From the Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

HEMIPLEGIC CEREBRAL PALSY CLINICAL PRESENTATION AND AETIOLOGY

Elsa Tillberg

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Hemiplegic Cerebral Palsy: Clinical Presentation and Aetiology

Thesis for Doctoral Degree (Ph.D.)

By

Elsa Tillberg

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Principal Supervisor:
M.D., Ph.D. Jonas K.E. Persson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Clinical Neurophysiology

Co-supervisor(s):
M.D., Assistant Professor Gerald Cooray
Karolinska Institutet
Department of Clinical Neuroscience
Division of Clinical Neurophysiology

Opponent:
Professor Kate Himmelmann
University of Gothenburg
Department of Clinical Sciences
Sahlgrenska Academy
Divison of Pediatrics

Examination Board
Professor Anders Hjern
Karolinska Institutet
Department of Medicine
Division of Social Epidemiology

Assistant Professor Margareta Dahl
Uppsala University
Department of Women`s and Children´s Health

Assistant Professor Karin Eeg-Olofsson
Uppsala University
Department of Neuroscience
Division of Clinical Neurophysiology

To the children

Popular science summary of the thesis

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development. These motor impairments can have different aetiologic backgrounds, occurring in the prenatal, perinatal or postnatal period. Cerebral palsy is the most common cause of childhood onset, lifelong disability in many countries. The motor impairment is classified as unilateral/ hemiplegic or bilateral. It is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment. These associated impairments can be more disabling than the motor disturbance itself. Epilepsy is common in cerebral palsy, present in 30-40 % of cases. Epilepsy is related to the underlying brain lesion. Children with cerebral palsy, epilepsy and intellectual disability constitute a large patient group in paediatric neurology (Cans et al., 2000; Stanley, 2000; Tillberg et al., 2008).

In the first part of this research we studied the motor impairments and associated impairments, in a population-based group of children with hemiplegic/unilateral cerebral palsy after cerebral infection. In **study I** we found a high frequency of epilepsy and intellectual disability in this group. In **study II** six children and 15 caregivers in this group were interviewed regarding the child's ability to participate in age-related activities. All reported great difficulties participating in age-related activities. Hygiene issues hindered children with a non-Swedish cultural background from participating in camps or swimming. **In study III** the severity of the motor disability in these children was assessed using the Movement Assessment Battery for Children and the Paediatric Disability Inventory. Balance and hand function were impaired in all. Motor difficulties dominated during pre-school years; difficulties with social and communication skills predominated in school-age children. In the second part of our research we studied a population-based group of hemiplegic children with different aetiologic backgrounds. In **study IV** we investigated aetiological background factors, clinical presentation including brain imaging, electroencephalogram (EEG) and epilepsy found in each child. Risk factors for cerbral palsy were present in 16 of the 21 participants. These risk factors for cerebral palsy are important for early identification. Any child with these risk factors should be offered a check-up by a paediatrician or a paediatric neurologist. Epilepsy was common and associated with combined grey and white matter injuries. In **study V** we investigated intellectual disability and its association with epilepsy and brain imaging in this population-based group of hemiplegic children. To assess cognitive ability, the Wechsler Intelligence Scale for Children-test was performed by an experienced psychologist. Intellectual disability was present in 38 % and uneven cognitive profiles in 57 %. Nine of the 21 children developed epilepsy. Together, these studies show that epilepsy, intellectual disability and uneven cognitive profiles are common in hemiplegic cerebral palsy. Individual cognitive assessment is recommended before school start.

Abstract

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development. These motor impairments can have different aetiologic backgrounds, occurring in the prenatal, perinatal or postnatal period. Cerebral palsy is the most common cause of childhood onset, lifelong disability in many countries. The motor impairment is classified as unilateral/ hemiplegic or bilateral. It is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment. These associated impairments can be more disabling than the motor disturbance itself. Epilepsy is common in cerebral palsy, present in 30-40 % of cases. Epilepsy is related to the underlying brain lesion. Children with cerebral palsy, epilepsy and intellectual disability constitute a large patient group in paediatric neurology. This thesis contains five clinical studies. The first part of the thesis comprises three clinical studies in which we described the motor impairments, and associated impairments, in a population-based group of children with hemiplegia/unilateral cerebral palsy after cerebral infection. In **study I** we found a high frequency of epilepsy and intellectual disability among the participants. In **study II** six children and 15 caregivers in this group were interviewed regarding the child`s ability to participate in age-related activities. All reported great difficulties participating in age-related activities. Hygiene issues hindered children with a non-Swedish cultural background from participating in camps or swimming. In **study III** the severity of the motor disability in these children was assessed using the Movement Assessment Battery for Children and the Paediatric Disability Inventory. Balance and hand function were impaired in all. Motor difficulties dominated during pre-school years, difficulties with social and communication skills predominated in school-age children. For the second part of the thesis we studied a population-based group of hemiplegic children, with different aetiologic backgrounds. In **study IV** we investigated both aetiologic background factors, clinical presentation including brain imaging, electroencephalogram (EEG) and epilepsy found in each child. Risk factors for cerbral palsy were present in 16 of the 21 participants. Risk factors are important for early identification. Any child with these risk factors should be offered a check-up by a paediatrician or paediatric neurologist. Epilepsy was common and associated with combined grey and white matter injuries. In **study V** we investigated intellectual disability and its association with epilepsy and brain imaging in this population-based group of hemiplegic children. Intellectual disability was present in 38 % and uneven cognitive profiles in 57%. Nine of the children developed epilepsy. Together, these studies show that epilepsy, intellectual disability and uneven cognitive profiles are common in hemiplegic cerebral palsy. Individual cognitive assessment is recommended before school start.

List of scientific papers

I. **Elsa Tillberg**, Ulrika Radell and Per Åmark (2008). Postnatal cerebral infection leading to hemiplegic cerebral palsy: Clinical description of 13 children in Stockholm, Sweden. Disability and Rehabilitation, 30:5, 338-347, DOI: 10.1080/09638280701463829.

II. Ulrika Radell, **Elsa Tillberg**, Eva Mattsson and Per Åmark (2008). Participation in age-related activities and influence of cultural factors - comments from youth and parents of children with postnatal post infectious hemiplegia in Stockholm, Sweden. Disability and Rehabilitation, 30:11,891-897, DOI: 10.1080/09638280701403999.

III. Ulrika Radell, **Elsa Tillberg**, Eva Mattsson and Per Åmark (2008). Postnatal cerebral infection leading to hemiplegic cerebral palsy: Functional limitations and disability of 13 children in Sweden. Disability and Rehabilitation, 30:25, 1910-1919, DOI: 10.1080/09638280701673641.

IV. **Elsa Tillberg**, Bengt Isberg, Jonas K.E. Persson (2020). Hemiplegic (unilateral) cerebral palsy in northern Stockholm: clinical assessment, brain imaging, EEG, epilepsy and aetiologic background factors. BMC Pediatrics (2020: (1) 20:116.

V. **Elsa Tillberg**, Jonas K.E. Persson (2024). Hemiplegic (unilateral) cerebral palsy in northern Stockholm: Intellectual disability and epilepsy. Seizure 120. 110-115.

Contents

List of abbreviations

ICD	Interrnational Classification of Diseases
IQ	Intelligence Quotient
WHO	World Health Organiation
CPUP	Follow-up Programme for People with Cerebral Palsy in Sweden
SCPE	Surveillance of Cerebrral Palsy in Europe
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1. Introduction

1.1 CEREBRAL PALSY

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007) .These motor impairments can have different aetiologic backgrounds, occurring in the prenatal, perinatal or postnatal period (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). Cerebral palsy is the most common cause of childhood onset, lifelong disability in many countries (Graham et al., 2016). The motor impairment is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment (Colver et al., 2014; Rosenbaum et al., 2007; Stanley, 2000). Epilepsy is common in cerebral palsy, present in 30-40 % of cases (Graham et al., 2016; Sellier et al., 2012; Zelnik et al., 2010). Epilepsy is related to the underlying brain lesion (Sellier et al., 2012). In term children with cerebral palsy, grey matter lesions are more common (Sellier et al., 2012). Few studies address specific EEG-patterns and semiology in cerebral palsy (Cooper et al., 2017) . Most studies of epilepsy in cerebral palsy are based on medical records, or information from cerebral palsy registers. Children with cerebral palsy, epilepsy and cognitive disability constitute a large patient group in paediatric neurology. An increasing number of register-based studies. address these impairments simultaneously(Ahlin et al., 2017; Delacy et al., 2016; Dos Santos Rufino et al., 2023; Sellier et al., 2012). Just a few direct clinical studies were found (El-Tallawy et al., 2014; Gururaj et al., 2003; Singhi et al., 2003). Due to the heterogeneity of cerebral palsy, it could be useful to study a subgroup, such as hemiplegic cerebral palsy (Cans et al., 2000; Stanley, 2000). We wanted to study aetiological background factors, clinical presentation including brain imaging, EEG, epilepsy, and intellectual abililty found in each child.

1.2 HISTORY

Hemiplegia has been recognized since ancient times (Christensen and Melchior, 1967). The first to describe spastic diplegia was Little, an orthopaedic surgeon in his famous 1862 paper “On the influence of abnormal parturition, difficult labours, premature birth and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities” (Little, 1966). He attributed cerebral palsy to perinatal factors. Freud’s “Clinical study of hemiplegia in children” was published in Vienna in 1891. It was a pioneer study, in which he described 35 children, whom he met at the Public Paediatric Institutes in Vienna over a period of two and a half years (Freud and Rie, 1891).

