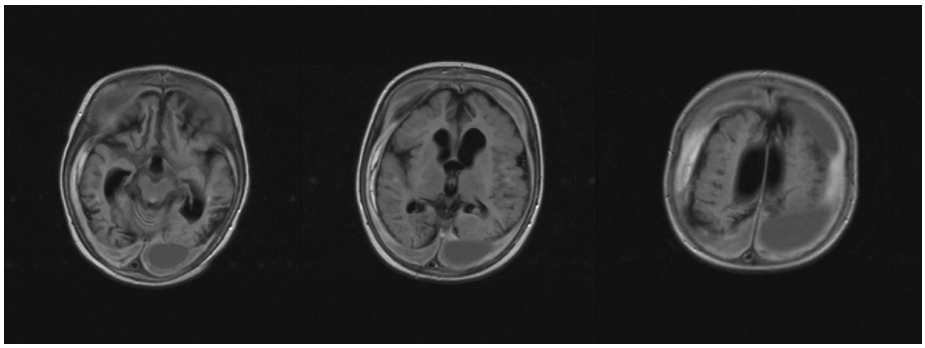
5.4 Outcome of SBS/ITBI

The follow-up study group included 22 children, all survivors (22/26) of the epidemiological study, 18 (82%) boys and 4 (18%) girls. Description of patients in acute period and during the follow-up is shown in Table 2.

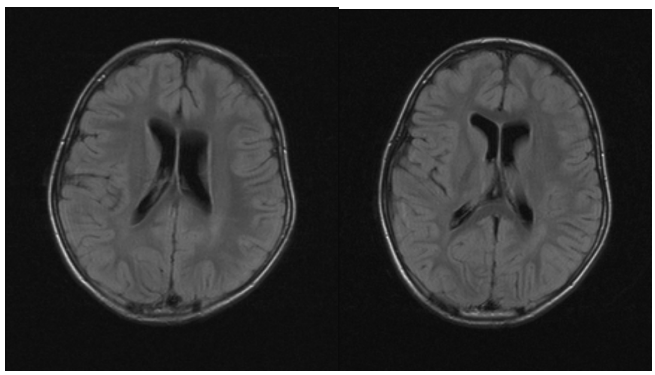
The mean age of children at follow-up was 5.2 years (range 2.4–9.0 years). The mean follow-up period was 4.67 years (range 2.3–8.6 years) (Table 2). A neurological assessment revealed severe motor problems in 5/22 children (22.7%), spastic tetraparesis in 2, hemiparesis in 2 and spastic diplegia in 1 case. 13/22 (59%) had light to moderate neurological symptoms which were also detected during psychological testing. Two children were institutionalized, one because of severe brain damage (hemiparesis, epilepsy) and abuse, while the other child was taken into the care of local authorities due to abuse.

Epilepsy was diagnosed on follow-up in 7/22 cases (32%), being intractable in 3 cases. All children with epilepsy were receiving antiepileptic medications: Phenobarbital, Valproic acid and Carbamazepin. All three of the children with intractable epilepsy also had severe motor problems: spastic tetraparesis in two and diplegia was present in one child. It is important to stress that epilepsy developed in 7 of 13 children who had seizures during the acute event.

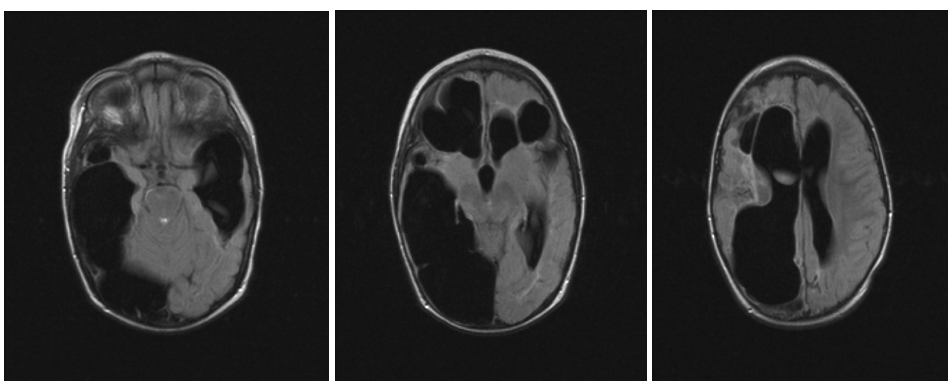
Imaging at follow up was performed with CT and/or MRT (T1-and T2 weighted imaging) in 20 of 22 survivors'. On Figure 7 several examples of imaginings are demonstrated. Normal imaging was found only in 1 child, mild signs of atrophy were present in 7, moderate in 8 and severe brain atrophy in 4 children. Parenchymal lesions were found during outcome investigations in 10 children. In 7 children lesions with high signal in T1 and T2 weighted images were found in periventricular white matter, 3 of them had the lesions in occipital lobe. In one child such focal lesions were found in thalamus. In two children large porencephalic cysts were found. Cortical atrophy, mainly in frontal region was diagnosed in all but one child.



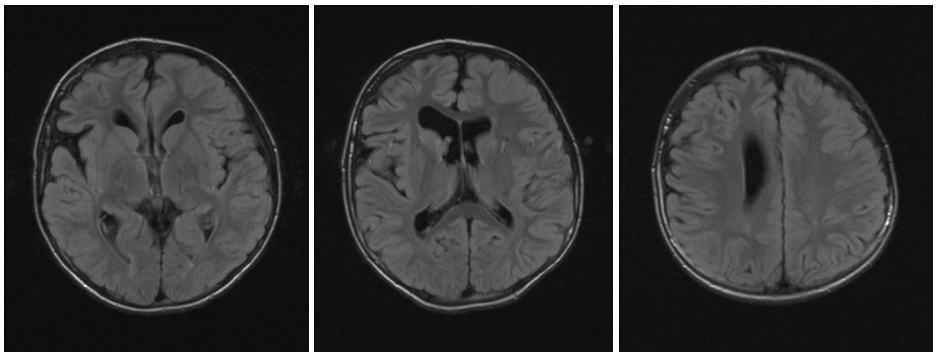
A.1 year and 4 months old boy with tetraplegia, profound developmental retardation and intractable epilepsy, MRI one year after the acute event



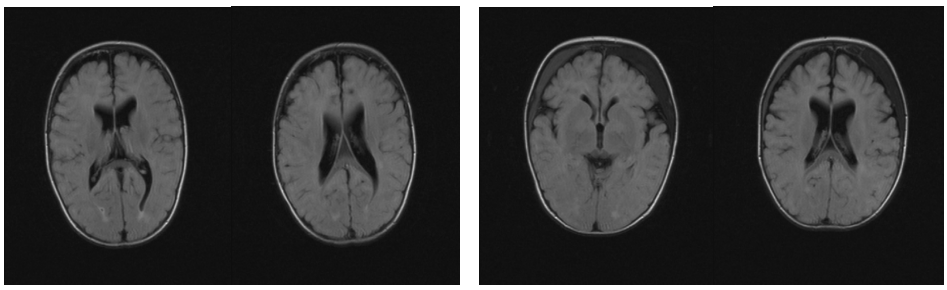
B. 3 years and 4 months old the boy is clumsy, has focal epilepsy, developmental problems (F83)



C. Four years old boy with spastic diplegia, intractable epilepsy and autism.



D. Nine years old boy, one of the two children who was considered healthy at the time of follow-up



E. A pair of (symptomatic in acute period) 1 year and 4 months old twins: spastic diplegia, developmental delay.

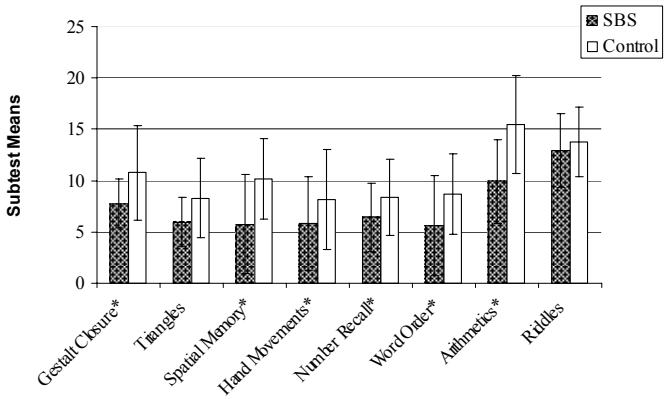
Figure 7. The examples of neuroimaging in some patients

The ophthalmological examination was performed in 17/22. Parents of five of the twenty-two children did not give their consent for ophthalmologic exam. Neither neurological examination nor psychological testing revealed major ophthalmologic problems in these children. In 4/22 (18%) patients serious ophthalmologic problems: i.e. optic atrophy and fibrous changes of retina were detected.

Delayed mental development was present in 17 /22 (77%) children: 3 children met the criteria for unspecified mental retardation (F79); in 2 children delayed milestones were diagnosed (R62.0); mixed specific developmental disorders (F83) were diagnosed in 11 and one child was found to have mixed disorder scholastic skills (F81.3) (Table 4). These children had been diagnosed by psychiatrists using the ICD-10 (1992). In five children psychological tests were within normal range.

Five children were excluded from psychological testing, four children because of severe developmental problems. One child was under the age limits of K-ABC

test 2 years and 6 months, the child was 2 years and 4 months. For final analyses with the K-ABC test, 17 children were included. We compared the development and cognitive profile of the SBS/ITBI children with the control group. The control group's performance was better in all of the K-ABC subtests (Figure 8)



* subtests differences are statistically significant: SBS (ITBI) children performed worse than control

Figure 8. Results of K-ABC subtests in control group and SBS group

A Mann-Whitney U test showed statistically significant differences (* $p < 0.001$) in all three sequential information processing subtests (Hand Movements, Number Recall, Word Order), two of three simultaneous subtests (Gestalt Closure, Spatial Memory) and in one achievement subtest (Arithmetics) (Table 4).

Table 4. K-ABC subtests differences in the SBS and control groups

	N		Median		U	Z	p-level
K-ABC subtests	SBS	Control	SBS	Control			
Gestalt Closure	17	95	6	11	424,5	–3,11	**0**
Triangles	17	95	6	9	579,5	–1,85	0,06
Spatial Memory	12	71	5	10	179,5	–3,19	**0**
Hand Movements	17	95	6	7,5	450,5	–2,89	**0**
Number Recall	17	95	6	8	451	–2,89	**0**
Word Order	17	94	5	8	439	–2,95	**0**
Arithmetic	15	95	7	16	378,5	–2,91	**0**
Riddles	11	95	14	14	471,5	–0,53	0,6

Children with SBS/ITBI performed these subtests significantly worse compared to children from the control group. We concluded that K-ABC subtests are suitable in order to differentiate two groups of children — those considered control and those with SBS/ITBI.

