Riitta Hannonen

Verbal and Academic Skills in Children with Type 1 Diabetes

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ABSTRACT

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This thesis aimed at assessing cognitive and early academic skills in children with type 1 diabetes. More specifically, the purpose was to describe the academic skills most likely to be adversely affected in children with diabetes and neurocognitive processes and disease-related mechanisms underlying these possible learning problems. An additional aim of the thesis was to combine a developmental neurocognitive theory of reading acquisition with recent developmental models of diabetes-related effects on the brain. The findings were based on neurocognitive assessments conducted in three cross-sectional studies using two samples of children with type 1 diabetes and healthy control groups. The findings indicated that the development of early academic skills can be affected in some children with type 1 diabetes. Children with early-onset diabetes had a threefold incidence of spelling problems compared to healthy children, and their performance in mathematics was also poorer than that of the control group. Problems in phonological processing were associated with the poorer development of early academic skills in children with early-onset diabetes or a history of severe hypoglycemia. In children with early-onset diabetes, poor glycemic control in the first year of diabetes was associated with poorer spelling accuracy at school age. The findings suggest that the age at diagnosis and metabolic balance during the child's development might affect the neurocognitive outcome. The integration of developmental neurocognitive theories and models of diabetes-related effects on cognition could lead to better understanding of developmental pathways in children with type 1 diabetes. This could improve the identification of children at risk for learning difficulties and possibilities of early intervention.

Keywords: type 1 diabetes, hypoglycemia, hyperglycemia, cognitive skills, academic skills, childhood

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ABBREVIATIONS

C	control group
CNS	central nervous system
CSII	continuous subcutaneous insulin infusion
D	diabetes group
DCCT	the Diabetes Control and Complications Trial
DCCT/EDIC	the Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications
DKA	diabetic ketoacidosis
ES	effect size
F	female
HbA1c	glycated hemoglobin
IGF	Insulin-like growth factor
JLD	the Jyväskylä Longitudinal Study of Dyslexia
M	male
n	group size
NEPSY	Developmental Neuropsychological Assessment
RAN	Rapid Automatized Naming Test
SD	standard deviation
SH	severe hypoglycemia
T1DM	type 1 diabetes
WISC-R	Wechsler Intelligence Scale for Children – Revised
WISC-III	Wechsler Intelligence Scale for Children – Third edition
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence - Revised

1 INTRODUCTION

Type 1 diabetes (T1DM) is a common chronic disease in childhood. It is characterized by insulin-deficiency caused by autoimmune destruction of β-cells in the pancreas. β-cells produce insulin, which is essential for glucose metabolism. Without insulin, the blood glucose level increases but the body cannot use glucose as energy. Consequently, the body starts to use fat as a source of energy, which leads to a life-threatening complication, ketoacidosis. Therefore, insulin replacement therapy is crucial in T1DM. The etiology of β-cell destruction and T1DM remains unknown, but interaction of genes and environment (e. g. toxins and infections) is hypothesized to initiate the autoimmune process (Craig, Hattersley, & Donaghue, 2009).

The incidence of type 1 diabetes is increasing throughout the world, and is highest in Finland. In the year 2005, 64.2 / 100 000 children under 15 years of age were diagnosed with T1DM, and the incidence rate is increasing, especially in children under five years of age (Harjutsalo, Sjöberg, & Tuomilehto, 2008). Therefore, T1DM has a considerable impact on Finnish society. For example schools and daycare centers face the special needs of children with T1DM, and their personnel need information about diabetes and training for the treatment of diabetes during the day when children are in their charge (Ministry of Social Affairs and Health, 2010).

The goal of treatment of T1DM is to maintain a near-normal blood glucose level (Rewers et al., 2009) by multiple daily injections of insulin or treatment with a continuous subcutaneous insulin infusion (CSII, "insulin pump") and by frequent blood glucose monitoring. This intensive treatment strategy has decreased long-term micro- and macrovascular complications of diabetes (e.g. retinopatia, neuropatia, nephropatia), but has also increased the incidence of severe hypoglycemia, i.e. a lower than optimal level of blood glucose (the Diabetes Control and Complications Trial, DCCT, 1993), especially in young children with diabetes (Bulsara, Holman, Davis, & Jones, 2004). However, a plateau has been observed in the incidence rates of severe hypoglycemia in the 2000s, although glycemic control has improved. This has been associated with the newer therapeutic strategies such as CSII, novel types of insulin

preparations and individualized educational approaches (Jones & Davis, 2003; Bulsara et al., 2004).

The treatment of diabetes requires continuous monitoring of the child, as the administration of insulin needs to be adjusted to the blood glucose level, meals, exercise and health. Since exogenous insulin does not act as naturally as physiological insulin production, children with diabetes constantly experience abnormal levels of insulin and glucose, which affect the wellbeing and brain function of the child. Parents and other caretakers bear the responsibility for the management of diabetes in a young child. As the child grows older, she or he has to learn effective self-management strategies, including planning and monitoring of diet and activity along with active decision-making and calculating of insulin dosages. This can be cognitively as well as psychosocially demanding (Gonder-Frederick, Cox, & Ritterband, 2002).