1.2.1 Registers for cerebral palsy

In order to monitor prevalence rates, especially within subgroups, it was considered necessary to study large populations. Registers for cerebral palsy were therefore established. The cerebral palsy register of western Sweden was founded as early as 1954 (Himmelmann and Sundh, 2015). The Victorian cerebral palsy register in Australia was established in 1986 (Reddihough et al., 2001). The Swedish Cerebral Palsy Follow-Up Programme (CPUP), initiated in 1994, became a Swedish national quality

register in the year 2005 ((https:// CPUP.se). Data in the CPUP register are collected at the local habilitation centres. The Surveillance of Cerebral Palsy in Europe (SCPE) began in 2000 as a network of cerebral palsy registers in 14 European countries (Cans et al., 2000).

1.3 DEFINITIONS

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development. These motor impairments can have different aetiologic backgrounds, occurring in the antenatal, perinatal or post-neonatal period (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). The motor impairment is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment. Children with cerebral palsy are commonly classified according to the SCPE guidelines (Cans et al., 2000). These guidelines are used to measure the functional loss associated with cerebral palsy and define criteria for each subtype of cerebral palsy, by distribution and type of motor impairment: hemiplegic (unilateral) or bilateral, spastic, dyskinetic or ataxic. A wide range of cerebral disorders, such as congenital malformation, prenatal circulatory disturbance, chromosome aberration, perinatal asphyxia, pre- or postnatal infection and postnatal trauma, have been indicated as aetiologic factors (Badawi et al., 1998). Cerebral palsy is also classified as being prenatal, perinatal or postnatal/post-neonatal according to the timing of the presumed insult (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). Earlier studies used the definition postnatal cerebral palsy. The cerebral lesion is often classified according to the anatomical site of the brain lesion: cerebral cortex, pyramidal tract, extrapyramidal system or cerebellum (Colver et al., 2014). The extent of the underlying cerebral lesion must also be recognized (Colver et al., 2014; Reid et al., 2014). The brain imaging patterns according to type, as classified by Reid, include white matter injury, grey matter injury, focal vascular insults and malformations (Reid et al., 2014).

1.4 AETIOLOGY

Since Fiona Stanley published her important book “Cerebral palsies: Epidemiology and causal pathways” there has been consensus that cerebral palsy results from multiple factors acting along a causal pathway (Stanley, 2000). A wide range of cerebral disorders, such as congenital malformation, prenatal circulatory disturbance, chromosome aberration, perinatal asphyxia, pre- or postnatal infection, and postnatal trauma have been indicated as aetiologic factors (Badawi et al., 1998). In “A systematic review of risk factors for cerebral palsy in children born at term in developed countries”, McIntyre et al., found 10 consistent risk factors for cerebral palsy in term children: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/ emergency caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infection. However, other risk factors such as maternal disease or being large for gestational age were not statistically significant. But these risk factors may work together along a causal pathway (McIntyre et al., 2013). Socioeconomic factors are important (Woolfenden et al., 2019), especially the educational level of the parents (Forthun et al., 2018; Himmelmann et al., 2011; Hjern and Thorngren-Jerneck, 2008), and have an impact on the prevalence of cerebral palsy. Prevalence is decreasing in high-income countries (Badawi et al., 2020; Himmelmann and Uvebrant, 2018).

1.4.1 Infection and/or skull trauma

Three earlier studies deal solely with postnatal cerebral palsy: Blair and Stanley, published in 1982 using data from Australia; Arens and Molteno, published in 1989 using data from South Africa; and Pharoah, Cook and Rosenbloom, published in 1989 containing data from England and Scotland (Arens and Molteno, 1989; Blair and Stanley, 1982; Pharoah et al., 1989). These studies all indicate that postnatally-acquired cerebral palsy is attributed to cerebral infection or skull trauma. Both of these causes are strongly associated with lower socioeconomic conditions, and therefore preventable.

1.4.2 Gestation

There is a gestational paradox: "Very strong relationship between prematurity and risk of cerebral palsy versus the fact that most patients with cerebral palsy are born at term" (Graham et al., 2016).

1.5 CLINICAL PICTURE IN HEMIPLEIC CEREBRAL PALSY

1.5.1 Motor impairment

The severity of the motor impairment in cerebral palsy varies widely (Colver et al., 2014).

1.5.2 Associated impairments

The motor impairment is often associated with visual and hearing deficits as well as epilepsy and cognitive impairment (Colver et al., 2014; Rosenbaum et al., 2007; Stanley, 2000).

1.5.3 Epilepsy in cerebral palsy

Epilepsy is an important adverse factor for cognitive function in cerebral palsy. (Cioni et al., 1999; Singhi et al., 2003; Wallace, 2001). It is common, present in 30-40 % of cerebral palsy cases (Graham et al., 2016; Pavone et al., 2020; Sellier et al., 2012; Zelnik et al., 2010). Stanley reported a higher occurrence of epilepsy in those with postnatally/post-neonatally acquired cerebral palsy (Stanley, 2000). Most studies of epilepsy in cerebral palsy are based on medical records, or information from cerebral palsy registers. Sellier et al.,described epilepsy, neonatal characteristics, associated impairments and subtypes of cerebral palsy in a large register-based study (Sellier et al., 2012).

1.5.3.1 Epilepsy in, specifically, hemiplegic cerebral palsy

Three studies address epilepsy in, specifically, hemiplegic cerebral palsy (Cioni et al., 1999; Uvebrant, 1988; Wanigasinghe et al., 2010). Uvebrant found epilepsy in 54 (34%) of 152 children with hemiplegic cerebral palsy in a population-based study. Focal epilepsy was the most common type. Right-sided hemiplegia was more frequently associated with epilepsy (29%) than left-sided (13%) (Uvebrant, 1988). Cioni et al studied 91 hemiplegic children in a large hospital-based series. Epilepsy was present in 35% of the participants (Cioni et al., 1999). Wanigasinghe et al.,,studied epilepsy in 63 children with hemiplegic cerebral palsy due to arterial ischaemic stroke: epilepsy was present in 34 children (54%), with focal seizures being most common (Wanigasinghe et al., 2010).

1.5.3.2 Electroencephalographic studies in hemiplegic cerebral palsy

The electroencephalogram (EEG) was abnormal in all children with epilepsy and in all postnatal cases in Uvebrant`s` study. Epilepsy proved to be the all-important determinant for electroencephalographic (EEG) pathology (Uvebrant, 1988). Wanigasinghe et al., in their study of epilepsy in hemiplegia due

to perinatal arterial ischaemic stroke, found focal epileptiform activity in the children with focal seizures (Wanigasinghe et al., 2010).

1.5.4 Epilepsy and intellectual disability in cerebral palsy

Intellectual disability and epilepsy are important accompanying impairments in cerebral palsy (Delacy et al., 2016; Reid et al., 2018; Sellier et al., 2012) Uvebrant's 1988 study of 152 children with hemiplegic cerebral palsy revealed intellectual disability in 18% of children, and that postnatal cases, compared to pre- and perinatal cases, more frequently developed epilepsy (Uvebrant, 1988). Intellectual disability was also found to be associated with epilepsy in another study from southwest Sweden (Carlsson et al., 2003). Sellier et al.,described epilepsy, neonatal characteristics, associated impairments and subtypes of cerebral palsy in a large register-based study. They found that 691 (25.6%) of the 2699 hemiplegic children had epilepsy. Epilepsy and/or intellectual impairment was related to a more widespread brain injury (Sellier et al., 2012).

1.5.5 Intellectual disability in cerebral palsy

Children with cerebral palsy, epilepsy and cognitive disability constitute a large patient group in paediatric neurology. A rising number of studies address intellectual disability in cerebral palsy (Gillies et al., 2018; Reid et al., 2018; Sigurdardottir et al., 2008). Most studies of intellectual disability in cerebral palsy are register-based and cognition is often described with a total value, the intelligence quotient (IQ) (Ahlin et al., 2017; Himmelmann and Uvebrant, 2011; Reid et al., 2018). Sigurdardottir et al., in a pioneer study from 2008, described the cognitive profiles in a complete national cohort of 127 children with cerebral palsy in Iceland. The children were tested with the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 2011) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Corporation, 1989). These are the most frequently used measures of intelligence quotient, at least in Western Europe and the USA (Corporation, 1989; Wechsler, 2011). Median intelligence quotients were lower than normal range, but a significant proportion of the children, especially those with hemiplegia, had normal scores (Sigurdardottir et al., 2008). Stadskleiv et al.,presented a direct study of intellectual disability in a population-based sample of 70 cerebral palsied children, of whom 35 were hemiplegic. In their study, 62.9% of the 35 children with hemiplegic cerebral palsy, had normal cognitive profiles, but 22.9% of these children with normal profiles had uneven cognitive profiles (Stadskleiv et al., 2018).

1.5.6 Brain imaging and epilepsy

Epilepsy is related to the underlying brain lesion (Legault et al., 2011; Reid et al., 2015; Sellier et al., 2012). In term children with cerebral palsy, grey matter lesions are more common (Sellier et al., 2012). Legault et al., found epilepsy more frequently in cerebral palsied children with cerebral vascular accident, or deep brain injury (Legault et al., 2011). In the study published by Reid et al., the prevalence of epilepsy was highest where there was diffuse cortical-subcortical involvement and white matter loss (Reid et al., 2015).