We do not address behavioural problems separately here, on most occasions they were related to mental development.

All children were scored according to GOS (Figure 9) and RDS (Figure 10).

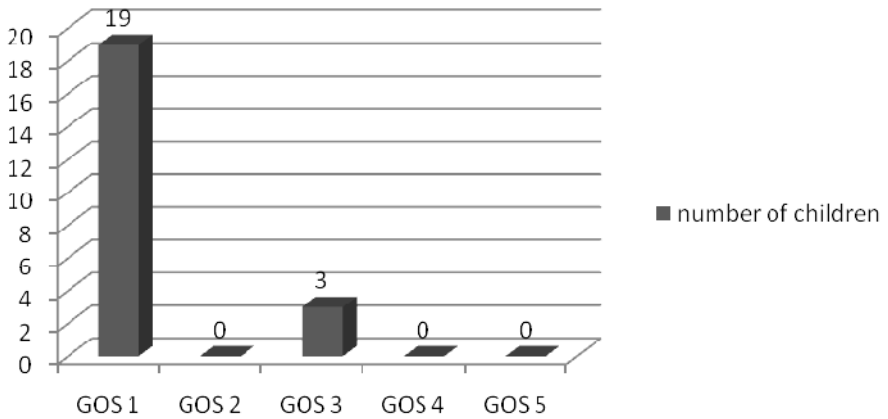


Figure 9. Distribution of patients according to GOS

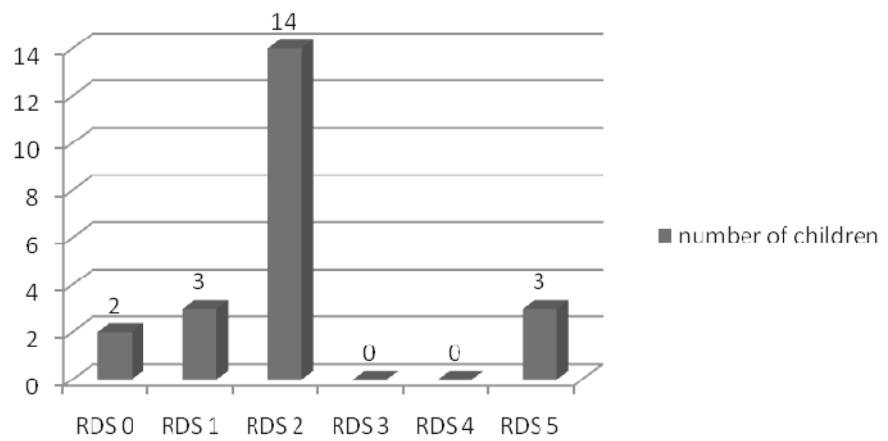


Figure 10. Distribution of children according to RDS

We found a statistically significant correlation between age at admission and outcome: the younger the age at injury the worse the outcome. The mean age at admission for a severe disability (GOS=3) was 1.7 (range 1–3) months and for a good recovery (GOS=1) the mean age was 4.1 (range 2–11) months (p=0.0505). We did not find a statistically significant correlation between the GCS and outcome scores, however there was a tendency towards correlation between the GCS and GOS (r=0.373; p=0.087). According to the RDS we found that only 2 children (9.1 %) were considered healthy, 3 (13.64%) had no significant disability despite minor symptoms (e.g. clumsiness, attention problems), 3 were severely disabled (13.64%) and 14 had a slight disability (63.62%).

According to the RDS (Figure 10) 2 children scored as healthy, 2 had slight disability, 14 had moderate disability and 3 were severly disabled. Expert opinion of two specialists who scored the children was more concordant with the RDS than the GOS. The RDS gives also large variability for scoring these children. There no differencies of expert opinions in the GOS of two speicalists but there was differences in 2 children scored with the RDS. The results of psychological tests was also more concordant with the RDS than the GOS.

Only 2/22 (9.1%) children were considered healthy at the time of follow-up.

5.4.1. Autopsy

Four children (two boys and two girls, aged from four days to one year) died. One baby was dead on arrival and one child was brain dead on admission and died 24 hours later, 2 children were identified from forensic database. The mortality rate in our study group was 15.4% (4/26). All four of the dead children were subjects of a forensic autopsy. In two cases a SDH was identified, one child had an epidural haematoma (with impact) and one had a SAH. In one who died at hospital the results of imaging showed brain oedema and SAH that was confirmed on autopsy. Retinal changes were identified in two cases: haemorrhages in one and ischemic changes in another. One of the babies had several ischemic areas in the brain, which could have been the result of repeated shaking/violent behaviour by caretakers. All of the children had several bruises on different areas of the body.

6. DISCUSSION

6.1. Incidence of SBS/ITBI

After the first diagnosis of SBS/ITBI in December 1999 we hypothesized that this is a rare syndrome in Estonia, but the pilot study confirmed higher incidence than expected of SBS/ITBI in Estonia and a nationwide study was initiated.

It is important to stress that there is no consensus on the terminology of SBS/ITBI. Though Richards et al. suggested the term "head injury" instead of SBS in 2006 it may not be the best option. The problem with the head injury definition is in its meaning — so by definition the mechanism of damage is unclear. According to this term "head injury" may include different kinds of inflicted brain injuries, while SBS refers to only one specific form of child abuse — inflicted brain injury by shaking the baby violently. Unfortunately the term "SBS" is really emotional, understandable to everybody and very clear, while other terms may and have caused confusion especially in the multilingual context. Without simple and concrete terminology scientific research is impossible. Unfortunately it was very clearly shown by Donohue (2003) in his attempt to meta-analyse all articles on SBS. According to our understanding the term "shaken baby syndrome" may be the best term for this condition in spite of its' social impact, but in literature during the last years the term "ITBI" is more often used.

The incidence in whole study group of SBS/ITBI in Estonia was 28.7 per 100 000 children under one year of age. It is important to underline that the children posed a diagnostic problem for doctors earlier as during the retrospective study most of the diagnoses were along the lines of:"subdural haematoma of unknown origin". This shows that the doctors were concerned when the history was not consistent with injuries. All children were thoroughly investigated for different pathologies but the possibility of child abuse (SBS) was not mentioned in case reports.

In the prospective study the incidence was 40.5:100 000 for children less than one year of age what is three times higher than in retrospective study 13.5:100 000 (40.5:100 000 vs 13.5:100 000 p=0.018). These results of our study confirmed the fundamentally different results from retro- and prospective studies demonstrated in literature and underline the importance of prospective studies. It is important to stress that the incidence of SBS/ITBI in our prospective study is almost two times higher (40.5:100 000 children under 1 year of age) than reported in the literature (24.6-29.7 per 100 000 children under 1 year of age Barlow et al. 2000, Keenan et al. 2003). Some authors (AAP 2001, King et al. 2003) are convinced that the reported incidence is the tip of iceberg and the actual incidence of SBS/ITBI is much higher but is difficult to establish (Fung et al. 2003). We are convinced that the incidence 40.5:100 000

per children under one year of age is the real incidence for severely and moderately injured infants with SBS/ITBI in Estonia, however some infants with mild injuries can be missed. This is be supported by the fact that incidence in different counties in Estonia is very variable being as high as 120.9 per 100 000 in Valga county and 191.3 per 100 000 children under one year of age in Võru county and no children with SBS were diagnosed in Lääne, Hiiu, Saare, Põlva, Rapla and Järva counties during the study period. The differences in the distribution of abused children may reflect relatively small number of children involved in the study but also access to medical care and the quality of care.

Discussing the reasons for high incidence of SBS/ITBI in Estonia is important to underline the well developed medical network with well educated doctors, good cooperation between family doctors and specialists of tertiary paediatric hospitals, and existing consensus documents, which have gave us possible to collect so many (almost all) patients. The same importance is the existence of protocol for evaluation the children with suspicion to SBS/ITBI in tertiary hospitals. However, why the SBS is so high in Estonia — is there some other possible explanations also available. It is interesting to find the clues to possible relations between stressful events and increased incidence of SBS/ITBI in literature. Keenan et al. (2004) demonstrates the increased incidence of both nTBI and SBS/ITBI after a natural disaster in North Carolina. Hurricane Floyd in North Carolina produced both, an increase in psychiatric symptoms as well as financial hardship and a loss of social ties for the families caught in the flooding. According to Keenan et al. (2004) it is possible that these factors played a role in the increase in SBS/ITBI and nTBI seen in eastern North Carolina. It is important to note that the increased risk of SBS/ITBI extended well past the immediate disaster period — returning to baseline in 6 months post-hurricane (Keenan et al. 2004). Parental stress has been related to child maltreatment in the first year of life (Keenan et al. 2004). We can speculate according to these data that the high incidence rate of SBS/ITBI in Estonia may result from parental stress due to different social reasons. Some support to this hypothesis gave the survey of Happy Planet Index where the people of Estonia are on the 173 place among 178 countries investigated (http://en.wikipedia.org), being the unhappiest population in Europe (http://www.neweconomics.org) and it once again underline the need for changes in governmental social care of people in Estonia.

The missing children with mild forms of SBS/ITBI may come to medical attention years later with chronic brain injuries and/or developmental delays, misleadingly interpreted then as perinatal brain damage (CP), described also by Gill et al. (2007). However, it is out of the scope of the study to find these children.

Our study is the very first nationwide report in Estonia on the incidence of SBS/ITBI highlighting the young age of victims (mean age of 3.9 months Figure 4). It is also important to stress that boys are at a greater risk of having SBS/ITBI as in our study group a predominance of boys is clearly pronounced

(3.3:1). The number of twins is high in our study (one pair of boys both having signs of SBS/ITBI; one girl from pair of twin girls and one boy from the pair of twin boys). Alexander et al (1996) emphasised the need of careful investigation (including MRI) of other children younger than 2 years of age in the family of children with SBS/ITBI. The week point of our study is that we did not examine other young children including twin brothers/sisters of these families.

In our study the mean age for boys at admission was 3.4 months and for girls 5.8 months, however this difference was not statistically significant. The children with SBS/ITBI in other studies are often older with mean age of 5.9 months in a study by Keenan et al. (2003) and 10.6 months in the report of Morad et al. (2002). In the study from Canada (King et al. 2003) the mean age of the infants on admission was 4.6 months which is quite similar to age of infants in our study. The tendency towards a younger age of patients with inflicted brain traumas (SBS) (mean age 10.6 mo) than in noninflicted brain traumas (35.6 mo) was reported by Ewing-Cobbs et al. (1998). The comparison of data in the literature is presented in Table 5.

Table 5. The number of patients, age on admission and mortality rate in different studies.