1.1 Neurocognitive Development in Children with T1DM

Neurocognitive functions in children with T1DM have been studied continuously over the past 30 years. Studies taking different approaches have contributed to a growing body of evidence of minor neurocognitive decrements in children with T1DM. Most of these studies have been cross-sectional, but some prospective studies have also been conducted (Northam et al., 1998; 2001; 2009; Rovet & Ehrlich, 1999; Schoenle, Schoenle, Molinari, & Largo, 2002). According to Northam et al. (1998), the cognitive development of the children with T1DM is similar to that of healthy controls at the onset of the disease, but after two years small negative changes in the performance of children with T1DM can be found. With longer disease duration, significant group differences between children with diabetes and healthy children have been found, but the cognitive development of children with T1DM remains within the normal age variation (Rovet & Ehrlich, 1999; Northam et al., 2001; 2009).

Cross-sectional studies with small sample sizes, wide age ranges and variable assessment methods have made it difficult to compare the results. To synthesize the findings of previous neurocognitive studies concerning children with T1DM, meta-analyses have been conducted. The general aim of a meta-analysis is to estimate the true "effect size" and its confidence interval using the weighted average of the findings. In current meta-analyses the common effect size (ES) is based on the standardized mean group differences between two groups (Cohen's d), e.g. children with diabetes and healthy children (Fritz, Morris, & Richler, 2011). The weighting of previous studies is based on the sample sizes. The meta-analyses (Gaudieri, Chen, Greer, & Holmes, 2008; Naguib, Kulinskaya, Lomax, & Garralda, 2009) have concluded that children with T1DM have slightly lower scores than healthy children in many cognitive domains. In particular, visuospatial skills, motor speed, attention, and academic skills, e.g. reading and writing are affected (Naguib et al., 2009). However, the effect of diabetes appears to be small (ES = -0.29 to -0.18). Previous research has

concentrated on intelligence, learning and memory, processing speed and attention (Gaudieri et al., 2008), while studies assessing verbal and academic skills have been scarce.

1.2 Risk Factors for Neurocognitive Development

The mechanism underlying the small cognitive decrements in children with diabetes has been unclear. The influence of abnormally low blood glucose levels (hypoglycemia) on the developing brain, especially in young children, has been suspected to contribute to these cognitive deficits. Therefore, the research on diabetes-related risk factors has concentrated on severe hypoglycemia and early onset-age of diabetes.

1.2.1 Early Age at Diabetes Onset

In many chronic conditions that affect brain functioning, earlier age at diagnosis predicts worse cognitive outcome than later onset of disease (Dennis, 2000). In children with T1DM, early onset-age has been defined as below four to seven years of age, depending on the study. It has been hypothesized that young children with diabetes are more vulnerable to metabolic extremes (e.g. severe hypoglycemia), because of the greater needs of glucose of the developing brain (McCall & Figlewicz, 1997). Since an increasing number of children in Finland are diagnosed with T1DM at a young age, it has become important to clarify the targets of their treatment – the balance between near-normal glucose levels and avoidance of severe hypoglycemias.

In a meta-analysis (Gaudieri et al., 2008), early onset-age had a small to moderate effect on neurocognitive development (ES = -0.49 to -0.28). Problems in learning and memory (Gaudieri et al., 2008), non-verbal intelligence (Ryan, Vega, & Drash, 1985; Northam, Anderson, Werther, Warne, & Andrewes, 1999; Ferguson et al., 2005; Northam et al., 2009), visuospatial skills (Ryan et al., 1985; Rovet, Ehrlich, & Hoppe, 1987), attention (Rovet & Alvarez 1997, Northam et al., 2001; Lin, Northam, Rankins, Werther, & Cameron, 2010) and processing speed (Ryan et al., 1985; Northam et al., 2001) have been associated with early-onset T1DM in children. In addition, earlier onset-age seems to predict poorer cognitive functioning in adults with long duration of T1DM (Brismar et al., 2007). Desrocher and Rovet (2004) have proposed that currently developing skills are at risk in a metabolic insult, e.g. hypoglycemia. Because posterior brain areas, associated with visuospatial functioning, develop before temporal and frontal areas (Chugani, Phelps, & Mazziotta, 1987), these functions are more likely to be affected in early-onset diabetes. However, the effects of early onset-age and severe hypoglycemia have been difficult to disentangle.