2 Literature review

2.1 HISTORY

Hemiplegia has been recognized since ancient times (Christensen and Melchior, 1967). The first to describe spastic diplegia was Little, an orthopaedic surgeon in his famous 1862 paper: “On the influence of abnormal parturition, difficult labours, premature birth and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities” (Little, 1966). He attributed cerebral palsy to perinatal factors. Freud’s “Clinical study of hemiplegia in children” was published in 1891. It was a pioneer study, in which he described 35 children, whom he met at the Public Paediatric Institutes in Vienna over a period of two and a half years (Freud and Rie, 1891). Freud was first to recognize the importance of prenatal aetiologic factors and was also aware of the importance of socioeconomic factors (Korzeniewski et al., 2018; Uvebrant, 1988). In his study he regretted that some of his case reports were incomplete, with no information about hereditary factors. But this lack was due to the fact that patients in public out-patients clinics in Vienna, at this time, were mainly from the poorest classes. Not only did he register the motor impairment, but also associated impairments such as epilepsy and intellectual disability (Freud and Rie, 1891)

2.2 REGISTERS FOR CEREBRAL PALSY

In order to monitor prevalence rates, especially within subgroups, it was considered necessary to study large populations. Registers for cerebral palsy were therefore established. The cerebral palsy register of western Sweden was founded as early as 1954 (Himmelmann and Sundh, 2015). The Victorian cerebral palsy register in Australia was established in 1986 (Reddihough et al., 2001). The Swedish Cerebral Palsy Follow-Up Program (CPUP), initiated in 1994, became a Swedish national quality register in the year 2005 (https://CPUP.se). Data in the CPUP register are collected at the local habilitation centres. The Surveillance of Cerebral Palsy in Europe (SCPE) began in 2000 as a network of cerebral palsy registers in 14 European countries (Cans et al., 2000). The subsequent process to standardize the definition of cerebral palsy, the inclusion and exclusion criteria, the classification and the description of clinical manifestations was initiated (Cans et al., 2000).

2.3 DEFINITIONS

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development. These motor impairments can have different aetiologic backgrounds, occurring in the antenatal, perinatal or post-neonatal period (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). The motor impairment is often associated

with visual- and hearing deficits as well as epilepsy and cognitive impairment. Children with cerebral palsy are commonly classified according to the SCPE guidelines (Cans et al., 2000). These guidelines are used to measure the functional loss associated with cerebral palsy and define criteria for each subtype of cerebral palsy, by distribution and type of motor impairment: hemiplegic (unilateral) or bilateral, spastic, dyskinetic or ataxic. A wide range of cerebral disorders, such as congenital malformation, prenatal circulatory disturbance, chromosome aberration, perinatal asphyxia, pre- or postnatal infection, and postnatal trauma have been indicated as aetiologic factors (Smithers-Sheedy et al., 2014). Cerebral palsy is also classified as being prenatal, perinatal or postnatal/post-neonatal according to the timing of the presumed insult (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). Earlier studies used the definition postnatal cerebral palsy. The cerebral lesion is often classified according to the anatomical site of the brain lesion: cerebral cortex, pyramidal tract, extrapyramidal system or cerebellum (Colver et al., 2014). The extent of the underlying cerebral lesion must also be recognized (Colver et al., 2014; Reid et al., 2014). The brain imaging patterns according to type, as classified by Reid et al., include white matter injury, grey matter injury, focal vascular insults and malformations (Reid et al., 2014). Due to the heterogeneity of cerebral palsy, it could be useful to study a subgroup, such as hemiplegic cerebral palsy (Cans et al., 2000; Stanley, 2000; Tillberg et al., 2020).

2.4 AETIOLOGY

Since Fiona Stanley published her important book “Cerebral palsies: Epidemiology and causal pathways”, there has been consensus that cerebral palsy results from multiple factors acting along a causal pathway (Stanley, 2000). A wide range of cerebral disorders, such as congenital malformation, prenatal circulatory disturbance, chromosome aberration, perinatal asphyxia, pre- or postnatal infection, and postnatal trauma have been indicated as aetiologic factors (Badawi et al., 1998). In “A systematic review of risk factors for cerebral palsy in children born at term in developed countries”, McIntyre et al.,found 10 consistent risk factors for cerebral palsy in term children: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/ emergency caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infection. However, other risk factors such as maternal disease or being large for gestational age were not statistically significant. But these risk factors may work together along a causal pathway (McIntyre et al., 2013). Socioeconomic factors are important (Woolfenden et al., 2019), especially the educational level of the parents (Forthun et al., 2018; Himmelmann et al., 2011; Hjern and Thorngren-Jerneck, 2008) and have an impact on the prevalence of cerebral palsy. Prevalence is decreasing in high-income countries (Badawi et al., 2020; Badawi et al., 1998; Himmelmann and Uvebrant, 2018). In the 2018 report from the cerebral palsy register of western Sweden, the prevalence of cerebral palsy was 1.96 per 1000 live births. However, children born outside Sweden and postnatal cases, older than 2 years, were excluded (Himmelmann and Uvebrant, 2018), so the real prevalence might be higher. According to the 2019 report “Refugee/immigrant children with cerebral palsy in the Swedish health care organization”, the prevalence of cerebral palsy for children born in Sweden was 1.99 per 1000 live births, compared to 3.40 per 1000 for children born outside Sweden. These immigrant children also had more severe functional impairments (Westbom, 2019).

In a recent study from Moldova, one of the countries in Europe with the lowest income per capita and with a relatively high infant and maternal mortality, the prevalence of cerebral palsy was 3.40 per 1000 live births. The proportions of children with severe motor disturbance, associated impairments

and children born at term were higher in Moldova, compared to those found by studies in other European countries (Gincota Bufteac et al., 2018) . Prevalence of cerebral palsy has become a good measure of the standard of health care, both in high- and low-income countries (Badawi et al., 2020; Gincota Bufteac et al., 2018).

2.4.1 Infection and/or skull trauma

Three earlier studies deal solely with postnatal cerebral palsy: Blair and Stanley, published in 1982 using data from Australia; Arens and Molteno, published in 1989 using data from South Africa; and Pharoah, Cook and Rosenbloom, published in 1989 containing data from England and Scotland (Arens and Molteno, 1989; Blair and Stanley, 1982; Pharoah et al., 1989). These studies all indicate that postnatally-acquired cerebral palsy is attributed to cerebral infection or skull trauma. Both of these causes are strongly associated with lower socioeconomic conditions, and therefore preventable.

2.4.2 Gestation

There is a gestational paradox: “Very strong relationship between prematurity and risk of cerebral palsy versus the fact that most patients with cerebral palsy are born at term” (Graham et al., 2016).

2.5 CLINICAL PICTURE IN HEMIPLEGIC CEREBRAL PALSY

Uvebrant, in his comprehensive population-based study of 169 children with hemiplegic cerebral palsy, from the cerebral palsy register of western Sweden, wanted to analyse the prevalence, aetiology and neurodevelopmental outcome in preterm and term children. In clinical follow- up of 152 children, 50% presented mild, 31 % moderate and 19% severe motor impairment. Additional impairments, such as intellectual disability, epilepsy, impaired vision, - hearing and -speech, were present in 42 % of the children (Uvebrant, 1988).

2.5.1 Motor impairment

The severity of the motor impairment in cerebral palsy varies widely (Colver et al., 2014). The severity of the motor disability can be assessed using the Movement Assessment Battery for Children (Movement ABC) This assesses fine-motor function, ball skills, static and dynamic balance, in children 4-12 years of age. The Movement ABC also takes into consideration speed, accuracy, and qualitative aspects of motor performance (Schulz et al., 2011). The Paediatric Evaluation Disability Inventory (PEDI) measures capacity and performance in three domains, to investigate functional abilities in three different categories (self-care, mobility and social function) in children between 6 months and 7 years. It can be used for children older than 7 years if their performance is below the norm (Haley et al., 2010). Early handedness was a strong predictor of hemiplegia in the study by Cohen and Duffner (Cohen and Duffner, 1981). Uvebrant found a mean age of 6 months for early handedness in congenital hemiplegia (Uvebrant, 2000).

2.5.2 Associated impairments

The motor impairment is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment (Colver et al., 2014; Rosenbaum et al., 2007; Stanley, 2000; Uvebrant, 1988).

2.5.2.1 Epilepsy in cerebral palsy

Epilepsy is an important adverse factor for cognitive function in cerebral palsy (Cioni et al., 1999; Singhi et al., 2003; Wallace, 2001). It is common, present in 30-40 % of cerebral palsy cases (Dos Santos Rufino et al., 2023; Graham et al., 2016; Pavone et al., 2020; Sellier et al., 2012; Zelnik et al., 2010). Stanley reported in 2000 a higher occurrence of epilepsy in those with postneonatally/ postnatally-acquired cerebral palsy (Stanley, 2000). Most studies of epilepsy in cerebral palsy are based on medical records, or information from cerebral palsy registers. Sellier et al., described epilepsy, neonatal characteristics, associated impairments and subtypes of cerebral palsy in a large register-based study (Sellier et al., 2012).