Author	Number of children	Mean age on admission	Died / %	Survivors
Ludwig et al. 84	20	5.8 mo	3 (15%)	17
Goldstein et al. 93	14	1.6 years	5 (36%)	9
Fischer 94	25	4.1 mo	4 (16%)	21
Holloway et al. 94	49	1 mo-8 year 30 children under 1 year	7 (14%)	42
Cho et al. 95	23	5.9 mo	3 (13%)	20
Duhaime et al. 96	84	6.4 mo	22 (26%)	62
Haviland et al. 97	15	7.6 mo	2 (13%)	13
Gilles et al. 98	14	12.2 mo	3 (21%)	11
Kivlin et al. 00	123	< 3 y	36 (29%)	87
Barlow et al. 00	44	5.9 mo	6 (14%)	38
King et al. 03	364	4.6 mo	69 (19%)	295
Karandikar et al. 2004	65	< 2 y	16 (24.6%)	49
Keenan et al. 2004	80	4 mo	18 (22.5%)	62
Talvik et al. 2006	**26**	**3.9 mo**	**4 (15.4%)**	**22**

It is important and interesting to stress that there were no children older than one year in our study. It is difficult to explain the young age of the children with SBS/ITBI in our study. But one possible explanation can be that the age of babies at admission to the hospital in our study is close to maximal crying periods according to Hunziker et al. (1986) (Figure 5). This is supported by our data demonstrating that 88.5% of parents of our children have complained about excessive crying of their children before admission to the hospital. It seems fair to conclude that parents need more information about the crying periods and reasons for crying in advance to minimize parents' frustration at crying and physicians should be more alert with parents complaining the excessive crying to prevent the brain injury. The influence of teaching and widely spread information can explaine also some decrease in the numbers of children with SBS/ITBI from year 2002, but the regular teaching courses for doctors and society should continue.

6.2. Clinical symptoms

The most frequent clinical sign in the children with SBS/ITBI was disturbances of consciousness. However, 10/26 (38.5%) children scored 13–14 on GCS. This demonstrated that despite of remarkable brain injury a considerable number of children were clinically in quite stable condition, which could be the reason for a misinterpretation of clinical signs. Only 8/26 (30.8%) were in critical condition with a GCS <=8, however, there were no data available for the dead children (4/26). The second most frequent clinical symptom were seizures in thirteen children (13/26–50%) (Table 2). Our data are in quite good correlation with other studies reporting the seizures in 45% (King et al. 2003) to 80% of children as a presenting symptom (Barlow et al. 2000b). Therefore, the presence of seizures without clear evidence of infection (temperature, laboratory evidence of infection) should be the indication for CT /MRI investigation in children under one year of life. Other neurological symptoms reported in our study (increase of muscular tone, brisk reflexes', Babinski signs etc) are also described by other authors (Minns and Busuttil 2004). However we do not find very helpful the classification proposed by Minns and Busuttil (2004) in our children.

RH were found in 57.7% of the children in our study. That is close to the numbers reported in literature 37.5%–85% (Duhamie et al. 1992, Goldstein et al. 1993, Ewing-Cobbs et al. 1998, Levin 2000, Morad et al. 2002, King et al. 2003) underlining the importance of ophthalmological investigation in these children.

The most frequent neuroradiological finding in our study group was SDH in 76.9% (20/26) of children which is similar to other studies. Morad et al. (2002) found SDH in 70/75 (93%) of SBS victims. Kivlin et al. (2000) in a post

mortem study of 27 children with SBS/ITBI demonstrated the presence of SDH, SAH or both in 25/27 (92.5%) of cases. All children in our study group were consulted by neurosurgeon, surgery was performed in 9/26 (34.6%) of children. It is also important to mention that 30–40% of the children with SBS/ITBI are repeatedly injured according to Alexander et al. (1990). Our study confirmed the same results — 34.6% of children (9/26) had repeated brain injury. Repeated brain injury was described also in the child from case report (paper IV). This is again stressing the importance of timely diagnosis and recognition of this syndrome to prevent repeated shaking.

It was an interesting observation that three children with SBS/ITBI had only developmental delay on admission. We are the only ones who have described developmental delay as presenting symptom of SBS/ITBI. These children are the ones most difficult to find and to diagnose, but in Estonia according to the consensus all children with developmental delay should be consulted (and investigated) in tertiary hospital by specialists for finding the causes. It is well documented that SBS/ITBI causes developmental arrest. On the other hand, given a large number of causes for developmental delay most certainly this is not the first diagnosis to suspect in this relatively common problem in the setting of paediatric/child neurology clinic. In our study group the clinical findings of children were limited to developmental delay but neuroradiological investigations revealed bilateral chronic SDH in all three children in the context of appropriate or missing history of brain damage. These findings are similar to authors reporting developmental delay in SBS/ITBI later (Ewing-Cobbs et al. 1998, Kuijraoka et al. 2004, Barlow et al. 2005).

Our data confirmed the matching time period of average maximal crying curve and SBS/ITBI curve (Figure 5) with about 2 weeks difference. This time lag from theoretical maximal crying time to statistical median time to shaking the baby by frustrated caretakers may be the last minute for specialists to counsel the parents if this is not done earlier. Most of the parents had been complaining before the event about child's excessive crying.

We may hope that the decreased number of children diagnosed with SBS/ITBI after 2002 (Figure 3) does not reflect decreasing interest in this subject with the end of this project but rather reflects increased awareness of professionals and society. It has been shown that the actual duration of crying at the given moment seems to be less relevant than the parents' perception of the crying of their infant in the long term (Reijneveld et al. 2004). Therefore, every time professionals are approached by a caretaker complaining of their babies' excessive crying this problem should receive quick and full attention by several specialists.

It is interesting that there were no surviving children with external signs of injury in our study group. It is possible that in spite of training medical professionals did not search thoroughly for milder external injuries.

It is important to bring forth that since early 2000 seminars and lectures concerning SBS/ITBI were introduced to inform and teach all medical

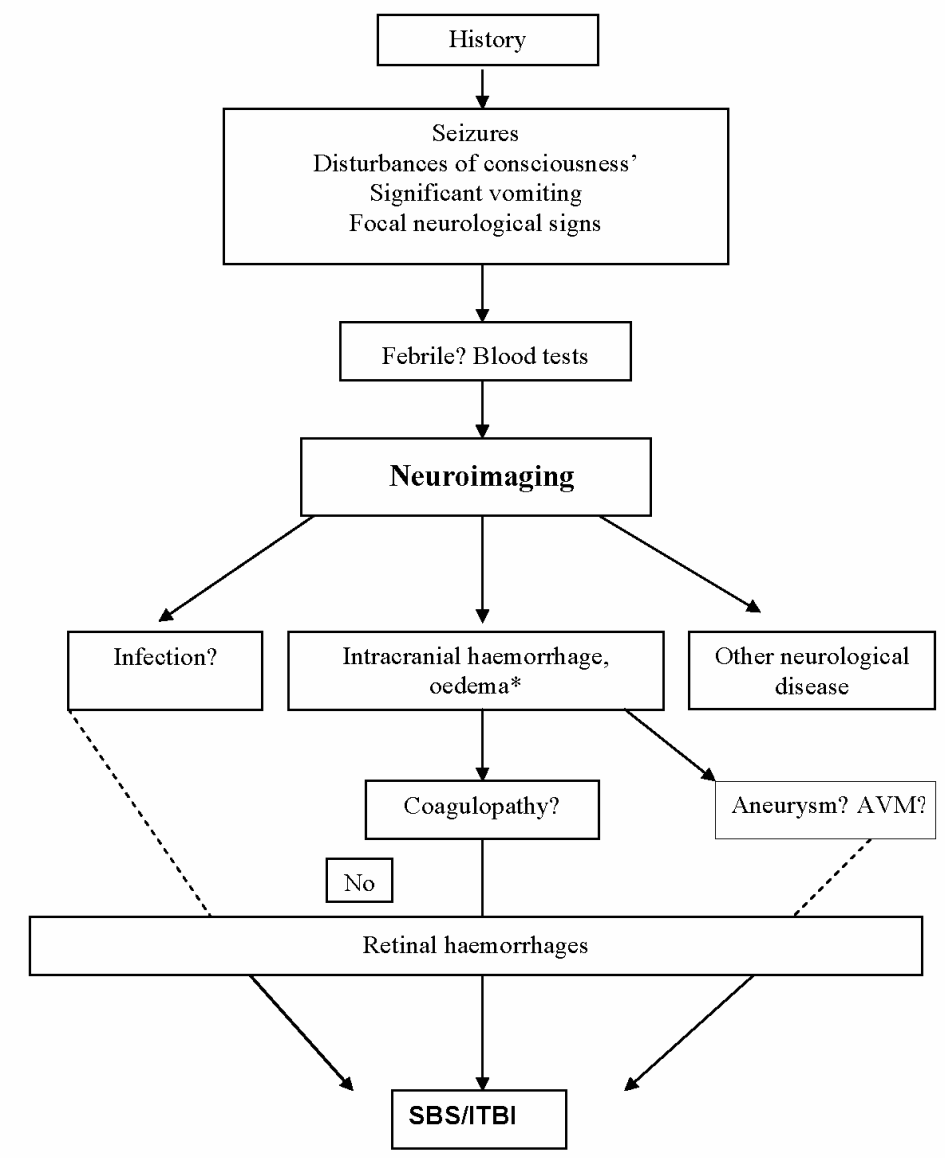
personnel and social workers about this particular form of child abuse. Also the information by special articles was spread via newspapers, local journals, women's journals to inform the society about the importance of delicate handling of babies and the dangers of shaking them. During the study period several teaching courses (seminars, lectures) for family physicians, paediatricians, paediatric neurologists and intensive care doctors were held with lecturers coming from other countries (particularly the US and the UK). This may be the reason for the identification of a relatively high incidence of SBS/ITBI in our study group, as the professionals were more attuned to the recognition and diagnosis of SBS/ITBI. The fact that from year 2002 the number of children with SBS/ITBI has decreased and stayed quite stable could support the success of teaching the society on different levels.

It is important to think about possible SBS/ITBI when the history and clinical signs are conflicting. The presenting signs and symptoms on admission may be non-specific (e.g. vomiting, seizures, disturbances of consciousness), which makes diagnosis difficult. On the other hand, timely diagnosis could save least 1/3 of children from repeated injuries. Therefore we propose the simplified diagnostic algorithm to diagnose the SBS/ITBI (Figure 12).

Besides the importance of early diagnosis of SBS/ITBI and preventing repeated shaking, the key issue is the prevention of child abuse per se. Today several teaching courses for doctors, health care specialists and medical students have been introduced to spread the information of SBS/ITBI in Estonia. SBS/ITBI is a compulsory component of all advanced educational programs for family doctors and medical students in their sixth year during medical school.