1.2.2 Severe Hypoglycemia

Hypoglycemia (a blood glucose level lower than normal) is the most common acute complication of diabetes treatment. Hypoglycemia can result from excess of insulin in relation to food and exercise. The signs and symptoms of hypoglycemia are caused by adrenergic activation or neurological dysfunction, and they are unpleasant: tremor, cold sweat, concentration and memory difficulties, blurred vision, behavioral and mood changes, and - in severe hypoglycemia - seizures and loss of consciousness (Clarke, Jones, Rewers, Dunger, & Klingensmith, 2009). Therefore, children and parents often fear hypoglycemia. In a milder hypoglycemic event, the child or the caregiver notices the signs of the suboptimal blood glucose level, and the child is given a carbohydrate snack, which raises the blood glucose level. Severe hypoglycemia can be defined as seizures or lowered level of consciousness associated with a suboptimal blood glucose level (below 4 mmol/L) or a need for assistance of another person to administer carbohydrate, glucagon or intravenous glucose (Workgroup on Hypoglycemia, American Diabetes Association, 2005; Clarke et al., 2009). Young children with diabetes may be at an increased risk for hypoglycemia, because they cannot recognize the signs themselves. It is also problematic to evaluate the food intake and the activity level of a young child.

Prolonged severe hypoglycemia can cause permanent brain damage and have serious long-term effects on cognition. In newborns and infants suffering, for example, from prematurity or persistent hyperinsulinemic hypoglycemia, prolonged and repeated hypoglycemia can have neurological effects ranging from subtle deficits to epilepsy and severe mental deficiency (Riikonen & Donner, 1979; Duvanel, Fawer, Cotting, Hohlfeld, & Matthieu, 1999; Hawdon, 1999; Aynsley-Green et al., 2000; Menni et al., 2001; Kumaran, Kar, Kapoor, & Hussain, 2010; Montassir, Maegaki, Ohno, & Ogura, 2010). Prolonged severe hypoglycemia leading to cortical injury has also been reported in adults (Chalmers et al., 1991; Fujioka et al., 1997).

Acute hypoglycemia affects brain function and causes cognitive disruption. Cognitively more complex tasks are more sensitive to acute hypoglycemia than simple tasks (Warren & Frier, 2005). Regardless the large number of studies, the long-term cognitive effects of severe hypoglycemia in children with T1DM have remained inconclusive. In some studies, severe hypoglycemia has been associated with poorer verbal (Rovet & Alvarez, 1997; Rovet & Ehrlich, 1999) and visuospatial skills (Rovet et al., 1987; Perantie et al., 2008; Aye et al., 2011), memory (Kaufman, Epport, Engilman, & Halvorson, 1999; Hershey et al., 2005; Aye et al., 2011) and attention (Bjørgaas, Gimse, Vik, & Sand, 1997; Rovet & Alvarez 1997; Rovet & Ehrlich, 1999). On the other hand, in other studies no such association has been found (Schoenle et al., 2002; Wysocki et al., 2003; Strudwick, Gardiner, Foster, Davis, & Jones, 2005). In a large prospective study in children and adolescents, a history of severe hypoglycemia has been associated with lower verbal intelligence (Northam et al., 2001; 2009) and poorer verbal skills, working memory and processing speed

(Lin et al., 2010), suggesting that avoiding severe hypoglycemia is warranted. However, in the meta-analyses, a history of severe hypoglycemia has had a medium effect on learning and memory (Blasetti et al., 2011) and only a nominal to small effect (ES = -0.06 to -0.21) on other cognitive skills (Gaudieri et al., 2008; Naguib et al., 2009).

1.2.3 Chronic Hyperglycemia and Diabetic Ketoacidosis

Hyperglycemia indicates poor glycemic control (usually measured by glycated hemoglobin level, HbA1c). It results from an inadequate balance between insulin replacement therapy, nutrition and exercise. Poor glycemic control can lead to long-term complications of diabetes (DCCT, 1993). However, achieving the target blood glucose level (HbA1c < 58 mmol/mol, HbA1c < 7.5%; Rewers et al., 2009) can be a demanding task in children and adolescents, and their HbA1c levels are often higher than optimal. There are several reasons for poor glycemic control in childhood. Lower HbA1c levels are often (Bulsara et al., 2004; but see also Ludvigsson & Nordfeldt, 1998) associated with an increased risk for severe hypoglycemia, which makes it difficult to balance between the risk of severe hypoglycemia and tight glycemic control. For example, an episode of severe hypoglycemia can lead to a decrease in insulin doses and therefore to poorer glycemic control (Tupola, Rajantie, & Åkerblom, 1998). Hormonal and emotional changes also affect glycemic control, especially in teenagers (Rewers et al, 2009).

Untreated hyperglycemia with an extremely high blood glucose level, insulin deficiency and increased level of counter regulatory hormones can lead to an acute life-threatening diabetic ketoacidosis (DKA), which has acute neurological effects. In Finland, the frequency of DKA at diagnosis in children diagnosed under five years of age was 16.5% during the years 2002 to 2005, but in children diagnosed under the age of two, the risk for DKA is higher (Hekkala et al., 2010; Komulainen et al., 1999).