2.5.2.2 Epilepsy in, specifically, hemiplegic cerebral palsy

Three studies address epilepsy in, specifically, hemiplegic cerebral palsy (Cioni et al., 1999; Uvebrant, 1988; Wanigasinghe et al., 2010). Uvebrant found epilepsy in 54 (34%) of 152 children with hemiplegic cerebral palsy in a population-based study in 1988. Focal epilepsy was the most common type. Right-sided hemiplegia was more frequently associated with epilepsy (29%) than left-sided (13%) (Uvebrant, 1988). Cioni,et al., studied 91 hemiplegic children in a large hospital-based series. Epilepsy was present in 35% of the participants (Cioni et al., 1999). Wanigasinghe et al., studied epilepsy in 63 children with hemiplegic cerebral palsy, due to arterial ischaemic stroke: epilepsy was present in 34 children (54%), with focal seizures being most common (Wanigasinghe et al., 2010).

2.5.2.3 Electroencephalographic studies in hemiplegic cerebral palsy

The electroencephalogram (EEG) was abnormal in all children with epilepsy and in all postnatal cases in Uvebrant`s study. Epilepsy proved to be the all-important determinant for EEG pathology (Uvebrant, 1988). Wanigasinghe et al.,in their study of epilepsy in hemiplegia due to perinatal arterial ischaemic stroke, found focal epileptiform activity in the children with focal seizures (Wanigasinghe et al., 2010).

2.5.2.4 Epilepsy and intellectual disability in cerebral palsy

Intellectual disability and epilepsy are important accompanying impairments in cerebral palsy (Carlsson et al., 2003; Delacy et al., 2016; Reid et al., 2018; Sellier et al., 2012; Uvebrant, 1988). Uvebrant's 1988 study of 152 children with hemiplegic cerebral palsy revealed intellectual disability in 18% of children, and that postnatal cases, compared to pre- and perinatal cases, more frequently developed epilepsy (Uvebrant, 1988). Intellectual disability was also found to be associated with epilepsy in another study from southwest Sweden (Carlsson et al., 2003). Sellier et al., described epilepsy, neonatal characteristics, associated impairments and subtypes of cerebral palsy in a large register-based study. They found that 691 (25.6%) of the 2699 hemiplegic children had epilepsy. Epilepsy and/or intellectual impairment was related to a more widespread brain injury (Sellier et al., 2012).

2.5.3 Intellectual disability in cerebral palsy

Intellectual disability is an important accompanying impairment in cerebral palsy (Korzeniewski et al., 2018; Reid et al., 2018; Sigurdardottir et al., 2008; Stadskleiv et al., 2018). The Wechsler Intelligence Scale for Children (WISC) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) are the most frequently used measures of intelligence quotient, at least in Western Europe and the USA (Corporation, 1989; Wechsler, 2011). The Full Scale Intelligence Quotient, in the WISC-test, is a

measure of specific cognitive domains: verbal comprehension, perceptual reasoning, working memory and processing speed (Kahalley et al., 2016; Wechsler, 2011). The General Ability Index, an optional composite score, is recommended when scores are low for working memory and processing speed (Raiford et al., 2008). It is less influenced by working memory and processing speed and compensates for low motor performance, to give a more accurate assessment of cognitive ability (Kahalley et al., 2016; Raiford et al., 2008). Most studies of intellectual disability in cerebral palsy are register-based and cognition is often described with a total value, the intelligence quotient (IQ) (Ahlin et al., 2017; Himmelmann and Uvebrant, 2011; Reid et al., 2018). In contrast, Sigurdardottir et al.,described the cognitive profiles of a complete national Icelandic cohort of 127 children with cerebral palsy, in a pioneer study from 2008. In their study they supplied information about gestational age, ambulatory status, hearing- and visual impairment and epilepsy. The children were tested using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). The median intelligence quotients were lower than normal range, but a significant proportion of the children, especially those with hemiplegia, had normal scores. Some of the children had a distinct discrepancy between language ability and performance. Sigurdardottir et al., found that children with uneven cognitive profiles, were at risk for nonverbal learning disability. Epilepsy, present in 27 % of this cohort, was associated with an independent effect on intelligence quotient. The authors stressed the importance of thorough intellectual assessment before school start (Sigurdardottir et al., 2008). Children with cerebral palsy, epilepsy and cognitive disability constitute a substantial proportion of the patient population in paediatric neurology. Since Sigurdardottir´s pioneer study in 2008, awareness of the importance of intellectual disability has increased. An increasing number of register-based studies describe these impairments simultaneously (Ahlin et al., 2017; Delacy et al., 2016; Reid et al., 2018; Sellier et al., 2012). In Reid`s 2018 population-based study of intellectual disability in cerebral palsy, using data from the cerebral palsy register of Victoria, Australia, a more extensive medical background was provided, with information about communication, neuroimaging classification and birth defects. Reid found intellectual disability, as a tested intelligence quotient, in 25.5 % of the hemiplegic children. Concomitant epilepsy was associated with a higher frequency of intellectual disability (Reid et al., 2018). Stadskleiv et al., on the other hand, presented a clinical study of intellectual disability in a population-based sample of 70 cerebral palsied children, of whom 35 were hemiplegic. Information was given about birth weight, gestational age, magnetic resonance imaging of the brain, and epilepsy. Children were tested with WPPSI/ WISC and other tests. In this study, 30 of the 35 hemiplegic children (86%) had normal cognitive profiles and five (14 %) showed intellectual disability. Uneven cognitive profiles were found in eight (36%) of the children with normal cognition (Stadskleiv et al., 2018).

2.5.4 Brain imaging

The cerebral lesion can be classified according to the anatomical site of the brain lesion: cerebral cortex, pyramidal tract, extrapyramidal system or cerebellum (Colver et al., 2014). The extent of the underlying cerebral lesion must also be recognized (Colver et al., 2014; Reid et al., 2014). The imaging patterns according to type, as classified by Reid et al., include white matter injury, grey matter injury, focal vascular insults and malformations (Reid et al., 2014).

2.5.4.1 Brain imaging and epilepsy

Epilepsy is related to the underlying brain lesion. In term children with cerebral palsy, grey matter lesions are more common (Sellier et al., 2012). Legault et al.,found epilepsy more frequently in

cerebral palsied children, with cerebral vascular accident, or deep brain injury (Legault et al., 2011). In the study published by Reid et al., the prevalence of epilepsy was highest where there was generalized cortical-subcortical involvement and white matter loss (Reid et al., 2015).

2.6 RISK FACTORS

In Stockholm, Sweden, only children included in the high-risk group are considered for special follow- up by a neonatologist or neurologist. This high-risk group encompasses major perinatal risk factors such as asphyxia, neonatal seizures, cerebral haemorrhage, hypoxic ischaemic encephalopathy, sepsis etc., leading to care in the neonatal unit. Birth before 28 weeks of gestation and/or children being small for gestational age are also included in the high-risk group of the Swedish Neonatal Society (Guidelines Swedish Neonatal Society, 2015). Children without major perinatal risk factors are examined by a general practitioner at the child health centre. Most patients with cerebral palsy are born at term (Graham et al., 2016). In “A systematic review of risk factors for cerebral palsy in children born at term in developed countries”, McIntyre found 10 consistent risk factors for cerebral palsy in term children: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/ emergency caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infection. However, other risk factors such as maternal disease or being large for gestational age were not statistically significant. But these risk factors may work together along a causal pathway (McIntyre et al., 2013).

3 Research aims

The main purpose of the first three studies was to describe the motor impairments and associated impairments in a population-based group of postnatal, post-infectious hemiplegic children. Another aim was to assess the population-based prevalence of postnatal, post-infectious hemiplegic cerebral palsy in Stockholm County. The objective of the two ensuing studies, was to investigate clinical presentation, epilepsy, electroencephalogram (EEG), brain imaging and intellectual disability, in a population-based group of children with hemiplegic cerebral palsy. The focus of all studies was to also identify aetiologic backgrounds and risk factors, to enable early identification and better care for these children.

4 Materials and methods

4.1 DEFINITIONS

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). The motor impairment is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment (Colver et al., 2014; Rosenbaum et al., 2007; Stanley, 2000). Participants were classified according to the Surveillance of Cerebral Palsy in Europe (SCPE) (Cans et al., 2000). Hemiplegia was defined as a unilateral motor disability. Intellectual disability was defined as an intelligence quotient (IQ) less than 70, in accordance with the World Health Organisation (WHO), International Classification of Diseases, Tenth Revision (ICD-10). The further subdivisions, IQ 50-69 as mild, IQ 35-49 as moderate, and IQ less than 35 as severe, were also made according to WHO (WHO 2004).

4.2 CLINICAL ASSESSMENT

All case records were reviewed with particular attention to the pathogenesis and to pre- peri- and postnatal risk factors for cerebral palsy. Case history included information about gestation, birth-weight, perinatal events, debut of clinical signs and age at diagnosis. Parents´occupation and educational level were also documented in the second part of the study. Consistent risk factors for cerebral palsy in term children according to Mc Intyre et al., (McIntyre et al., 2013), such as low birth weight, meconium aspiration, caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome and neonatal infection, were documented. Other risk factors such as maternal disease, or being large for gestational age, were also noted. Postnatal risk factors included cerebral infection, head trauma or surgery. All participants were examined by the same paediatric neurologist (ET) in the first and second part of the study. The neurological examination included assessment of cranial nerves, head circumference, muscle tone, motor impairment, tendon reflexes and the Babinski plantar response. Debut of clinical signs of motor impairment, and age at diagnosis were documented. Special focus was laid on impaired hand function and delayed, or abnormal walking.

In **study III** the severity of the motor disability was assessed by the paediatric physiotherapist using the Movement Assessment Battery for Children (Schulz et al., 2011). The Paediatric Disability Inventory was used to investigate functional abilities in three different categories: self-care, mobility and social function (Haley et al., 2010).