Important step was the opening the "crying/irritable baby" clinic in 2002 at Children's Clinic of Tartu University Hospital with specially trained multidisciplinary team (child neurologist, paediatrician, psychologist) to consult the babies and to support parents who feel that their babies are crying too much. This altogether may be the reason for the decrease of the number of cases with SBS /ITBI from 2002.

During the pilot study in most of the cases (71%) the children were at home with their father prior to the injuries which is consistent with the data in the literature (King et al. 2003). In a study by King et al. (2003) the perpetrator was identified in 66% of cases, with the biological father being most common (50%), followed by the stepmother/male partner (20%) and then the biological mother (12%). Why the male person are more often the perpetrators is complicated to explained, may be their resistance to babies crying is less pronounced as far the feelings being father are not so natural as being a mothers ones after nine months living together. During the nationwide study, according to police recommendation no specific questions about the caretaker of the child before the admission were asked by medical personnel. This should be a task for police officers.



* see imaging

Figure 12. When to think about possible SBS/ITBI?

The difficulties in the diagnoses of SBS/ITB even after an implementation of a good programme was well demonstrated in the case report (paper IV) of the three months old boy with undiagnosed femur's fracture at the first contact with medical professionals who was admitted in critical condition 3 weeks later with two subdural haematomas and with poor outcome in 18 months. We can speculate that if the fracture was diagnosed during the first visit the following events of shaking could have been prevented.

6.3 Outcome

The results of our prospective population based outcome study confirmed that SBS/ITBI is a serious medical and social problem. In the survival group only 2 /22 children (9.1%) were considered healthy and only one of them had normal brain MRI. Three children were severely disabled (13.5%). All of the other children 17/22 (77.5%) had some degree of neurological and/or developmental problems with pathological findings on MRI. Keenan et al. (2006) stressed that young children with SBS/ITBI have a much worse outcome than the older ones. Our study confirmed these results: there was a significant correlation between the younger age at insult and worse outcomes ($p=0.0505$). The literature about pathogenesis and autopsy report has stressed the importance of axonal damage in SBS (Geddes et al. 2001, Reichard et al. 2003, Dolinak et al. 2006), some authors point out the possibility of combined injury (Ghatan et al. 2002). The results of MRI investigations in our study group during the follow up period showed the white matter damage was pronounced in almost all children. Cortical atrophy, mainly in frontal region was diagnosed in all but one child. Several authors (Eslinger et al. 2004, Barlow et al. 2005) have described the frontal atrophy in the context of behavioural problems. Our results of cortical atrophy in children with SBS/ITBI are in good correlation with these results, however specific analysis of behavioural problems was out of scope of this study. Three children of our study group had atrophy in occipital area associated with cortical visual impairment also described by Barlow et al (2005).

The group of families of children with SBS/ITBI are a very fragile group for follow-up studies. After the diagnosis of child abuse is made they often are reluctant to participate in any kind of further medical investigations. This is a common problem for all follow-up studies of SBS/ITBI victims. The comparison of outcome of survivors in our study with other studies from the literature is presented in Table 6.

Table 6. The results of outcome studies (including our study)

Author	Number of children with follow-up data/ number of survivors	Follow up period	Severe disability	Moderate disability	Mild disability	Healthy children
Ludwig et al.19 84	17/17	NA	Morbidity 10 (50%)			7 35%
Goldstein et al. 1993	9/9	Discharge	7 50% Vegetative 1 (7%)			1 7%
Fischer et al. 1994	10/21	10.1 y (8-15 y)	6 60%		1 10%	3 30%
Holloway et al. 1994	42/42	Discharge	19 39%		14	9 39%
Bonnier et al. 1995	13/21	7 y	Vegetative 1 (7%) 3 (23%)	4 (17%)	3 23%	1 7%
Cho et al. 1995	20/20	3.2 y	Vegetative 3 13% 9 (39%)	4 (17%)		4 17%
Duhaime et al.1996	14/62	9 y	6 (43%) One died on follow-up	2 (14%)		5 36%
Haviland et al. 1997	13/13	3mo-3y	7 (47%)	4 (27%)	1 7%	1 7%
Gilles et al. 1998	11/11	1.5 y	6 (55%)	3 (27%)	2 (18%)	
Ewing-Cobbs et al. 1999	28/28	3 mo	4 (17%)	17 (61%)		7 (25%)
Kivlin et al. 2000	56/87	2.2 y	26 (46%)		8 (14%)	22 (39%)
Barlow et al. 2000	36/38	3 y	8 (19%)	8 (19%)	6 (14%)	14 (33%)
King et al. 2003	295/295	Discharge	34 (12%) vegetative	143 (48%)	97	21 (7%)

Author	Number of children with follow-up data/ number of survivors	Follow up period	Severe disability	Moderate disability	Mild disability	Healthy children
Bonnier et al. 2003	23/23	6 y	14 (61%)	8 (35%)		1 (4%)
Karandikar et al. 2004	45/49	2 y	11/45	6/45		25/45
Keenan et al. 2004	62/62	Discharge		28 (75.7%)		34 (45.3%)
Keenan et al. 2006	41/62	1 y		29		12
Barlow et al. 2005	25/55	3.3 y	36%	16%	16%	
Talvik et al. 2006	**22/22**	**4.67 y (2.3–8.6)**	**3 (13.64%)**	**14 (63.62%)**	**3 (13.64%)**	**2 (9.1%)**

*NA- not available *y — years *mo - months

A longer follow-up period is reported by Karandikar et al. (2004) Bonnier et al. (2003) and Barlow et al. (2005) with very different outcome results: the number of healthy children being variable from 4% to 55 %. The strength of our follow up study lies in the inclusion of all survivors and was not influenced by the severity and consequently not by outcome of included children. Therefore we hope that it is demonstrating a realistic picture of outcome of a population-based group of children with SBS/ITBI.

Probably, factor like the young age of our children that adversely influenced the outcome was also important (Talvik et al. 2006, Makaroff et al. 2003).

Our study demonstrated that 91% of survivors had problems. It does not differ from other studies reviewed by Makaroff et al. (2003). This also proves that despite these children being in a more or less stable clinical condition during the period of abuse (10/26 children had the GCS =>13), they experience a lot of developmental problems later. However, our data are not final, as far as stating that a mixed specific developmental disorder could be a significant sign for much more serious problems in the future (such as conduct problems, learning disabilities at school age). It is important to stress that in order to show the real outcome of these children long-term follow-up studies are needed, including a consensus on outcome measures used.

In addition, evaluating outcome depends on selected outcome measures and times of follow-up.

To evaluate the possible difference between two outcome scoring systems we scored all children both with GOS and RDS. According to the GOS *good recovery* (GOS 1) also includes minor motor and physical deficits (Appendix 3), which can sometimes be misleading and giving the impression of a relatively good outcome for these children. In our study we used the expertise of two investigators to compare the results of the GOS and RDS. According to the GOS the outcome of our children was GOS 1 for 19 of children and GOS 3 for 3 patients; however, it does not reflect the large variety of the problems of these children. Using the RDS according our results was more reliable and the results of two investigators were a different in only in two cases: whether to classify these two children in RDS 2 or RDS1.

In summary, according to our analysis with GOS and RDS there was a remarkable difference in the results. GOS scored good results for most of the children — it was possible to classify most of them as having good outcome (Figure 10). The results of RDS according to our opinion were more informative and reflected more the real range of problems (Figure 11).

It is very important to stress that there is no one good outcome measure for children after TBI. The RDS is more informative giving large range information to group children for a scientific research but a combination of outcome scales and psychological testing is most informative and reliable for individuals.

Serious visual impairment (such as: optic atrophy, fibrous changes of retina) was found in 4/17 (23%) investigated patients. In our study neither a neurological examination nor psychological testing revealed any major visual

problems in five children who were not examined as their parents were claimed that they did not have any visual problems. This is consistent with other authors who describe visual problems in 25% of survivors (Kivlin et al. 2000), however Barlow et al. (2005) described that 40% of survivors had significant impairment and furthermore they assumed that the abnormalities may be underestimated.

At the same time psychological tests revealed problems with visual information processing (Gestalt Closure, Word Order, Arithmetic), visual and auditory memory (Spatial Memory and Number Recall) and visuomotor integration and memory (Hand Movements) — in these subtests the differences between the study group and control group were statistically significant. Kivlin et al (2000) have shown that visual impairment can result from occipital lobe injuries, as it was documented in our three children.

Our results showed the disturbances in functions that can have prognostic value for educational achievements. Memory plays a significant future role in learning and affirming academic achievement (Arithmetic). To assess factual and acquired knowledge we used two subtests: Arithmetic and Riddles. We found differences between SBS/ITBI and the control group only in Arithmetic, but not in the Riddles, which is more sensitive to verbal skills and knowledge. To control the stability of these results acquired knowledge and verbal skills should be tested again more specifically after some years as verbal knowledge will be of great importance in academic achievements.

Long-term follow-up study after SBS/ITBI is needed especially before school and during the first school years for a final establishment of the cognitive functioning of these children in order to reveal the squeal on cognitive function in order to create of individual habilitation programs based on the results of tests.

The number of children taken into the care of local authorities in our study is very low compared to other countries but this is due to our legislation system.

Differences in outcome are due to heterogeneous group of patients in different studies: either PICU patients (Cho et al. 1995, Haviland et al. 1997) or those admitted to hospital due to disturbances of consciousness (Keenan et al. 2006, Barlow et al. 2005). Our study included patients admitted due to developmental delay and because of clinical findings and the results of examinations the diagnosis of SBS/ITBI was confirmed. Taking into account the high incidence of SBS/ITBI in Estonia and the large variability of outcome we could speculate that this could be the true incidence for severe and moderate cases of SBS/ITBI and outcome for these children is poor.

7. CONCLUSIONS

1. The incidence of SBS/ITBI (40.5 per 100 000 children under one year of age) in Estonia is highest in the world published in the literature (in Scotland 24.6 and in North Carolina 29.7 per 100 000 children under one year of age) and was almost three times higher in prospective study than in retrospective study (13.5 per 100 000 children under one year). The mortality rate was 15.6%.
   - Boys are at greater risk (boys/girls ratio is 3.3:1) to have SBS.
   - Boys are admitted at an earlier age (mean 3.4 mo, girls 5.8 mo).
   - Twins are at greater risk ($p=0.002$).
2. Disturbances of consciousness and seizures without evidence of infection are highly suggestive of SBS/ITBI and indication for neuroimaging.
   - Most of the children (GCS > 13 in 10/26) were in stable condition on admission in spite of serious brain injury (SDH in 76.9%, SAH 11.5%).
3. The outcome the children with SBS/ITBI, potentially healthy children is devastating:
   - 90.9% of children have developmental problems.
   - Severe motor problems were found in 5 children (22.7%) (spastic tetraplegia in 2 children, spastic hemiparesis in 2 children, spastic diplegia in 1 child).
   - Three of the twenty-two (13.64%) were severely disabled; the remainder 17 had various degrees of motor and/or cognitive dysfunction.
   - Epilepsy was diagnosed in 7/22 (32%) with SBS/ITBI, being intractable in 3 cases.
4. The most informative tool was Rankin Disability score in evaluation of outcome of children with SBS/ITBI. According to Rankin Disability only two children scored as healthy. Glasgow outcome score was not that informative.
5. Cognitive dysfunction was documented in all 17 SBS/ITBI children tested with K-ABC. All children (17) scored lower than control group ($p<0.001$).