The impact of chronic hyperglycemia on mental efficiency has been acknowledged in adults with T1DM (the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, DCCT/EDIC, 2007; Musen et al., 2008; Jacobson et al., 2011), but has been less studied in children. It has been suggested that the effects of chronic hyperglycemia are seen after many years of disease, in adolescence at the earliest (Desrocher & Rovet, 2004). However, chronic hyperglycemia or poor glycemic control has been associated with poorer academic (Kaufman et al., 1999; McCarthy, Lindgren, Mengeling, Tsalikian, & Engvall, 2003; Parent, Wodrich, & Hasan, 2009) and verbal skills (Perantie et al., 2008; Patiño-Fernández et al., 2010; Aye et al., 2011) and poorer working memory (Lin et al., 2010) in children, although some studies have not found this association (Rovet & Alvarez, 1997; Northam et al., 2001; Wysocki et al., 2003; Hershey et al., 2005; Ohman et al., 2010). In a prospective study (Schoenle et al., 2002), boys with early-onset T1DM and poorer glycemic control, especially in the beginning of the disease, showed poorer development in intelligence than other children with diabetes. DKA has

been found to affect memory (Ghetti, Lee, Sims, Demaster, & Glaser, 2010) and other cognitive functions (Shehata & Eltayeb, 2010). Otherwise, long-term cognitive effects of DKA have not been studied in children.

Differences in the methodology used to measure glycemic control have perhaps contributed to the inconsistent findings. Some studies of children with T1DM have used only the most recent HbA1c value as a measure of glycemic control (Rovet et al., 1987; McCarthy et al., 2003) or have not measured glycemic control in association with cognitive measures (Ryan et al., 1985; Strudwick et al., 2005). However, some recent studies have counted lifetime mean glycemic control (Schoenle et al., 2002; Wysocki et al., 2003; Hershey et al., 2005) or exposure to hyperglycemia (Perantie et al., 2008; Northam et al., 1999; 2001; 2009; Lin et al. 2010), which has made the estimation of glycemic control more accurate (Northam & Lin, 2010).

1.3 Neuroanatomical and Functional Findings in Children with T1DM

In children with T1DM, several neuroanatomical and functional changes have been found which can contribute to the underlying mechanisms of cognitive problems. Diffuse alterations in gray and white matter densities in the temporal, frontal and hippocampal areas, thalamus and insular cortex have been observed in children with T1DM (Northam et al., 2009). Aye et al. (2011) have found reduced age-related growth in white matter and hippocampal volumes in children with T1DM. In addition, changes in brain metabolism (Sarac et al., 2004; Northam et al., 2009), cerebral perfusion (Salem, Matta, Tantawy, Hussein, & Gad, 2002; Tupola et al., 2004) and electrical activity (Hyllienmark, Maltez, Dandenell, Ludvigsson, & Brismar, 2005; Shehata & Eltayeb, 2010) have been found. These findings are related to neuropathological processes, such as gliosis and demyelination (Northam et al., 2009), and changes in neurotransmitters, vascular reactivity and blood-brain barrier (McCall & Figlewicz, 1997).

The known risk factors for cognitive deficits have also been associated with cerebral abnormalities. People who have been diagnosed with diabetes at a young age have been reported to have more ventricular atrophy, larger lateral ventricles (Ferguson et al., 2005) and greater prevalence of mesial temporal sclerosis (Ho et al., 2008). This suggests that brain development is vulnerable to diabetes-related metabolic events in the early years of childhood. Changes in gray and white matter volumes (Perantie et al., 2007; Ho et al., 2008; Northam et al., 2009), brain metabolism (Northam et al., 2009) and EEG (Hyllienmark et al., 2005) have been associated with both recurrent hypoglycemia and hyperglycemia. The temporal and frontal areas and basal ganglia (Salem et al., 2002; Hyllienmark et al., 2005; Perantie et al., 2007; Northam et al., 2009) seem to be especially vulnerable to diabetes-related effects. These same brain areas are also involved in verbal functioning.

Nevertheless, neuroanatomical and functional alterations as well as cognitive problems have also been found in children without the diabetes-related risk factors, indicating that the known risk factors are not the only causes of neurocognitive problems in T1DM. Blood glucose in all children with diabetes is often at a non-optimal level, and fluctuation of blood glucose and insulin can affect brain metabolism and function, and influence cognitive development (Northam & Lin, 2010). In addition, T1DM is related to changes in hormones and neurotransmitters, which can alter brain function. For example, Insulin-like growth factors (IGF) are peptides that regulate cell growth and metabolism, and it is assumed that IGF-I is associated with the development of various brain areas involved in cognitive functioning (Berger, 2001). For example, IGF-I levels are lower in children with autism (Riikonen, 2007) and symptomatic infantile spasms (Riikonen, Jääskeläinen, & Turpeinen, 2010). IGF levels are also lower in children with diabetes (Bideci, Camurdan, Cinaz, Dursun, & Demirel, 2005). IGF-I deficiency has been related to smaller growth of the brain (Lupien, Bluhm, & Ishii, 2006) and neuronal death in the hippocampus (Li, Zhang, Grunberger, & Sima, 2002) in diabetic rats. So far, these risk factors have been studied mainly in animal models. On account of the methodological demands, they have not yet been assessed in studies concerning cognitive development in children.