EEG was recorded according to the 10-20 system, 20 minutes registration with alert patient. All available computerized tomography (CT)-scans and/or magnetic resonance imaging, (MRI)-scans of the brain were collected and reviewed by an experienced radiologist.

4.2.1 Cognitive assessment

The Wechsler Intelligence Scale for Children (WISC) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) are the most frequently used measures of intelligence quotient, at least in Western Europe and the USA (Corporation, 1989; Wechsler, 2011). The Full Scale Intelligence Quotient, in the WISC-test, is a measure of specific cognitive domains: verbal comprehension,

perceptual reasoning, working memory and processing speed (Kahalley et al., 2016; Wechsler, 2011). The General Ability Index, an optional composite score, is recommended when scores are low for working memory and processing speed (Raiford et al., 2008). It is less influenced by working memory and processing speed and compensates for low motor performance, to give a more accurate assessment of cognitive ability (Kahalley et al., 2016; Raiford et al., 2008). The Wechsler Intelligence Scale for Children (WISC) was used for cognitive assessment in most of the participants (Wechsler, 2011). Some pre-school children were assessed with the Griffiths Mental Development Scales (Luiz et al., 2001). Information about speech- and language development was based on a speech therapist`s clinical assessment in **studies I-III,** and according to Andersen et al., in **study IV-V,** (Andersen et al., 2008).

4.2.2 Case identification

In the first part of the thesis **(studies I-III),** children with hemiplegic cerebral palsy, subsequent to a cerebral infection in the perinatal period up to the age of 7 years, participated. Children were identified via a written survey sent to all paediatric neurologists and developmental specialists at the hospitals in Stockholm and to all 13 Outpatient Habilitation Clinics in Stockholm County. In the second part **(studies IV-V**), children aged 7 to 16 years, fulfilling the SCPE-criteria of hemiplegic cerebral palsy, were identified via the Swedish Cerebral Palsy Follow-Up Programme (CPUP), the national Swedish cerebral palsy register (https://CPUP.se). A written survey to make contact with these children, was also sent to all Outpatient Habilitation Clinics in northern Stockholm.

4.2.3 Ethical considerations

The studies were performed in accordance with the Declaration of Helsinki and approved by the Regional Ethical Review Board in Stockholm: ethical permit numbers 98-291 and 2012/835-31/2. A written information sheet was read out to, and informed written consent was obtained from all participating parents. In the second part of the thesis, children were also identified via the national Swedish Cerebral Palsy Follow-Up Program, CPUP (https://CPUP.se). Upon registration in the CPUP, parents/ caregivers are informed that their child´s data can be used for research purposes, and that they may opt out at any time. All Swedish healthcare regions now participate in the CPUP (Knudsen et al., 2022).

5 Results

The first part of the thesis described the prevalence, motor impairments, and associated impairments in a population-based group of children with postnatal, post-infectious hemiplegic cerebral palsy. The group comprised 13 children, (7 girls and 6 boys) with a mean age of 9.5 years (range 1—17 years)**.**

In **study I** the point prevalence of postnatal, post-infectious hemiplegic cerebral palsy in the whole group, in Stockholm County, was 0.03/ 1000. But the point prevalence was 0.37/ 1000 in an immigrant dominated suburb. In the complete group of children with postnatal, post-infectious, hemiplegia in Stockholm County, most of the participants´ parents (19/26) and six of the participants were born outside Sweden. Aetiologic background factors were also documented. Four of the participants had consistent risk factors for cerebral palsy in term children according to McIntyre et al (2013), and one was also born preterm. Brain imaging findings, a CT-scan and/or MRI were very variable: six participants showed bilateral lesions and only two showed normal examinations. The majority of the examinations showed some level of cortical involvement. We found a high frequency of epilepsy and intellectual disability in the whole group of children with postnatally acquired post-infectious cerebral palsy. Anti-epileptic drugs had been prescribed in seven of the 13 participants (50%), because of partial or generalized tonic-clonic seizures. Only one child displayed no epilepsy and a normal EEG. The EEG abnormalities were variable, with focal and /or generalized alterations. For nine of the children, the results of an assessment conducted by a child psychologist were available: six exhibited mild, and three moderate intellectual disability.

In **study II** six youths and 15 caregivers were interviewed regarding the child's ability to participate in age-related activities. All reported great difficulties participating in age-related activities. Hygiene issues hindered children with a non-Swedish cultural background from participating in camps or swimming. In **study III** the severity of the motor disability was assessed using the Movement Assessment Battery for Children (Schulz et al., 2011) and the Paediatric Disability Inventory to investigate functional abilities in three different categories: self-care, mobility and social function (Haley et al., 2010). Balance and hand function were impaired in all participants. The non-hemiplegic side was also tested and found to be affected in most cases. Motor difficulties predominated during pre-school years. Difficulties with social and communication skills predominated in school-age children.

The second part of the thesis focused on studies of a population-based group of hemiplegic children with different aetiologic backgrounds. This group included 21 children (15 boys and 6 girls) aged 7 to 15 years, 15 boys and six girls with a mean age of 11 years. In **study IV** we investigated aetiologic background factors, clinical presentation including brain imaging, electroencephalogram (EEG) and epilepsy in each child. More than half of the 42 parents of the participants had lower educational level. Parental professions varied. Five children were born preterm and five were delivered by caesarean section. Parturition was rapid in two children, prolonged in one. Two children were small for gestational age and two were large for gestational age. Neonatal seizures occurred in two children, for one of them concomitantly with asphyxia. Two of the five preterm children presented additional risk factors. Postnatal skull trauma and/or cerbral operation was present in four children, one of them born preterm. Only five of the 21 children had no pre-, peri-or postnatal risk factors for cerebral palsy.

Debut of motor impairment was observed in the first year of life in 16 children. Early handedness was present in more than 90 % of the children. Abnormal or delayed walking was present in eight children. Age at diagnosis varied from 2 months to 6 years (!).

Brain imaging, a CT-scan and/ or MRI, revealed left-sided lesions in 11, right-sided in six and bilateral lesions in three children. Seven children showed white matter injury only; five children had focal vascular insults affecting both white and grey matter. The extent of the lesion varied from slight periventricular leucomalacia to loss of most of the left hemisphere. Nine of the 21 children (40 %) developed epilepsy. Seven of the nine children who developed epilepsy showed focal epilepsy; two had generalized seizures. Epilepsy onset was from 1 to 12 years of age. Five children were seizure-free, with or without antiepileptic drugs. Focal abnormalities in the EEG were the main findings. All children who developed neonatal seizures, or epilepsy later on, showed both white and grey matter injury.

In **study V** we investigated intellectual disability and its association with epilepsy and brain imaging in this population-based group of hemiplegic children. Intelligence quotient (IQ) varied between 40 and 108. Normal cognitive ability was found in 13, mild impairment in five and moderate impairment in three children. Intellectual disability was present in five of the nine children with epilepsy. Intellectual disability was present in 38 % of the participants and uneven cognitive profiles in 57%. The General Ability Index was estimated for eight children and found to be higher than their Full Scale IQ.

6 Discussion

Cerebral palsy is an umbrella term for motor impairments that share features of a non-progressive brain injury, acquired during the early stages of its development (Rosenbaum et al., 2007).These motor impairments can have different aetiologic backgrounds, occurring in the prenatal, perinatal or postnatal period (Colver et al., 2014).The motor impairment is often associated with visual- and hearing deficits as well as epilepsy and cognitive impairment (Colver et al., 2014; Graham et al., 2016; Rosenbaum et al., 2007). An increasing number of studies address these impairments simultaneously (Ahlin et al., 2017; Delacy et al., 2016; Dos Santos Rufino et al., 2023; Sellier et al., 2012).

In the first part of the thesis we described the point prevalence, motor impairments, associated impairments and participation in a population-based group of children with hemiplegia/unilateral cerebral palsy after cerebral infection. The point prevalence was 0.37/1000 in an immigrant dominated suburb and 0.03/1000 in Stockholm County (Tillberg et al., 2008). The high prevalence of hemiplegia in this suburb dominated by immigrants, could reflect the impact of socioeconomic factors. Most of the parents of the participants in the complete group, were born outside Sweden. Socioeconomic factors are important (Stanley, 2000), especially the educational level of the parent (Delacy et al., 2016; Forthun et al., 2018; Himmelmann et al., 2011; Hjern and Thorngren-Jerneck, 2008). The report "Refugee/immigrant children with cerebral palsy in the Swedish health care organization" was published in 2019 (Westbom, 2019). According to this report, the prevalence of cerebral palsy for children born in Sweden was 1.99 per 1000 live births, compared to 3.40 per 1000 for children born outside Sweden. These immigrant children also had more severe functional impairments (Westbom, 2019). In **study I,** common infecting agents were tuberculosis, malaria or unspecified febrile illness (Tillberg et al., 2008). These agents are still endemic in Indonesia, according to a 2020 study: "Epidemiology of cerebral palsy in Sumba Island, Indonesia" (Jahan et al., 2020). These infections are strongly associated with poor socioeconomic conditions. The prevalence of cerebral palsy is decreasing in high income countries (Himmelmann and Uvebrant, 2018; Tharaldsen et al., 2022). Prevalence of cerebral palsy has become a good measure of the standard of health care, both in high- and low- income countries (Badawi et al., 2020; Gincota Bufteac et al., 2018).