REFERENCES

Agran PF, Anderson C, Winn D, Trent R, Walton-Haynes L, Thayer S. Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age. Pediatrics. 2003 Jun;111(6 Pt 1):e683–92.

Alexander RC, Levitt CJ, Smith WL. (2001). Abusive head trauma, in: *Child Abuse: Medical Diagnosis and Management*, 2nd ed. R.M. Reece and S. Ludwig (eds), Lippincott, Williams & Wilkens: Philadelphia, pps. 47–81.

Alexander RC, Sato Y, Smith W, Bennett T. Incidence of impact trauma with cranial injuries ascribed to shaking. Am J Dis Child 1990; 144:724–6.

Alexander RC, Smith WL. Investigating abuse in the asymptomatic twin. Archives Pediatrics & Adolescent medicine 1996; 150(4): 444–445.

American Academy of Pediatrics Committee on Child Abuse and Neglect. Shaken baby syndrome: Rotational Cranial Injuries — Technical Report. Pediatrics 2001; 108:206–210.

American Academy of Pediatrics. Diagnostic imaging of Child abuse Pediatrics 2000 (updated online 2007); 105:1345–1348.

Ball WS Jr. Nonaccidental craniocerebral trauma (child abuse): MR imaging. Radiology 1989; 173:609–610.

Barlow KM, Gibson RJ, McPhillips M, Minns RA. Magnetic resonance imaging in acute non-accidental head injury. Acta Paediatr 1999;88: 734–40.

Barlow KM, Milne S, Minns RA. A retrospective epidemiological analysis of non-accidental head injury in children in Scotland over the last 15 years. Scott Med J 1998; 43:112–14.

Barlow KM, Minns RA. Annual incidence of shaken impact syndrome in young children. Lancet. 2000 Nov 4;356(9241):1571–2, a.

Barlow KM, RA. The relationship between intracranial pressure and outcome in non-accidental head injury. Dev Med Child Neurol 1999; 4: 220–225.

Barlow KM, Spowart JJ, Minns RA. Early posttraumatic seizures in non-accidental head injury: relation to outcome. Dev Med Child Neurol.2000;42:591–594, b.

Barlow KM, Thomson E, Johnson D, Minns RA. Late neurologic and cognitive sequelae of inflicted traumatic brain injury in infancy. Pediatrics, 2005; 116(2): e174–85.

Barlow KM, Thompson E, Johnson D, Minns RA. The neurological outcome of non-accidental head injury. Pediatr. Rehabil. 2004 **7,** 195–203.

Bechtel K, Berger R. Inflicted traumatic brain injury: making the diagnoses in the emergency department. Clinical Pediatric Emergency Medicine 2006; 7 (3):138–142.

Beers SR, Berger RP, Adelson PD. Neurocognitive outcome and serum biomarkers in inflicted versus non-inflicted traumatic brain injury in young children. J of Neuro-trauma 2007;24(1):97–105.

Bonnier C, Nassogne M- C, Evrard P. Outcome and prognosis of whiplash shaken infant syndrome; late consequences after a symptom-free interval. Developmental Medicine in Child Neurology 1995;37: 943–956.

Bonnier C, Nassogne M-C, Saint-Martin C, Mesples B, Kadhim H, Sebire G. Neuroimaging of intraparenchymal lesions predicts outcome in shaking baby syndrome. Pediatrics 2003; 112:808–814.

Blumenthal I. Shaken baby syndrome. Postgraduate Medical Journal 2002; 78:732–735.

Caffey J. On the theory and practice of shaking infants. Its potential residual effects of permanent brain damage and mental retardation. Am J Dis Child. 1972 Aug;124(2):161–9.

Carty H, Radcliffe J. The shaken infant syndrome: Parents and other carers need to know of its dangers. BMJ 1995; 310:344–345.

Cho DY, Wang YC, Chi CS. Decompressive craniotomy for acute shaken/impact baby syndrome. Pediatric Neurosurgery 1995; 23: 192–198.

Cirovic S, Bhola RM, Hose DR, Howard IC, Lawford PV, Parsons MA. Mechanistic hypothesis for eye injury in infant shaking: an experimental and computational study. Forensic Science, Medicine & Pathology 2005; 1(1): 53–59.

Coody D, Brown M, Montgomery D, Flynn A, Yetman R. Shaken baby syndrome: Identification and prevention for nurse practitioners. J of Ped Health Care 1994; 8:50–56.

Demaerel P, Casteels I, Wilms G. Cranial imaging in child abuse European Radiology 2002; 12:849–857.

Dias MS, Backstrom J, Falk M, Li V. Serial radiography in the infant shaken impact syndrome. Pediatr Neurosurg. 1998; 29:77–85.

Dolinak D, Reichard R. An overview of inflicted head injury in infants and young children, with review of β-amyloid precursor protein immunohistochemistry. Arch Pathol Lab Med 2006; 130: 712–17.

Donohoe M. The evidence-based medicine and shaken baby syndrome: part I: literature review, 1966–1998. Am J Forensic Med Pathol. 2003;24(3):239–42.

Duhaime A., Alario A., Lewander W, Schut L, Sutton LN, Seidl TS, Nudelman S, Budenz D, Hertle R, Tsiaras W. Head injury in very young children: mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. Pediatrics 1992 **90,** 179–185.

Duhaime AC, Christian C, Moss E, Seidl T. Long-term outcome in infants with the shaking –impact syndrome. Pediatr Neurosurg 1996; 24:292–298.

Duhaime AC, Christian CW, Rorke LB, Zimmerman RA. Nonaccidental head injury in infants--the "shaken-baby syndrome". N Engl J Med. 1998 Jun 18;338(25):1822–9.

Duhaime AC, Gennarelli TA, Thibault LE, Bruce DA, Marquiles SS, Wiser R. The shaken baby syndrome. A clinical, pathological, and biomechanical study. J Neurosurg 1987; 66(3): 409–15.

Dykes LJ. The whiplash shaken infant syndrome: what has been learned? Child Abuse Negl. 1986;10(2):211–21.

Elmer, E. and Gregg, G. S. Developmental characteristics of abused children. Pediatrics 1967, 40: 596–602.

Eltermann T, Beer M, Girschick J. Magnetic resonance imaging in child abuse. J Child Neur 2007;22:170–175.

Emerson MV, Pieramici DJ, Stoessel KM, Berreen JP, Gariano RF. Incidence and rate of disappearance of retinal hemorrhage in newborns. Ophthalmology 2001; 108:36–39.

Eslinger PJ, Flaherty-Craig CV, Benton AL. Developmental outcomes after early prefrontal cortex damage. Brain Cogn. 2004;55:84–103.

Ewing- Cobbs L, Kramer L, Prasad M, Canales DN, Louis PT, Fletcher JM, Vollero H, Landry SH, Cheung K. Neuroimaging, Physical, and Developmental Findings After

Inflicted and Noninflicted Traumatic Brain Injury in Young Children Pediatrics 1998; 102 (2):300–307.
Ewing-Cobbs L, Prasad M, Kramer L, Landry S. Inflicted traumatic brain injury: relationship of developmental outcome to severity of injury. Pediatr. Neurosurg. 1999; **31,** 251–258.
Feldman K, Bethel R, Shugerman R, Grossman D, Grady M, Ellenbogen R. The cause of infant and toddler subdural hemorrhage: a prospective study. Pediatrics. 2001 Sep;108(3):636–46.
Fischer H, Allasio D. Permanently damaged: long-term follow-up of shaken babies. Pediatrics 1994; 33:696–698.
Fung EL, Nelson EA, Sung RY, Poon WS. Unexplained subdural hematoma in young children. Pediatr Int 2003; 45(4):497.
Fung EL, Sung RY, Nelson EA, Poon WS. Unexplained subdural hematoma in young children: is it always child abuse? Pediatrics International 2002; 44:37–42.
Geddes JF, Hackshaw AK, Vowles GH, Nickols CD, Whitwell HL. Neuropathology of inflicted head injury in children. Patterns of brain damage. Brain 2001;124:1290–8.
Geddes JF, Plunkett J. The evidence base for shaken baby syndrome. BMJ 2004;328:719–720.
Geddes JF, Tasker RC, Hackshaw AK, Nickols CD, Adams GGW, Whitwell HL, Scheimberg I. Dural haemorrhage in non-traumatic infant deaths: does it explain the bleeding in "shaken baby syndrome"? Neuropathology and Applied Neurobiology 2003; 29:14–22.
Geddes JF, Vowles GH, Hackshaw AK, Nicols CD, Scott IS, Whitwell HL. Neuropathology of inflicted head injury in children. Brain 2001; 124 (7):1299–1306.
Ghatan S, Ellenbogen RG. Pediatric spine and spinal cord injury after inflicted trauma. Neurosurg Clin N Am 2002; 13(2):227–33.
Gill J, Morotti R, Tranchida V, Morhaime J, Mena H. Delayed homicides due to infant head injury initially reported as natural (cerebral palsy) deaths. Pediatr Dev Path 2007; 22.
Gilles EE, Nelson MD. Cerebral complications of nonaccidental head injury in childhood. Pediatr Neurol 1998; 19:119–128.
Gilles EE, McGregor ML, Levy-Clarke G. Retinal hemorrhage asymmetry in inflicted head injury: a clue to the pathogeneses? J of Pediatrics 2003; 143 (4):494-499.
Gnanaraj L, Gilliland MG, Yahya RR, Rutka JT, Drake J, Dirks P, Levin AV. Ocular manifestations of crush head injury in children. Eye 2007; 21(1):5–10.
Goldstein B, Kelly MM, Bruton D, Cox C. Inflicted versus accidental head injury in critically injured children. Crit Care Med 1993; 21:1328–1332.
Guthkelch AN. Infantile subdural haematoma and its relationship to whiplash injuries. Br Med J. 1971 May 22;2(5759):430–1.
Hadley MN, Sonntag VKH, Rekate HL, Murphy A. The infant whiplash-shake injury syndrome. A clinical and pathological study. Neurosurgery 1989; 24:536–540.
Harding B, Risdon RA, Krous HF. Shaken baby syndrome. BMJ 2004; 328:720–721.
Haviland J, Russell RI. Outcome after severe non-accidental head injury. Arch Dis Child 1997; 77:504–507.
Hettler J, Greenes DS. Can the initial history predict whether a child with head injury has bee abused? Pediatrics 2003;111:602–607.
Holloway M, Bye AM, Moran K. Non-accidental head injury in children. Medical Journal of Australia 1994; 160:786–789.