1.4 The Changing Paradigm in the Studies of Neurocognitive Development in Children with T1DM

Earlier neurocognitive studies in children with T1DM have concentrated on the impact of complications, especially severe hypoglycemia, because severe hypoglycemia has detrimental acute effects on brain metabolism and function, and because the increased need of glucose has been assumed to render the young, developing brain more vulnerable to hypoglycemic insult (McCall & Figlewicz, 1997). The inconclusive findings on the long-term effects of severe hypoglycemia in children and the repeated observation that a history of severe hypoglycemia is not associated with cognitive decline in adolescents and young adults (DCCT/EDIC, 2007; Musen et al., 2008) indicates that the association of complications and cognitive development may depend on the age of the person and duration of the disease.

Desrocher and Rovet (2004) have proposed that severe hypoglycemias occurring at different ages affect ongoing skill development in childhood, and that chronic hyperglycemia in adolescence influences the development of executive functions. Ryan (2006) in turn has suggested that hyperglycemia at the beginning of early-onset diabetes disturbs structural and functional development of the brain, which leads to vulnerability to a later brain insult, e.g. an episode of severe hypoglycemia. Biessels, Deary and Ryan (2008) have proposed that the brain is vulnerable to diabetes-related insults at times of

major changes in the brain, e.g. in childhood and in old age, but not in early or middle adulthood. These hypotheses have sought to explain why there is diversity in neurocognitive outcomes in people with T1DM. In the past few years there has been a change in the paradigm towards a neurodevelopmental model. It has been acknowledged that the child's age and developmental phase can influence the impact of a metabolic insult on brain function (Figure 1; Northam & Lin, 2010). In general, earlier brain damage has a worse cognitive outcome than an insult later in childhood (Anderson et al., 2009). Interest has also begun to be shown in a larger variety of metabolic complications and their interactions (Schoenle et al., 2002; Perantie et al., 2008; Ghetti et al. 2010; Lin et al., 2010).

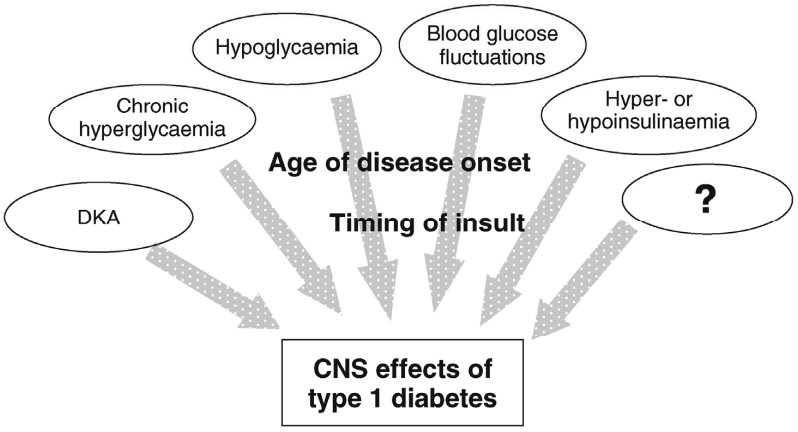

FIGURE 1 Possible causes of central nervous system (CNS) changes in type 1 diabetes (in Northam & Lin, 2010; reproduced with permission by John Wiley and Sons).

1.5 The Development of Verbal Skills and Early Academic Skills

Learning to read and write is an important goal in the first years at school. In general, reading acquisition in Finland is fast because the Finnish orthography is regular and has consistent grapheme-phoneme correspondence. One third of the children learn to read words before school entry (at the age of seven), and almost all children during the first school year (Aro, 2004). However, the reading skills of children in the first school years show wide variation, with many children experiencing problems in reading speed, accuracy and/or comprehension (Torppa et al., 2007). The Jyväskylä Longitudinal Study of Dyslexia (JLD) has identified risk factors of reading disorder (dyslexia) in a large, prospective study of children with and without familial risk for dyslexia.

The findings suggest that genetic vulnerabilities interact with environmental factors (such as parental interaction and reading habits) and influence brain function and the development of cognitive and linguistic skills underlying reading skills (Lyytinen et al., 2004b).

The acquisition of academic skills – reading, spelling and mathematics - requires well-coordinated information processing at the coding, storing and retrieving levels of visual and verbal information (Vellutino, Fletcher, Snowling, & Scanlon, 2004). The most important underlying skills required in these processes are basic verbal skills, which develop during childhood before reading instruction. Phonological awareness (ability to perceive a word's sound structure and its components) and naming speed (automatized retrieval from the long-term memory) are the most important predictors of reading acquisition, but the development of reading and spelling is also predicted by letter knowledge, verbal short-term memory, pseudoword repetition and expressive vocabulary (McCardle, Scarborough, & Catts, 2001; Lyytinen et al., 2004b; Vellutino et al., 2004). Phonological skills are strongly associated with reading accuracy (Puolakanaho et al., 2008) and rapid automatized naming (naming speed) with reading fluency (Wolf, Bowers, & Biddle, 2000; Torppa et al., 2007).