Risk factors

Pre-peri- and postnatal risk factors were present in both parts of this thesis. Four of the 13 participants in the first part had risk factors for cerebral palsy in term children, according to McIntyre (McIntyre et al., 2013). Reid et al., found an over-representation of preterm children in their 2006 study of post-neonatally acquired cerebral palsy (Reid et al., 2006). Low birth weight was also a risk factor (Reid et al., 2006). In a recent study from Norway, a higher proportion of children with post-neonatally acquired cerebral palsy, were born preterm (Tharaldsen et al., 2022). In the second part of this thesis, 13 of the 21 children had consistent risk factors according to McIntyre (McIntyre et al., 2013). Eight had a low birthweight, five children were born preterm, two were small for gestational age, two were large for gestational age, and four had postnatal skull trauma and/or cerebral operation. Only five children had no pre- peri- or postnatal risk factor for cerebral palsy (Tillberg et al., 2020). Risk factors for cerebral palsy may work together along a causal pathway (McIntyre et al., 2013). Pre -peri- or postnatal risk factors for cerebral palsy, present in 16 of the 21 participants in the second part of this study, are important for early case identification. In Stockholm, Sweden only children included in the

high risk group with severe risk factors are considered for special follow up by a neonatologist or neurologist according to the Swedish Neonatal Society (Society, 2015).

Motor impairment

In **study II,** six youths and 15 caregivers were interviewed regarding the child s ability to participate in age-related activities. All reported great difficulties participating in age-related activities (Radell et al., 2008a). In a recent study of long term course of difficulty in participation of individuals with cerebral palsy, 151 individuals with cerebral palsy, without intellectual disability, 16-34 years of age, were investigated. A high percentage, 41-95 % experienced difficulty in participation (van Gorp et al., 2019). In **study III** the use of methodology standardized for age, revealed that balance and hand function were impaired in all participants. The non-hemiplegic side was also tested and found to be also affected in most cases. Motor difficulties dominated during pre-school years. Difficulties with social and communication skills predominated in school-age children (Radell et al., 2008b). Tharaldsen et al., found a strong association between post-infectious, post-neonatal cerebral palsy and more severe motor- and associated impairments (Tharaldsen et al., 2022). Spastic hemiplegia was the most common type in the studies of post-neonatal cerebral palsy from Australia (Reid et al., 2006) and Norway (Tharaldsen et al., 2022). We suggest that future research on the severity of the motor impairment in hemiplegic cerebral palsy, should include reliable age appropriate tests of motor function. In **study IV,** debut of motor impairment, as observed by parents, was evident in the first year of life in 16 children. Early handedness was present in more than 90 % of the children. Abnormal or delayed walking was present in eight children. Age at diagnosis varied from 2 months to 6 years (!) (Tillberg et al., 2020). Early handedness was a strong predictor of hemiplegia in the 1981 studies by Cohen and Duffner (Cohen and Duffner, 1981). Uvebrant found a mean age of 6 months for early handedness in congenital hemiplegia (Uvebrant, 2000). Early handedness should also imply early specialist evaluation! In Japan all children can meet a pediatrician for regular care (http://japanhealthinfo./com/child-health-and-childcare/pediatrics).

Associated impairments

Epilepsy

In the first part of this thesis, in the study published in 2008, we found a high frequency of epilepsy and intellectual disability in a group of postnatal, post-infectious hemiplegic children (Tillberg et al., 2008). Uvebrant, already in his 1988 thesis: “Hemiplegic Cerebral Palsy. Aetiology and Outcome”, found that the prevalence of total handicap was highest in postnatal cases (Uvebrant, 1988). In a recent study from Norway of post- neonatally acquired cerebral palsy, hemiplegic cerebral palsy was the dominating subtype. The children with post-neonatally acquired cerebral palsy had more associated impairments than children with pre-and perinatally acquired cerebral palsy (Tharaldsen et al., 2022). We found a high frequency of epilepsy in the hemiplegic children, 50% in **study I** (Tillberg et al., 2008) and 40 % **in study IV** (Tillberg et al., 2020). Epilepsy is commonly associated with cerebral palsy, present in 30-40 % of cases (Dos Santos Rufino et al., 2023; Graham et al., 2016; Pavone et al., 2020; Sellier et al., 2012; Zelnik et al., 2010) . In our study IV epilepsy was present in about 40 % of the children, the same level as in many larger studies (Cooper et al., 2022; Dos Santos Rufino et al., 2023; Sellier et al., 2012). In recent studies from tertiary centers, K Archana et al., found epilepsy in 26% of 300 children with cerebral palsy and in 30 % of those with spastic hemiplegia (K et al., 2022). Hyein et al., found epilepsy in 36.9 % of 268 children with cerebral palsy (Hyein, 2023). In

study I the frequency of epilepsy was higher in the cases of postnatally acquired hemiplegia, which agrees with findings from the studies by Uvebrant (Uvebrant, 1988) and Tharaldsen (Tharaldsen et al., 2022). Few direct clinical studies address epilepsy in, specifically, hemiplegic cerebral palsy: Uvebrant and Cioni et al., found epilepsy in 34-35 % of the children with focal epilepsy as the most common type (Cioni et al., 1999; Uvebrant, 1988). Wanigasinghe et al (2010) studied children with hemiplegic cerebral palsy due to arterial ischaemic stroke: epilepsy was present in 54%, with focal seizures being most common. Focal seizures were also most common in hemiplegia in the study by Pavone et al., (Pavone et al., 2020), which agrees with the findings from **study IV** (Pavone et al., 2020).

The electroencephalogram (EEG) was abnormal in all children with epilepsy and in all postnatal cases in Uvebrants's 1988 study of hemiplegia. Epilepsy proved to be the all-important determinant for EEG pathology (Uvebrant, 1988). Wanigasinghe et al., in the 2010 study of epilepsy in hemiplegia due to perinatal arterial ischaemic stroke, found focal epileptiform activity in the children with focal seizures. Focal abnormalities in the EEG were also the main findings in **study IV** (Tillberg et al., 2020).

Intellectual disability

Intellectual disability and epilepsy are important accompanying impairments in cerebral palsy, which often affect the child´s development and education (Ahlin et al., 2017; Delacy and Reid, 2016; Reid et al., 2018; Sellier et al., 2012; Stadskleiv et al., 2018). In **study I,** all the children assessed by a child psychologist displayed mild or moderate intellectual disability (Tillberg et al., 2008). Children with postnatally-acquired cerebral palsy are known to have a high rate of intellectual disability (Arens and Molteno, 1989; Pharoah et al., 1989; Tharaldsen et al., 2022). Tharaldsen et al., suggests that future research should include more detailed information about children with post-neonatally acquired cerebral palsy (Tharaldsen et al., 2022). In register-based studies, assessment of cognition is often described with a total value, the intelligence quotient (IQ), but as Reid (Reid et al., 2018) points out, summary scores may misinterpret the child`s actual level of functioning, through the inclusion of tasks that require speed or fine motor response. The results of **study V,** like the clinical studies of Sigurdardottir et al., (Sigurdardottir et al., 2008) and Stadskleiv et al., (Stadskleiv et al., 2018), also show the importance of cognitive assessment, as uneven cognitive profiles were found in 57 % of the children (Tillberg and Persson, 2024). Sigurdardottir et al., also highlights the fact that children with cerebral palsy often have uneven cognitive profiles. **In study V** the General Ability Index was estimated for eight children and found to be higher, at a significant level, than their Full Scale IQ, suggesting that the General Ability Index can give a more accurate understanding of cognitive ability in children with uneven cognitive profiles (Kahalley et al., 2016). In Iceland all children with cerebral palsy, who are seen at the national developmental center, have a cognitive assessment performed at 5-6 years of age (Sigurdardottir, 2020). In the guidelines of the Swedish Cerebral Palsy Registry, cognitive assessment of all children with cerebral palsy is recommended (https:// CPUP.se). However, in clinical practice this is not yet a routine in Sweden. In their study of the implementation of the cerebral palsy cognition project in Sweden and Norway, Stadskleiv et al., found that only 7 % of the cerebral palsied children in Sweden had cognitive assessments performed (Stadskleiv et al., 2021). According to Ann Alriksson-Schmidt, associate professor at the CPUP, it is still the case that only a limited number of children with cerebral palsy are tested in Sweden. There are also large regional variations (Alriksson-Schmidt, 2024). In the population-based studies of Sigurdardottir et al., and Reid et al., a strong correlation between intellectual disability and the presence of epilepsy was

found, when hemiplegic children were tested with cognitive scales (Reid et al., 2018; Sigurdardottir et al., 2008). In **study I** most of the participants displayed intellectual disability and/ or delayed speech or language impairment. Epilepsy was present in 50% (Tillberg et al., 2008) In **study V,** nine of the 21 hemiplegic children (40%) had developed epilepsy, focal in seven and generalized in two cases (Tillberg et al., 2020). Intellectual disability was present in three of the children with focal epilepsy, and in the two children with generalized seizures. In this study, children with malformations and focal vascular insults, had the highest rate of intellectual disability. Several studies have shown that grey matter injuries and malformations are associated with an increased risk of epilepsy and/or intellectual disability (Dos Santos Rufino et al., 2023; Himmelmann and Uvebrant, 2011; Reid et al., 2015).