Hunziker UA, Barr RG. Increased carrying reduces infant crying: A randomized controlled trial. *Pediatrics*, 1986; *77*: 641–648.

ICD-10 classification of mental and behavioral disorders. World Health Organization, 1992.

Jayawant S, Parr J. Outcome following subdural haemorrhage in infancy. Arch Dis Child 2007; 92: 343–347.

Jayawant S, Rawlison A, Gibbon F, Price J, Schulte J, Sharpeles P, Sibert JR, Kemp AM. Subdural hemorrhages in infants: population based study. Br Med J 1998; 317:1558–61.

Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. Lancet 1975; 1 (7905):480–4.

Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. JAMA 1999; 281:621–626.

Johnson B. and Morse, H. A. Injured children and their parents. Children1968, 15: 147–152.

Karandikar S, Coles L, Jayawant S, Kemp AM. The neurodevelopmental outcome in infants who have sustained a subdural haemorrhage from non-accidental head injury. Child Abuse Review 2004; 13 (3): 178–187.

Kaufman AS, Kaufman NL. K-ABC. Kaufman Assessment Battery for children. Administrative and Scoring Manual. AGS 1983.

Kaufman AS, Kaufman NL. *K-ABC.* Kaufman Assessment Battery for children. Interpretative Manual. AGS 1983.

Keenan HT, Marshall SW, Nocera MA, Runyan DK. Increased incidence of inflicted traumatic brain injury in children after a natural disaster. Am J of Preventive Medicine 2004; 26(3):189–193.

Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF, Sinal SH. A population based study of inflicted traumatic brain injury in young children. JAMA 2003; 290:621–626.

Keenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF. A population-based comparison of clinical and outcome characteristics of young children with serious inflicted and noninflicted traumatic brain injury. Pediatrics. 2004 Sep;114(3):633–9.

Keenan HT, Runyan DK, Nocera M. Child outcomes and family characteristics 1 year after severe inflicted or noninflicted traumatic brain injury. Pediatrics 2006a; 117 (2): 317–324.

Keenan HT, Runyan DK, Nocera M. Longitudinal follow-up of families and young children with traumatic brain injury. Pediatrics 2006b; 117 (4):1291–7.

King WJ, MacKay M, Sirnick A, Canadian Shaken Baby Study Group. Shaken baby syndrome in Canada: clinical characteristics and outcomes of hospital cases. CMAJ Jan 2003; 168 (2): 155–9.

Kivlin JD, Simons KB, Lazoritz S, Ruttum MS. Shaken baby syndrome. Ophthalmology 2000;107:1246–1254.

Kochanek PM, Berger RP, Margulies SS, Jenkins LW. Inflicted Childhood Neurotrauma: New Insight into The Detection, Pathobiology, Prevention, and Treatment of Our Youngest Patients with Traumatic Brain Injury. Journal of Neurotrauma Jan 2007, Vol. 24, No. 1: 1–4.

Kocher MS, Kasser JR. Orthopaedic aspects of child abuse. J Am Acad Orthop Surg 2000; 8:10–20.

Koelfen W, Freund M, Dinter D, Schmidt B, Koenig S, Schultze C. Long-term follow up of children with head injuries-classified as "good recovery" using the Glasgow Outcome Scale: neurological, neuropsychological and magnetic resonance imaging results. Eur J Pediatr. 1997 Mar;156(3):230–5.

Kuijraoka Y, Sato M, Tsuruta W, Yanaka K, Takeda T, Matsumura A. Shaken baby syndrome manifesting as chronic subdural hematoma :hematoma: importance of single photon emission computed tomography for treatment indications — case report. Neurol Med Chir (Tokyo), 2004 ; 44(7):359–62.

Landry SH, Swank P, Stuebing K, Prasad M, Ewing-Cobbs L. Social competence in young children with inflicted traumatic brain injury. Dev Neuropsychol. 2004;26(3):707–33.

Lantz P, Sinai S, Stanton C, Weaver R. Perimacular retinal folds from childhood head trauma: case report with critical appraisal of current literature. BMJ 2004; 326:294–5.

Leventhal JM, Thomas SA, Rosenfield NS, Markowitz RI. Fractures in young children. Distinguishing child abuse from unintentional injuries. Am J Dis Child 1993; 147:87–92.

Levin AV. Retinal hemorrhage and child abuse. In TJ David ed. Recent advances in paediatrics No 18. Churchill Livingstone, London 2000:151–219.

Lichtenberger EO. The Kaufman tests — K-ABC and KAIT In: Kaufman A.S., & Kaufman, N. L. (Eds). Specific learning disabilities and difficulties in children and adolescents, pp.97–141. Cambridge University Press 2001.

Ludwig S, Warman M. Shaken baby syndrome: a review of 20 cases. Ann Emerg Med 1984; 13: 105–107.

Lücke T, Pfister S, Dürken M. Neurodevelopmental outcome and haematological course of a long-term survivor with homozygous alpha-thalassaemia: Case report and review of the literature. Acta Pediatrica, 2005; 94:1330–1343.

Makaroff KL, Putnam F. Outcomes of infants and children with inflicted traumatic brain injury. Dev Med Child Neurol 2003, 45: 497–502.

Makoroff KL, Cecil KM, Care M, Ball WS Jr. Elevated lactate as an early marker of brain injury in inflicted traumatic brain injury. Pediatric Radiology 2005; 35(7):668–676.

Martin HP, Beezley P, Conway EF, Kempe CH. The development of abused children. Advances in Pediatrics 1974, 21: 25–73.

Minns RA, Busuttil A. Patterns of presentation of the shaking baby syndrome. Four types of inflicted brain injury dominate. BMJ 2004; 328:766.

Morad Y, Avni I, Capra L, Case ME, Feldman K, Kodsi SR, Esernio-Jenssen D, Lukefahr JL, Levin AV. Shaken baby syndrome without intracranial hemorrhage on initial computed tomography. Journal of AAPOS 2004; 6:521–7.

Morad Y, Kim YM, Armstrong DC, Huyer D, Mian M, Levin AV. Correlation between retinal abnormalities and intracranial abnormalities in the shaken baby syndrome. Am J Ophthalmol 2002; 134:354–359.

Newton AW, Vandeven AM. Update on child maltreatment. Curr Opin Pediatr 2007; 19:223–9.

Prasad MR, Kramer LA, Ewing-Cobbs L. Cognitive and neuroimaging findings in physically abused preschoolers. Arch Dis Child 2005; 90(1):82– 85.

Reece MR. The evidence base for shaken baby syndrome. Response to editorial from 106 doctors. BMJ 2004; 328:1316–1317.

Reichard RR, White CL, Hogan RN, Hladik CL, Dolinak D. Beta-amyloid precursor protein immunohistochemistry in the evaluation of pediatric traumatic optic nerve injury. Ophthalmology 2004; 111(4):822–7.

Reichard RR, White CL, Hladik CL, Dolinak D. Beta-amyloid precursor protein staining of nonaccidental central nervous system injury in pediatric autopsies. J Neurotrauma 2003; 20(4):347–55.

Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. Pediatrics. 2001 Oct;108(4):893–7.

Reijneveld SA, van der Wal MF, Brugman E, Sing RA, Verloove-Vanhorick SP. Infant crying and abuse. Lancet. 2004 Oct 9-15;364(9442):1340–2.

Richards PG, Bertocci GE, Bonshek RE, Giangrande PL, Gregson RM, Jaspan T, Jenny C, Klein N, Lawler W, Peters M, Rorke-Adams LB, Vyas H, Wade A. Shaken baby syndrome. Arch Dis Child 2006; 91:205–206.

Sabbadini M, Bonanni R, Carlesmo GA, Caltagirone C. Neuropsychological assessment of patients with severe neuromotor and verbal disabilities. Journal of Intellectual Disability Research 2001, 45:169–179.

Sattler JM Assessment of Children Cognitive Applications. Fourth Edition. San Diego: M. Sattler, Publisher, Inc 2001.

Sato Y, Yuh WTC, Smith WL, Alexander RC, Kao SCS, Ellerbroek CJ. Head injury in child abuse: evaluation with MR imaging. Radiology 1989;173:653–657.

Schermann L, Sedin G. Cognitive function at 10 years of age in children who have required neonatal intensive care. Acta Pediatrica, 2004; 93:1619–1629.

Sezen F. Retinal hemorrhage in newborn infants. British Journal of Ophthalmology 1970; 55:248–253.

Sinal SH, Ball MR. Head trauma due to child abuse: serial computerized tomography in diagnoses and management. South Med J. 1987; 80:1505–1512.

Sivit CJ, Taylor GA, Eichelberger MR. Visceral injury in battered children: changing perspective. Radiology 1989; 173:659–661.

Smith WL. Imaging in child abuse. In Helfer ME ed. The battered child. University of Chicago Press, Chicago 1997:221–247.

Statistics Estonia: http://pub.stat.ee/px-web.2001/dialog/statfilere.asp

Steele BF, Pollock CB. A psychiatric study of parents who abuse infants and small children. In: Helfer RE, Kempe CH, eds. The Battered Child. 2nd ed. Chicago IL: university of Chicago Press; 1974:89–133.

Swenson J, Levitt C. Shaken baby syndrome diagnosis and prevention. Minn Med 1997; 80:41–44.

Talvik I, Metsvaht T, Leito K, Põder H, Kool P, Väli M, Lintrop M, Kolk A, Talvik T. Inflicted traumatic brain injury (ITBI) or shaken baby syndrome (SBS) in Estonia. Acta Paediatrica 2006; 95:799–804.

Theodore AD, Chang JJ, Runyan DK, Hunter WM, Bangdiwala SI, Agans R. Epidemiologic features of the physical and sexual maltreatment of children in the Carolinas. Pediatrics. 2005 Mar; 115(3):e331–7.

Van der Wal MF, van den Boom DC, Pauw-Plomp H, de Jonge GA. Mothers' reports of infant crying and soothing in a multicultural population. Arch Dis Child. 1998 Oct;79(4):312–7.

Wechsler D. Manual for the Wechsler Intelligence Scale for Children — Third Edition. San Antonio: The Psychological Corporation. 1991.