In regular orthographies such as Finnish, reading problems are more often related to speed than accuracy of reading whereas problems in reading accuracy are more prevalent in irregular orthographies such as English (Aro & Wimmer, 2003; Vellutino et al., 2004). However, accuracy and intact phonological skills are required in spelling in all alphabetic systems (Vellutino et al., 2004). In Finnish, phonological perception of phonemic duration is crucial in reading and spelling (Pennala et al., 2010), because the meaning of a Finnish word changes as the duration of a phoneme changes from short to long, e.g. kuka (who) – kukka (flower).

Problems in reading and mathematics often co-occur (Räsänen & Ahonen, 1995). Although arithmetical skills are based on innate numerosity (Butterworth, 2010), verbal skills are associated with the development of complex skills such as calculation (Koponen, Aunola, Ahonen, & Nurmi, 2007). In fact, calculation is associated with similar underlying language-based cognitive processes as reading and spelling. These include phonological processing, naming speed and phonological memory (Hecht, Torgesen, Wagner, & Rashotte, 2001), although attention and other complex processes such as nonverbal problem solving also predict skills in mathematics (Fuchs et al., 2005).

1.5.1 Verbal and Academic Skills in Children with T1DM

In children with T1DM, previous research in cognitive skills has concentrated on intelligence, learning and memory, processing speed and attention (Gaudieri et al., 2008), and only little attention has been paid to verbal and academic skills. The studies assessing verbal skills have focused on complex skills such as verbal intelligence (Rovet & Alvarez, 1997; Rovet & Ehrlich, 1999; Schoenle et al., 2002; Northam et al., 2001; 2009) and verbal learning and memory (Northam et al., 2001; Fox, Chen, & Holmes, 2003; Lin et al., 2010). Among the basic verbal

skills, poorer verbal short-term memory has been related to early-onset diabetes (Ryan et al., 1985) and severe hypoglycemia (Kaufman et al., 1999; Northam et al., 1999). Phonological skills have been assessed in only one study (Kaufman et al., 1999), and naming speed has not been assessed at all. Basic verbal skills develop during childhood and can therefore be vulnerable in early-onset diabetes and hence affect the development of academic skills.

While most children with T1DM do not exhibit problems regarding academic achievement (McCarthy, Lindgren, Mengeling, Tsalikian, & Engvall, 2002), at the group level their achievement is slightly lower than that of other students (Dahlquist & Källén, 2007; Gaudieri et al., 2008; Naguib et al., 2009). Lower achievement has been reported mainly in reading (Ryan et al., 1985; Kaufman et al., 1999; McCarthy et al., 2003; Naguib et al., 2009) and writing (Kaufman et al., 1999; Parent et al., 2009; Naguib et al., 2009), but not in mathematics (Ryan et al., 1985; Hagen et al., 1990; McCarthy et al., 2003). Lower school marks or higher risk for learning problems has been associated with longer duration of diabetes (Ryan et al., 1985; Kovacs, Goldston, & Iyengar, 1992), early onset-age (Ryan et al., 1985), poor metabolic control (Kaufman et al., 1999; McCarthy et al., 2003; Parent et al., 2009) and a history of severe hypoglycemia (McCarthy et al., 2003). The effects of diabetes and its complications seem to last throughout compulsory education (Kokkonen, Lautala, & Salmela, 1994; Dahlquist & Källén, 2007; Northam et al., 2009), which impairs the further educational and vocational possibilities of some people with diabetes and delays their social maturation in early adulthood (Kokkonen et al., 1994).

Basic verbal skills have not been studied in children with T1DM, although these skills develop during early childhood and are crucial for the acquisition of academic skills. Therefore, the assessment of basic verbal skills may reveal the mechanism underlying the possibly affected development of academic skills in children with T1DM. Also, the well-described developmental trajectory of verbal and reading skills included in the model of reading acquisition provides a developmental neurocognitive framework to study the cognitive processes vulnerable to early brain insult related to T1DM and its metabolic complications.

2 AIMS OF THE THESIS

The aims of the thesis are twofold. The first aim is to assess cognitive functioning (Study I), especially verbal and academic skills (Study II), and the associations between cognitive skills and diabetes-related risk factors (Studies I and III) in children with T1DM. Secondly, the developmental neurocognitive model of early reading is applied to the development of academic skills in children with early-onset T1DM (Study II) and combined with the models of diabetes-related risk factors (Study III).