Strength

A strength of these studies is that, in contrast to many studies, the participants were evaluated in direct clinical examination by a child physiotherapist, paediatric neurologist and child psychologist all with long eperience. Many studies of cerebral palsy and epilepsy are based on information from cerebral pallsy registers, but have no direct clinical examination of the participants. Direct clinical studies can be a valuable complement to studies based solely on information from cereral palsy registers.

Limitations

In the first part of the thesis, 13 of the 14 children fullfilling the inclusion criteria of the study, participated. However, in the second part, fewer than half of the eligible subjects participated, which may have biased the results. It is likely that the parents of the children with most problems consented to participate, being more motivated to have an assessment of the children's difficulties.

7 Conclusions

Cerebral infection at an early age can cause hemiplegic cerebral palsy with a high frequency of associated impairments and also involvement of the non-hemiplegic side. The infectious origin probably gives rise to a wider brain injury.

Pre- peri- and postnatal risk factors for cerebral palsy may work together along a causal pathway. They are important for prevention and early identification. Any child with these risk factors should be offered a check-up by a paediatrician or paediatric neurologist.To avoid diagnostic delay, any child with early impaired handfunction and/or abnormal walking should also be offered a checkup by a specialist.

Intellectual disability and/or epilepsy in hemiplegic cerebral palsy are related to the underlying brain lesion.Intellectual disability is an important accompanying impairment in cerebral palsy, which often affects the child`s development and education. Together, these studies show that epilepsy, intellectual disability and uneven cognitive profiles are common in hemiplegic cerebral palsy. Individual cognitive assessment is therefore recommended before school start.

Early identification and individual cognitive assessment before school start should facilitate the children`s participation in society!

8 Points of perspective

Risk factors for cerebral palsy are important for early identification. Any child with these risk factors should be offered a check-up by a paediatrician or paediatric neurologist. Together these studies show that epilepsy, intellectual disability and uneven cognitive profiles are common in hemiplegic cerebral palsy. Intellectual disability is an important accompanying impairment in cerebral palsy, which often affects the child´s development and education. Individual cognitive assessment before school start is recommended.

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10 References

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https://CPUP.se.

Ahlin, K., Jacobsson, B., Nilsson, S., Himmelmann, K., 2017. Antecedents and neuroimaging patterns in cerebral palsy with epilepsy and cognitive impairment: a population-based study in children born at term. Acta Obstet Gynecol Scand 96, 828-836.

Alriksson-Schmidt, A., 2024.

Andersen, G.L., Irgens, L.M., Haagaas, I., Skranes, J.S., Meberg, A.E., Vik, T., 2008. Cerebral palsy in Norway: prevalence, subtypes and severity. Eur J Paediatr Neurol 12, 4-13.

Arens, L.J., Molteno, C.D., 1989. A comparative study of postnatally-acquired cerebral palsy in Cape Town. Dev Med Child Neurol 31, 246-254.

Badawi, N., McIntyre, S., Hunt, R.W., 2020. Perinatal care with a view to preventing cerebral palsy. Dev Med Child Neurol.

Badawi, N., Watson, L., Petterson, B., Blair, E., Slee, J., Haan, E., Stanley, F., 1998. What constitutes cerebral palsy? Dev Med Child Neurol 40, 520-527.

Blair, E., Stanley, F.J., 1982. An epidemiological study of cerebral palsy in Western Australia, 1956-1975. III: Postnatal aetiology. Dev Med Child Neurol 24, 575-585.

Cans, C., Guillem, P., Baille, F., Arnaud, C., Chalmers, J., Cussen, G., McManus, V., Parkes, J., Dolk, H., Hagberg, G., Hagberg, B., Hensey, O., Dowding, V., Jarvis, S., Colver, A., Johnson, A., Surmann, G., Krageloh-Mann, I., Michaelis, R., Pharoah, P., Platt, M.J., Topp, M., Udall, P., Torrioli, M.G., Miceli, M., Wichers, M., van Nieuwenhuizen, O., Europe, S.C.P., 2000. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Developmental Medicine and Child Neurology 42, 816-824.

Carlsson, M., Hagberg, G., Olsson, I., 2003. Clinical and aetiological aspects of epilepsy in children with cerebral palsy. Dev Med Child Neurol 45, 371-376.

Christensen, E., Melchior, J., 1967. Cerebral palsy-a clinical and neuropathological study. W. Heinemann Med Books. Ltd., London.

Cioni, G., Sales, B., Paolicelli, P.B., Petacchi, E., Scusa, M.F., Canapicchi, R., 1999. MRI and clinical characteristics of children with hemiplegic cerebral palsy. Neuropediatrics 30, 249-255.

Cohen, M.E., Duffner, P.K., 1981. Prognostic indicators in hemiparetic cerebral palsy. Ann Neurol 9, 353-357.

Colver, A., Fairhurst, C., Pharoah, P.O., 2014. Cerebral palsy. Lancet 383, 1240-1249.

Cooper, M.S., Mackay, M.T., Dagia, C., Fahey, M.C., Howell, K.B., Reddihough, D., Reid, S., Harvey, A.S., 2022. Epilepsy syndromes in cerebral palsy: varied, evolving and mostly self-limited. Brain.

Cooper, M.S., Mackay, M.T., Fahey, M., Reddihough, D., Reid, S.M., Williams, K., Harvey, A.S., 2017. Seizures in Children With Cerebral Palsy and White Matter Injury. Pediatrics 139.

Corporation, T.P., 1989. Manual for the Wechsler Preschool and Primary Scale of Intelligence-Revised.

Delacy, M.J., Reid, S.M., 2016. Profile of associated impairments at age 5 years in Australia by cerebral palsy subtype and Gross Motor Function Classification System level for birth years 1996 to 2005. Dev Med Child Neurol 58 Suppl 2, 50-56.

Delacy, M.J., Reid, S.M., Australian Cerebral Palsy Register, G., 2016. Profile of associated impairments at age 5 years in Australia by cerebral palsy subtype and Gross Motor Function Classification System level for birth years 1996 to 2005. Dev Med Child Neurol 58 Suppl 2, 50-56.

Dos Santos Rufino, A., Påhlman, M., Olsson, I., Himmelmann, K., 2023. Characteristics and Challenges of Epilepsy in Children with Cerebral Palsy-A Population-Based Study. J Clin Med 12.

El-Tallawy, H.N., Farghaly, W.M., Shehata, G.A., Badry, R., Rageh, T.A., 2014. Epileptic and cognitive changes in children with cerebral palsy: an Egyptian study. Neuropsychiatr Dis Treat 10, 971-975.

Forthun, I., Strandberg-Larsen, K., Wilcox, A.J., Moster, D., Petersen, T.G., Vik, T., Lie, R.T., Uldall, P., Tollanes, M.C., 2018. Parental socioeconomic status and risk of cerebral palsy in the child: evidence from two Nordic population-based cohorts. Int J Epidemiol.

Freud, S., Rie, O., 1891. Klinische Studie uber die halbseitige Cerebrallähmung der Kinder. verlag von Moritz Perles, vienna.

Gillies, M.B., Bowen, J.R., Patterson, J.A., Roberts, C.L., Torvaldsen, S., 2018. Educational outcomes for children with cerebral palsy: a linked data cohort study. Dev Med Child Neurol 60, 397-401.

Gincota Bufteac, E., Andersen, G.L., Torstein, V., Jahnsen, R., 2018. Cerebral palsy in Moldova: subtypes, severity and associated impairments. BMC Pediatr 18, 332.

Graham, H.K., Rosenbaum, P., Paneth, N., Dan, B., Lin, J.P., Damiano, D.L., Becher, J.G., Gaebler-Spira, D., Colver, A., Reddihough, D.S., Crompton, K.E., Lieber, R.L., 2016. Cerebral palsy. Nat Rev Dis Primers 2, 15082.

Gururaj, A.K., Sztriha, L., Bener, A., Dawodu, A., Eapen, V., 2003. Epilepsy in children with cerebral palsy. Seizure 12, 110-114.

Haley, S.M., Coster, W.I., Kao, Y.C., Dumas, H.M., Fragala-Pinkham, M.A., Kramer, J.M., Ludlow, L.H., Moed, R., 2010. Lessons from use of the Pediatric Evaluation of Disability Inventory: where do we go from here? Pediatr Phys Ther 22, 69-75.

Himmelmann, K., Ahlin, K., Jacobsson, B., Cans, C., Thorsen, P., 2011. Risk factors for cerebral palsy in children born at term. Acta Obstet Gynecol Scand 90, 1070-1081.

Himmelmann, K., Sundh, V., 2015. Survival with cerebral palsy over five decades in western Sweden. Dev Med Child Neurol 57, 762-767.

Himmelmann, K., Uvebrant, P., 2011. Function and neuroimaging in cerebral palsy: a population-based study. Dev Med Child Neurol 53, 516-521.

Himmelmann, K., Uvebrant, P., 2018. The panorama of cerebral palsy in Sweden part XII shows that patterns changed in the birth years 2007-2010. Acta Paediatr 107, 462-468.

Hjern, A., Thorngren-Jerneck, K., 2008. Perinatal complications and socio-economic differences in cerebral palsy in Sweden - a national cohort study. BMC Pediatr 8, 49.

http://japanhealthinfo./com/child-health-and-childcare/pediatrics, J.h.i.C.h.a.C.

Hyein, Y.J., YH; Jee, M K, 2023. Characteristics of epilepsy in children with cerebral palsy: A single tertiary center study. Annals of Child Neuroogy 32, 257-270.