Wechsler D. Manual for the Wechsler Preschool and Primary Scale of Intelligence — Revised. San Antonio: The Psychological Corporation. 1989.

Wheeler PL. Shaken baby syndrome — an introduction to the literature. Child Abuse Review 2003; 12(6):401–415.

Wilkerson WS, Han DP, Rappley MD, Owings CL. Retinal hemorrhage predicts neurologic injury in the shaken baby syndrome. Arch Ophthalmol 1989; 107:1472–1474.

Zimmerman RA, Bilaniuk LT, Bruce D, Schut L, Uzzell B, Goldberg HI. Computed tomography of craniocerebral injury in the abused child. Radiology 1979; 130:687–690.

SUMMARY IN ESTONIAN

RAPUTATUD LAPSE SÜNDROOM EESTIS: EPIDEMIOLOOGIA JA KAUGTULEMUSED

Raputatud lapse sündroom (RLS) (inglise keeles *shaken baby syndrome*) ehk tekitatud traumaatiline ajukahjustus (*inflicted traumatic brain injury)* ehk mitte õnnetusel tekkinud ajukahjustus (*non-accidental brain injury*) on kirjanduse andmetel sage haigestumise ning suremuse põhjus väikelastel (Makaroff jt 2003). Kochanek koos kaasautoritega (2007) rõhutab, et RLS on kõige sagedaseim surma põhjus alla 2-aastastel lastel. Vaatamata sellele, et Guthkeltch ja Caffey kirjeldasid RLS-i juhtumeid vastavalt 1971. ja 1972. aastal, diagnoositi RLS Eestis esimest korda 1999. aastal. Sellest tulenevalt püstitasime hüpoteesi, et raputatud lapse sündroomi (RLS) Eestis ei esine või esineb väga harva. Selle hüpoteesi kinnituseks planeerisime pilootuuringu (1991–2001), mis kinnitas selle imikute väärkohtlemise vormi (RLS) suhteliselt sagedast esinemist Eestis.

RLS-i esinemissagedust on raske uurida ning tavaliselt võetakse aluseks subduraalsete hematoomide (SDH) esinemissagedus (Barlow jt 2000). Ameerika Pediaatria Akadeemia avaldatud juhtkirjas pööratakse tähelepanu sellele, et RLS-i esinemissagedus on suurem kui kirjanduses pakutud ning diagnoositud lapsed moodustavad ainult "jäämäe tipu" (AAP 2001, King jt 2003). Jayawanti ja kaasautorite (1998) poolt läbiviidud uuringus Šotimaal ja Walesis diagnoositi subduraalseid hematoome alla aastastel lastel 21:100 000 ning autorite arvates umbes 85% nendest on tekkinud väärkohtlemise (raputamise) tulemusena.

Raputatud lapse sündroomi esinemissagedust on vähe uuritud ja populatsioonipõhiseid uuringuid on teadaolevalt vaid kolm. Šotimaal tehti kindlaks prospektiivse uuringu tulemusena, et RLS-i esinemissagedus on 24,6:100 000 alla aastase lapse kohta, mis oli kaks korda suurem retrospektiivse uuringu tulemusest (11,2:100 000 alla aastase lapse kohta) (Barlow jt 2000). 2003. aastal publitseeritud Põhja- Carolinas läbiviidud uuringu tulemusena leiti, et haigestumus RLS-i on 29,7:100 000 alla aastase lapse kohta (Keenan jt 2003). Kanadas läbiviidud uuringus, mis kattis umbes 85% pediaatrilisest teenindusest, diagnoositi 10 aasta jooksul (1988–1998) RLS-i 364 lapsel ning autorite arvates satub Kanadas igal aastal umbes 40 last haiglasse RLS-i diagnoosiga (King jt 2003). Kirjanduse andmetel moodustavad poisid 62% raputatud lapse sündroomiga lastest (Keenan jt 2003).

Raputatud lapse sündroomile iseloomulik triaad on: aju-, silma- ja skeleti kahjustused (Richards jt 2006). Kliiniline sümptomatoloogia võib olla varieeruv — mittespetsiifilistest (isutus, rahutus, oksendamine, aktiivsuse vähenemine) kergematel juhtudel kuni tüüpiliste raske ajukahjutuse sümptomiteni (teadvushäire, krambid, oksendamine, neuroloogiline kolde sümptomatoloogia) (Jenny jt 1999).

Esmase diagnoosi püstitamise järgselt 1999. aastal planeeriti pilootuuring: retrospektiivne osa 1. jaanuarist 1991 kuni 31. detsembrini 1999 ning prospektiivne osa 1. jaanuarist 2000 kuni 31. detsembrini 2001. Pilootuuring kinnitas raputatud lapse sündroomi suhtelisest kõrget esinemissagedust ja vajadust läbi viia populatsioonipõhine kogu Eestit haarav uuring.

Töö eesmärgid

1. Uurida RLS-i esinemist Eestis
2. Uurida RLS-i kliinilisi sümptomeid
3. Uurida RLS-iga laste kaugtulemusi (kognitiivsed, neuroloogilised)

Patsiendid ja metoodika

Peale pilootuuringu tulemusi käivitati populatsioonipõhine uuring, mis koosnes kahest osast: epidemioloogiline uuring ja kaugtulemuste uuring. Epidemioloogiline uuring koosnes retrospektiivsest osast (1997–1999) ja prospektiivsest osast (2000–2003). Uuringusse olid kaasatud SA Tartu Ülikooli Kliinikumi lastekliinik, Anestesioloogia ja Intensiivravi Kliinik ning Tallinna Lastehaigla.

Enne uuringu alustamist kooskõlastati diagnoosi kriteeriumid, mis olid kontrollitud pilootuuringu käigus.

Retrospektiivselt vaadati läbi kõik ajukahjustusega hospitaliseeritud laste haiguslood, prospektiivse uuringu ajal käsitleti kõiki ajukahjustusega hospitaliseeritud lapsi vastavalt diagnoosi kriteeriumitele ja uuringu protokollile. Kasutati järgmisi diagnoosi kriteeriume:

- ajukahjustusele viitavad kliinilised sümptomid (teadvushäire, krambid),
- radioloogilistes uuringutes viited traumaatilisele ajukahjustusele (difuusne turse,
- SDH, subarahnoidaalne hemorraagia, kontusioonikolded, fraktuurid — skeletis, koljuluudes),
- trauma puudumine anamneesis või kahjustuste mittevastavus anamneesile,
- reetina hemorraagiad,
- vere ning ainevahetuse haigustele viitavate laboratoorsete muutuste puudumine.

Uuringu teise osa moodustas raputatud lapse sündroomiga laste kaugtulemuste uurimine:

- neuroloogiline leid,
- psühholoogilised testid,
- nägemise kontroll.

Tulemused

Uuringuperioodi vältel diagnoositi RLS 26 lapsel, kellest 6 olid tüdrukud (23%) ja 20 poisid (77%). Imikute vanus oli keskmiselt 3,9 kuud (4 päeva — 12 kuud). Poisid hospitaliseeriti nooremas eas kui tüdrukud: vastavalt 3,4 kuud ja 5,8 kuud, kuid erinevus ei olnud statistiliselt tõenäone. Uuringu grupis oli üks paar kaksikuid poisse ning üks tüdruk kaksikute paarist ja üks poiss kaksikute paarist, seega moodustasid kaksikud 15,4%, mis on oluliselt kõrgem võrreldes Eesti populatsioonis olevate kaksikutega 2,12% (p=0,002).

Uuringuperioodi vältel oli haigestumus RLS-i 28,7:100 000 alla aastase lapse kohta, samas võrreldes prospektiivse ja retrospektiivse uuringu tulemusi on haigestumust vastavalt 40,5 ja 13,5:100 000 alla aastase lapse kohta, seega oli haigestumus prospektiivses uuringus 3 korda kõrgem. Uuringuperioodil suri neli last (2 poissi ja 2 tüdrukut, vanuses 4 päeva – 1 aasta), seega suremus oli meie uuringugrupis 15,4%.

Sagedasemaks kliiniliseks sümptomiks hospitaliseerimisel oli teadvushäire, samas kriitilises seisus (GCS <= 8 palli) oli vaid 8/26 (30,8%). Esmase sümptomina esinesid krambid 13/26 imikul. Kolm imikut hospitaliseeriti uuringuteks seoses arengus mahajäämusega. Reetina hemorraagiad esinesid 57,7% lastel (15/26). Kõikidel uuritud lastel olid ajutrauma tunnused piltdiagnostikas (KT/MRT) 23/26 või lahangul (4), ühel lapsel, keda uuriti kompuutertomograafiaga ja kes suri, kinnitus KT leid ka lahangul. Kõige sagedasemaks leiuks oli subduraalsete hematoomide esinemine — 20/26 (76,9%), subarahnoidaalne hemorraagia esines 3/26 (11,5%) lapsel, intratserebraalne hemorraagia oli 2 lapsel (7,7%) ning epiduraalne ühel lapsel (3,9%). Üheksal imikul (34,6%) olid viited korduvale väärkohtlemisele (erinevas vanuses subduraalsed hematoomid, paranevad fraktuurid).

On oluline rõhutada, et enamus lapsevanemaid olid pöördunud eelnevalt lapse liigse nutu või rahutuse tõttu kas perearsti või lastearsti poole 23/26 (88,5%), mis oli aga ilmselt jäänud piisava tähelepanuta.

Kaugtulemuste uuring toimus aastatel 2005–2006. Tänu heale koostööle perearstidega ja sotsiaaltöötajatega ning korduvatele eelnevatele helistamistele õnnestus meil uurida kõiki ellujäänud lapsi (22/22).

Laste keskmine vanus järelkontrollil oli 5,2 aastat (2,4–9,0 aastat). Neuroloogilisel uurimisel leiti väljendunud motoorikahäire 5/22 (spastiline tetraparees 2, hemiparees 2 ja dipleegia 1 lapsel), 13/22 lapsel olid kerged või mõõdukad probleemid (kohmakus). Nägemise kontrolli läbisid 17 last, kellest 4-l esinesid tõsised oftalmoloogilised probleemid nagu nägemisnärvide atroofia, reetina fibroossed muutused. Viie lapse vanemad ei olnud nõus silmaarsti konsultatsiooniga, kuid psühholoogilised testid ei toonud välja neil suuri nägemisega seotud häireid.

Kaufmani testiga oli võimalik uurida 17 last 22st. Uuringut ei saanud läbi viia 5 lapsel — 4 lapsel oli sügav puue, ühe lapse vanus ei vastanud Kaufmani

testi vanusele. Kaufmani testi tulemused olid kõigil RLS-i läbiteinutel oluliselt madalamad kui kontrollgrupi lastel ($p<0,001$).