The aims of the original studies were as follows:

1. to assess the effects of diabetes and severe hypoglycemia on neurocognitive functioning in children with T1DM (Study I)

2. to assess the effects of early-onset T1DM on basic verbal and academic skills in the early school years and the neurocognitive processes associated with learning deficits in children with early-onset diabetes (Study II)

3. to separate the effects of early onset-age and severe hypoglycemia on verbal and academic skills and on the incidence of learning problems (Study III)

4. to assess the effects of diabetes-related risk factors and their timing on the development of verbal and academic skills in children with early-onset T1DM (Study III)

3 OVERVIEW OF THE ORIGINAL STUDIES

3.1 Methods

3.1.1 Participants

The characteristics of the participants are presented in Table 1. Study I consisted of 21 children with T1DM and 10 healthy control children. The children with diabetes were outpatients at a pediatric clinic of a central hospital. They were divided into two groups according to whether or not they had a history of severe hypoglycemia (SH+ and SH-). All the children attending the outpatient clinic who had experienced severe hypoglycemia and met the criteria for age (from 5 to 12 years) and normal developmental milestones were included in the study. The SH+ group was matched with the SH- and control groups for sex, age and parents' education. In the children with diabetes, the duration of diabetes ranged from 1 year 9 months to 9 years 7 months. The control group consisted of children from a local sports club or of the hospital personnel.

The participants of Studies II and III were 63 children with T1DM who were outpatients of four pediatric diabetes clinics of tertiary care hospitals, and 92 control children without T1DM. Children with T1DM who had been diagnosed before 5 years of age and were 9 to 10 years of age and in the 3rd grade at school at the time of the assessment were eligible for inclusion. Exclusion criteria were native language other than Finnish and a diagnosed neurological disorder. The data were collected over three consecutive years. In the children with T1DM, the duration of diabetes ranged from 4 years 6 months to 9 years 2 months. In Study II, children with T1DM were compared with the healthy control group, and in Study III, the children with T1DM were divided according to whether or not they had a history of severe hypoglycemia (SH+ and SH-) and compared with the control group.

The children comprising the control group in the Jyväskylä Longitudinal Study of Dyslexia (JLD, Lyytinen et al., 2001) were selected for the control group of Studies II and III. The children in this group had been followed from

birth in order to study their language development and the predictors and precursors of dyslexia. The control group was assessed at the same age and using the same tests as the diabetes group. The children in the control group did not have familial risk for dyslexia, defined as at least one parent and one other close relative who had problems with reading and spelling. In the diabetes group, 19% of the parents reported familial risk for dyslexia. Therefore, the children in the diabetes group with familial risk for dyslexia were excluded from Study II. In Study III, familial risk for dyslexia was used as a covariate in the statistical analyses.

TABLE 1 Characteristics of the Participants in the Original Studies

	Study I			Study II		Study III		
n	31			143		155		
Gender F/M, n	17 / 14			65 / 78		71 / 84		
Age, range;	5y 6m – 11y 11m			9y 2m – 10 y 6m		9y 2m – 10 y 6m		
mean (SD)	9y 4m (1y 11m)			9y 9m (0y 3m)		9y 9m (0y 3m)		
Groups	SH+	SH-	C	D	C	SH+	SH-	C
n	11	10	10	51	92	37	26	92

SH = history of severe hypoglycemia, C = control group, D = diabetes group

3.1.2 Measures

The procedures, tasks and analyses are presented in detail in the original articles. The cognitive measures are shown in Table 2 and diabetes-related measures in Table 3.

In Study I, the children participated in the neuropsychological assessment over two or three sessions. The blood glucose level of the children with diabetes was measured before each assessment session to ascertain that their blood glucose value was > 3 mmol/L. At the beginning of the assessment a structured interview on the child's cognitive development, learning difficulties and special education needs was administered to the parent. Data on diabetes (see Table 3) were acquired from the child's medical records. The control group was assessed separately, after the assessment of the diabetes group.

The neuropsychological assessment in Study I included the NEPSY, a Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1997). The NEPSY is a neuropsychological test for children 3 to 12 years of age. It consists of subtests designed to assess neuropsychological development in five functional domains: Attention/Executive Functions, Language, Sensorimotor Functions, Visuospatial Processing, and Memory and Learning. Each age group has its own standardized normative values. Of the 30 NEPSY subtests, 16 were administered (Table 2). Verbal short-term memory was assessed by the digit span forward, and it was included in the neuropsychological domain of Memory and Learning. The Finnish version of the Wechsler Intelligence Scale for Children–Revised (WISC-R; Wechsler, 1984) or Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler, 1995) was used to assess general intelligence.

In Studies II and III, the neuropsychological assessment lasted two hours with a break after one hour. The children's blood glucose level was measured before and after the assessment. The blood glucose level was required to be between 4 to 18 mmol/L during the assessment. The child's mother filled in a structured questionnaire on the development, school and learning history of her child and on reading difficulties and the socio-economic situation of the family. Data on diabetes (see Table 3) was acquired from the child's medical records.