Jahan, I., Al Imam, M.H., Karim, T., Muhit, M., Hardianto, D., Das, M.C., Smithers-Sheedy, H., Badawi, N., Khandaker, G., 2020. Epidemiology of cerebral palsy in Sumba Island, Indonesia. Dev Med Child Neurol 62, 1414-1422.

K, A., Saini, L., Gunasekaran, P.K., Singh, P., Sahu, J.K., Sankhyan, N., Sharma, R., Bhati, A., Yadav, J., Sharawat, I.K., 2022. The Profile of Epilepsy and its characteristics in Children with Cerebral Palsy. Seizure 101, 190-196.

Kahalley, L.S., Winter-Greenberg, A., Stancel, H., Ris, M.D., Gragert, M., 2016. Utility of the General Ability Index (GAI) and Cognitive Proficiency Index (CPI) with survivors of pediatric brain tumors: Comparison to Full Scale IQ and premorbid IQ estimates. J Clin Exp Neuropsychol 38, 1065-1076.

Knudsen, M., Stadskleiv, K., O'Regan, E., Alriksson-Schmidt, A.I., Andersen, G.L., Hollung, S.J., Korsfelt, Å., Ödman, P., 2022. The implementation of systematic monitoring of cognition in children with cerebral palsy in Sweden and Norway. Disabil Rehabil, 1-10.

Korzeniewski, S.J., Slaughter, J., Lenski, M., Haak, P., Paneth, N., 2018. The complex aetiology of cerebral palsy. Nat Rev Neurol 14, 528-543.

Legault, G., Shevell, M.I., Dagenais, L., 2011. Predicting comorbidities with neuroimaging in children with cerebral palsy. Pediatr Neurol 45, 229-232.

Little, W.J., 1966. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities. Clin Orthop Relat Res 46, 7-22.

Luiz, D.M., Foxcroft, C.D., Stewart, R., 2001. The construct validity of the Griffiths Scales of Mental Development. Child Care Health Dev 27, 73-83.

McIntyre, S., Taitz, D., Keogh, J., Goldsmith, S., Badawi, N., Blair, E., 2013. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. Dev Med Child Neurol 55, 499-508.

Pavone, P., Gulizia, C., Le Pira, A., Greco, F., Parisi, P., Di Cara, G., Falsaperla, R., Lubrano, R., Minardi, C., Spalice, A., Ruggieri, M., 2020. Cerebral Palsy and Epilepsy in Children: Clinical Perspectives on a Common Comorbidity. Children (Basel) 8.

Pharoah, P.O., Cooke, T., Rosenbloom, L., 1989. Acquired cerebral palsy. Arch Dis Child 64, 1013-1016.

Radell, U., Tillberg, E., Mattsson, E., Amark, P., 2008a. Participation in age-related activities and influence of cultural factors--comments from youth and parents of children with postnatal post infectious hemiplegia in Stockholm, Sweden. Disabil Rehabil 30, 891-897.

Radell, U., Tillberg, E., Mattsson, E., Amark, P., 2008b. Postnatal cerebral infection leading to hemiplegic cerebral palsy: functional limitations and disability of 13 children in Sweden. Disabil Rehabil 30, 1910-1919.

Raiford, S.E., Weiss, L.G., Rolfhus , E., Coalson, D., 2008. General Abiliy Index WISC IV. http://images.pearsonclinical.com.

Reddihough, D.S., Baikie, G., Walstab, J.E., 2001. Cerebral palsy in Victoria, Australia: mortality and causes of death. J Paediatr Child Health 37, 183-186.

Reid, S.M., Dagia, C.D., Ditchfield, M.R., Carlin, J.B., Reddihough, D.S., 2014. Population-based studies of brain imaging patterns in cerebral palsy. Dev Med Child Neurol 56, 222-232.

Reid, S.M., Dagia, C.D., Ditchfield, M.R., Reddihough, D.S., 2015. Grey matter injury patterns in cerebral palsy: associations between structural involvement on MRI and clinical outcomes. Dev Med Child Neurol 57, 1159-1167.

Reid, S.M., Lanigan, A., Reddihough, D.S., 2006. Post-neonatally acquired cerebral palsy in Victoria, Australia, 1970-1999. J Paediatr Child Health 42, 606-611.

Reid, S.M., Meehan, E.M., Arnup, S.J., Reddihough, D.S., 2018. Intellectual disability in cerebral palsy: a population-based retrospective study. Dev Med Child Neurol 60, 687-694.

Rosenbaum, P., Paneth, N., Leviton, A., Goldstein, M., Bax, M., Damiano, D., Dan, B., Jacobsson, B., 2007. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 109, 8-14.

Schulz, J., Henderson, S.E., Sugden, D.A., Barnett, A.L., 2011. Structural validity of the Movement ABC-2 test: factor structure comparisons across three age groups. Res Dev Disabil 32, 1361-1369.

Sellier, E., Uldall, P., Calado, E., Sigurdardottir, S., Torrioli, M.G., Platt, M.J., Cans, C., 2012. Epilepsy and cerebral palsy: characteristics and trends in children born in 1976-1998. Eur J Paediatr Neurol 16, 48-55.

Sigurdardottir, S., 2020. Personal communication.

Sigurdardottir, S., Eiriksdottir, A., Gunnarsdottir, E., Meintema, M., Arnadottir, U., Vik, T., 2008. Cognitive profile in young Icelandic children with cerebral palsy. Dev Med Child Neurol 50, 357-362.

Singhi, P., Jagirdar, S., Khandelwal, N., Malhi, P., 2003. Epilepsy in children with cerebral palsy. J Child Neurol 18, 174-179.

Smithers-Sheedy, H., Badawi, N., Blair, E., Cans, C., Himmelmann, K., Krageloh-Mann, I., McIntyre, S., Slee, J., Uldall, P., Watson, L., Wilson, M., 2014. What constitutes cerebral palsy in the twenty-first century? Dev Med Child Neurol 56, 323-328.

Society, S.N., 2015. Guidelines.

Stadskleiv, K., Jahnsen, R., Andersen, G.L., von Tetzchner, S., 2018. Neuropsychological profiles of children with cerebral palsy. Dev Neurorehabil 21, 108-120.

Stadskleiv, K., van Walsem, M.R., Andersen, G.L., Bergqvist, L., Bøttcher, L., Christensen, K., Heyerdahl, D., Hollung, S.J., Høye, H., Jahnsen, R., Klevberg, G.L., Lindquist, B., Passmark, H., Rike, P.O., Rodby-Bousquet, E., Alriksson-Schmidt, A.I., 2021. Systematic Monitoring of Cognition for Adults With Cerebral Palsy-The Rationale Behind the Development of the CPCog-Adult Follow-Up Protocol. Front Neurol 12, 710440.

Stanley, F.B., E, Alberman, E. , 2000. Cerebral palsies: Epidemiology and causal pathways. Mac Keith press.

Tharaldsen, G., Hollung, S.J., Vik, T., Andersen, G.L., 2022. High occurrence of perinatal risk factors and more severe impairments in children with postneonatal cerebral palsy in Norway. Acta Paediatr 111, 812-819.

Tillberg, E., Isberg, B., Persson, J.K.E., 2020. Hemiplegic (unilateral) cerebral palsy in northern Stockholm: clinical assessment, brain imaging, EEG, epilepsy and aetiologic background factors. BMC Pediatr 20, 116.

Tillberg, E., Persson, J.K.E., 2024. Hemiplegic (unilateral) cerebral palsy in northern Stockholm: Intellectual disability and epilepsy. Seizure 120, 110-115.

Tillberg, E., Radell, U., Amark, P., 2008. Postnatal cerebral infection leading to hemiplegic cerebral palsy: clinical description of 13 children in Stockholm, Sweden. Disabil Rehabil 30, 338-347.

Uvebrant, P., 1988. Hemiplegic cerebral palsy. Aetiology and outcome. Acta Paediatr Scand Suppl 345, 1-100.

Uvebrant, P., 2000. Congenital Hemiplegia, Clinicsin developmental Medicine. Mac KeithPress.

Wallace, S.J., 2001. Epilepsy in cerebral palsy. Dev Med Child Neurol 43, 713-717.

van Gorp, M., Van Wely, L., Dallmeijer, A.J., de Groot, V., Ketelaar, M., Roebroeck, M.E., 2019. Long-term course of difficulty in participation of individuals with cerebral palsy aged 16 to 34 years: a prospective cohort study. Dev Med Child Neurol 61, 194-203.

Wanigasinghe, J., Reid, S.M., Mackay, M.T., Reddihough, D.S., Harvey, A.S., Freeman, J.L., 2010. Epilepsy in hemiplegic cerebral palsy due to perinatal arterial ischaemic stroke. Dev Med Child Neurol 52, 1021-1027.

Wechsler, D., 2011. Wechsler Intelligence Scale for children. NCS Pearson Inc, Stockholm.

Westbom, L.H.G., 2019. Refugee/immigrant children with cerebral palsy in the Swedish health care orgaisation. Läkartidningen 116, 1-4.

Woolfenden, S., Galea, C., Smithers-Sheedy, H., Blair, E., McIntyre, S., Reid, S., Delacy, M., Badawi, N., 2019. Impact of social disadvantage on cerebral palsy severity. Dev Med Child Neurol 61, 586-592.

Zelnik, N., Konopnicki, M., Bennett-Back, O., Castel-Deutsch, T., Tirosh, E., 2010. Risk factors for epilepsy in children with cerebral palsy. Eur J Paediatr Neurol 14, 67-72.