Laste seisundit hinnati ka GOS ja RDS skooringute alusel ning selgus, et ainult 2/22 last võis lugeda terveks. Meie tulemused näitasid, et RDS on oluliselt informatiivsem ja täpsem nende laste seisundi hindamiseks.

Epilepsia oli diagnoositud 7 lapsel 22-st ning 3 juhul oli tegemist ravile raskesti alluva epilepsiaga.

Diskussioon

Raputatud lapse sündroomiga (RLS) seotud epidemioloogilisi uuringuid on vähe (Barlow jt 2000, Keenan jt 2003, King jt 2003). RLS-i sagedus Eestis on 40,5:100 000 alla aastase lapse kohta, mis on kõrgem kui siiani kirjanduses avaldatud (29:100 000). Miks esineb raputatud lapse sündroomi Eestis nii sageli, on raske põhjendada, kuid kindlasti on oma osa hästiarenenud ja koostöövalmis arstiabi süsteemil, mille tõttu lapsed suunatakse haiglasse, kus uuringud tehakse vastavalt uuringu protokollile. Teiselt poolt on Eestis problemaatiline sotsiaalne foon, seda kinnitavad ka õnnelikkuse ja eluga rahulolu uuringud, kus eestlased on kõige õnnetumad inimesed Euroopas (http://www.neweconomics.org). Teisalt on sündroomi esinemissagedus erinevates maakondades erinev (Võrus 120:100000, Valgas 191:100 000, Põlvas ja Läänemaal 0), mis võiks viidata ka erinevale arstiabi kättesaadavusele või ka arstide mitteküllaldasele teadlikkusele raputatud lapse sündroomi sümptomitest. On siiski tõenäoline, et kõik raske ning keskmise kahjustusega lapsed on hospitaliseeritud ning diagnoositud. Oluline on rõhutada, et enamus lapsevanemaid on pöördunud eelnevalt abi saamiseks lapse liigse nutmise või rahutuse tõttu nii perearstide kui spetsialistide poole, kuid probleemide tõsisust ei ole ilmselt piisavalt mõistetud.

Raputatud lapse sündroomiga laste kaugtulemused on halvad, ainult 2 last 22-st olid uurimishetkel terved.

Järeldused

1. RLS-i sagedus (40,5:100 000 alla aastase lapse kohta) Eestis prospektiivse uuringu andmeil on seni meditsiinikirjanduse andmeil maailmas kõrgeim (Šotimaa 24,6 ja Põhja-Carolina 29,7:100 000 alla aastase lapse kohta). Haigestumine oli prospektiivse uuringu tulemusel 3 korda kõrgem kui retrospektiivses uuringus (13,5:100 000 alla aastase lapse kohta). Suremus oli 15,6%.
   a. Poisse raputatakse sagedamini kui tüdrukuid, poiste/tüdrukute suhe oli uuringugrupis 3,3:1.

   b. Poisid hospitaliseeritakse nooremas eas (keskmine vanus 3,4 kuud; tüdrukutel 5,8 kuud).
   c. Kaksikuid oli uurimisgrupis 15,4%, mis on oluliselt kõrgem kui üld-populatsioonis, seega kaksikud moodustavad riskigrupi RLS-i suhtes (p=0,002).
2. Teadvusehäire ning krambid ilma infektsiooni tunnusteta on viide võimalikule raputatud lapse sündroomile ja on näidustus piltdiagnostikaks.
   a. Enamus lapsi on hospitaliseerimisel stabiilses seisundis (GCS > 13 10/26) vaatamata tõsisele ajukahjustusele (SDH 76,9%, SAH 11,5%).
3. Eelnevalt potentsiaalselt tervete RLS-i laste kaugtulemused on tõsised:
   a. Arengulised probleemid esinesid 90,9 % RLS-i läbiteinud lastest.
   b. Tõsine motoorikahäire esines 5/22 (22,7%) (spastiline tetraparees 2 lapsel, spastiline hemiparees 2 lapsel, spastiline dipleegia 1 lapsel).
   c. Epilepsia diagnoositi 7/22 (32%) RLS-i läbi teinud lapsel, kusjuures kolmel juhul oli tegemist ravile raskesti alluva epilepsiaga.
   d. Kolm last kahekümne kahest olid raske puudega (13,64%), ülejäänutel olid erineva raskusega kognitiivsete funktsioonide häired.
4. Rankini skaala (RDS) on informatiivsem kui GOS skaala raputatud lapse sündroomi läbiteinud laste kaugtulemuste hindamisel. Rankini skaala järgi kuulusid tervete laste gruppi ainult kaks last.
5. Psühholoogilised testid K-ABC-ga näitasid RLS-i läbiteinud lastel (17) oluliselt madalamaid tulemusi võrreldes kontrollgrupiga (p<0,001).

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APPENDIX

Appendix 1. Modified Glasgow Coma Scale for Infants

Eye opening	Spontaneous To verbal stimuli To pain only No response	4 3 2 1
Verbal response	Coos and babbles Irritable cries Cries to pain Moans to pain No response	5 4 3 2 1
Motor response	Moves spontaneously and purposefully Withdraws to touch Withdraws in response to pain Decorticate posturing in response to pain Decerebrate posturing in response to pain No response	6 5 4 3 2 1

Appendix 2. K-ABC subtests description

Subtest	Description
Sequential Scale	
Gestalt Closure	naming an object in partially completed picture
Triangles	assembling identical triangles into the pattern previously exposed model
Spatial Memory	recalling the placement of previously briefly exposed pictures
Simultaneous Scale	
Hand Movements	repeating the series of earlier performed hand movements
Number Recall	repeating the series of digits as previously said
Word Order	touching the series of pictures in the same sequence as named before
Achievement Scale	
Arithmetic	solve the tasks using the knowledge of numbers and mathematical concepts and skills
Riddles	naming the concept by given list of characteristics

Appendix 3. Glasgow Outcome Score

GOS=1 good recovery	Capacity to resume normal occupational and social activities, although there may be minor physical or mental deficits or symptoms
GOS=2 moderate disability	Independent and can resume almost all activities of daily living. Disabled to the extent that they can not participate in a variety of social and work activities.
GOS=3 severe disability	No longer capable of engaging in most precious personal, social or work activities. Limited communication skills and have abnormal behavioral or emotional responses. Typically are partially or totally dependent on assistance from others in daily living.
GOS=4 persistent vegetative state	Not aware of surroundings or purposely responsive to stimuli.
GOS=5 dead	

Appendix 4. Rankin Disability Score

Rankin=0	No symptoms at all
Rankin=1	No significant disability despite symptoms, able to carry out all usual duties and activities.
Rankin=2	Slight disability. Unable to carry out all normal activities but able to look after own affairs without assistance.
Rankin=3	Moderate disability requiring some help but able to walk without assistance.
Rankin=4	Moderately severe disability. Unable to walk without assistance, and unable to attend to own bodily needs without assistance.
Rankin=5	Severe disability. Bedridden, incontinent and requiring constant nursing care and attention.

PUBLICATIONS

I

Talvik I, Vibo R, Metsvaht T, Männamaa M,
Jüri P, Heidmets L-T, Hämarik M, Talvik T.
Raputatud lapse sündroom. Eesti Arst 2002; 81 (1): 23–29.

II

Talvik I, Metsvaht T, Leito K, Põder H, Kool P,
Väli M, Lintrop M, Kolk A, Talvik T.
Inflicted traumatic brain injury (ITBI) or shaken baby syndrome (SBS) in Estonia.
Acta Paediatr 2006; 95 (7): 799–804.

III

Talvik I, Männamaa M, Jüri P, Leito K, Põder H, Hämarik M, Kool P, Talvik T.
Outcome of infants with inflicted
traumatic brain injury (shaken baby syndrome) in Estonia.
Acta Paediatr 2007; 96 (8): 1164–1168.

IV

Talvik I, Lintrop M, Metsvaht T, Talvik T.
Millal mõelda raputatud lapse sündroomile:
kirjanduse ülevaade ning haigusjuhu kirjeldus.
Eesti Arst 2007; 6: 420–423.

V

Talvik I, Vibo R, Metsvaht T, Talvik T.
Shaken baby syndrome in Estonia.
Europ J of Paediatr Neurol 2001; 5 (5): A141
(Abstracts for the 4th International Congress of the European Paediatric Neurology Society).

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Professional employment

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Scientific work

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Membership in professional organizations

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Publications

- Beilmann A, Napa A, Sööt A, Talvik I, Talvik T. Prevalence of childhood epilepsy in Estonia. Epilepsia 1999; 40(7):1011–9.
- Beilmann A, Napa A, Hämarik M, Sööt A, Talvik T, Talvik T. Incidence of childhood epilepsy in Estonia. Brain dev 1999; 21(3):166–74.
- Talvik I, Õunap K, Bartch O, Uibo O, Talvik T. Boy with celiac disease, malformations, and ring chromosome 13 with deletion 13q32-->qter. Am J Med Genet. 2000 Aug 28; 93(5):399–402.
- Salur L, Uibo O, Talvik I, Justus I, Metsküla K. Talvik T, Uibo R. The high frequency of celiac disease among children with neurological disorders. Eur J Neurol. 2000 Nov; 7(6):707–11.
- Talkop ÜA, Talvik I, Sõnajalg M, Sibul H, Kolk A, Piirsoo A, Warzok R, Wulff K, Whnert MS, Talvik T. Early onset of cardiomyopathy in two brothers with X-linked Emery-Dreifuss muscular dystrophy. Neuromuscul Disord. 2002 Nov; 12(9):878–81.
- Talkop ÜA, Kahre T, Napa A, Talvik I, Sööt A, Piirsoo A, Sander V, Talvik T. A descriptive epidemiological study of Duchenne muscular dystrophy in childhood in Estonia. Eur J Paediatr Neurol. 2003; 7(5):221–6.
- Vaidla E, Talvik I, Kulla A, Kahre T, Hämarik M, Napa A, Metsvaht T, Piirsoo A, Talvik T. Descriptive epidemiology of spinal muscular atrophy type I in Estonia. Neuroepidemiology. 2006; 27(3):164–8.
- Talvik I, Koch K, Kolk A, Talvik T. Chronic paroxysmal hemicrania in a 3-year, 10-month-old female. Pediatr Neurol. 2006 Mar; 34(3):225–7.
- Vaidla E, Tavik I, Kulla A, Sibul H, Maasalu K, Metsvaht T, Piirsoo A, Talvik T. Neonatal spinal muscular atrophy type 1 with bone fractures and heart defect. J Child Neurol. 2007 Jan; 22(1):67–70.

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Teaduslik töö

Erihuvid: raputatud lapse sündroom, epilepsia, degeneratiivsed haigused.

Osalemine teadusseltsides

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