Verbal and academic skills in Studies II and III were assessed with sensitive, partly computerized tasks developed to measure early academic skills and their underlying neurocognitive processes. Perception of phonemic length is a same-different judgement task of phonemic length in non-words (Cognitive Workshop program, developed by the Universities of Dundee and Jyväskylä) and assesses phonological processing. Non-word repetition (a subtest of the NEPSY, Korkman et al., 1997) assesses phonological processing and repetition of the phonology of non-words. Rapid Automatized Naming Test (RAN; Ahonen, Tuovinen, & Leppäsaari, 2003) assesses the speed of naming. Digit span forward assesses verbal short-term memory. Reading accuracy was assessed using measures of the accuracy of oral text reading, oral pseudo-word text reading and single non-word reading (3- and 4-syllable non-words presented on a computer screen; Cognitive Workshop program). Reading speed was assessed using measures of the speed of oral text reading, oral pseudo-word text reading, single non-word reading, reading rapid words (Finnish words presented on a computer screen for 80 ms; Cognitive Workshop program) and oral word list reading (a subtest of the Lukilasse test; Häyrinen, Serenius-Sirve, & Korkman, 1999). Spelling accuracy was assessed by asking the child to spell a series of words and non-words. Mathematics was assessed using measures of the speed of verbal counting and measures of the accuracy of verbal counting and arithmetic. The verbal and academic skill variables were computed using standardized z-scores from the individual tasks (standardization was based on the mean and SD of the comparison group). General intelligence was assessed with the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1999).

TABLE 2 Cognitive Domains, Tests and Tasks Used in the Original Studies

Domain	Test / Task	Study I	Study II	Study III
General Intelligence	WISC-R[1] / WPPSI-R[2]	X		
	WISC-III[3]		X	X
Attention/Executive Functions	Tower[4]	X		
	Auditory Attention and Response Set[4]	X		
	Visual Attention[4]	X		
Verbal/Language Functions	Phonological Processing[4]	X		
	Comprehension of Instructions[4]	X		
	Speeded Naming[4]	X		
	Verbal Fluency[4]	X		
	Perception of Phonemic Length		X	X
	Non-word Repetition[4]		X	X
	Rapid Automatized Naming[5]		X	X
Sensorimotor Functions	Fingertip Tapping[4]	X		
	Visuomotor Precision[4]	X		
	Finger Discrimination[4]	X		
Visuospatial Processing	Design Copying[4]	X		
	Arrows[4]	X		
	Picture Perception[4]	X		
Memory and Learning	Picture Recognition[4]	X		
	Memory for Names[4]	X		
	List Learning[4]	X		
	Digit Span Forward	X	X	X
Reading Accuracy	Oral Text Reading		X	X
	Oral Pseudo-word Text Reading		X	X
	Single Non-word Reading		X	X
Reading Speed	Oral Text Reading		X	X
	Oral Pseudo-word Text Reading		X	X
	Single Non-word Reading		X	X
	Reading Rapid Words		X	X
	Oral Word List Reading[6]		X	X
Spelling Accuracy	Spelling Words		X	X
	Spelling Non-words		X	X
Mathematics	Verbal Counting		X	X
	Arithmetic		X	X

[1] WISC-R, Wechsler Intelligence Scale for Children - Revised (Wechsler, 1984)
[2] WPPSI-R Wechsler Preschool and Primary Scale of Intelligence - Revised (Wechsler, 1995)
[3] WISC-III Wechsler Intelligence Scale for Children – 3rd edn. (Wechsler, 1999)
[4] a subtest of the NEPSY (Korkman et al., 1997)
[5] RAN, Rapid Automatized Naming Test (Ahonen et al., 2003)
[6] a subtest of the Lukilasse Test (Häyrinen et al., 1999)

TABLE 3 The Diabetes-related Measures Used in the Original Studies

Measure	Study I	Study II	Study III
Age at diagnosis	X	X	X
Duration of diabetes	X		
Initial Ketoacidosis (DKA)	X		XX
Occurrence of Severe Hypoglycemia (SH)	XX	X	XX
- age at first episode			XX
HbA1c			
- the most recent	X	X	XX
- mean during the disease		X	XX
- 1 year after diagnosis			XX
Insulin Treatment Regimen		X	X

X=variable is used in group comparisons or as a descriptive measure
XX=variable is used in measuring the association with cognitive skills

3.2 Summary of the Results

3.2.1 Study I: Neurocognitive Functioning in Children with Type-1 Diabetes with and without Episodes of Severe Hypoglycaemia

The aim of the study was to assess the effect of diabetes and severe hypoglycemia on neurocognitive functioning in children with a comprehensive neuropsychological assessment.

Both groups with T1DM (SH+ and SH-) had poorer verbal short-term memory than the healthy control children. The children with a history of severe hypoglycemia were poorer than the control children in phonological processing. In addition, the children with a history of severe hypoglycemia had more neuropsychological deficits, learning difficulties and need for part-time special education than the children in the other groups. The results suggested that severe hypoglycemia may be a risk factor for learning due to deficits in auditory-verbal functions. However, the study was unable to fully differentiate the effects of early onset-age of diabetes and severe hypoglycemia.

3.2.2 Study II: Verbal and Academic Skills in Children with Early-Onset Type 1 Diabetes

Based on the findings of Study I, Study II aimed at assessing the verbal and academic skills and the neurocognitive processes associated with learning problems in both children with early-onset diabetes and healthy control children, who were in the same grade at school and had recently acquired the basic skills of reading, spelling and mathematics. In addition, the severity of reading disability in children with diabetes was studied using the criteria for dyslexia.

The performance of the children with early-onset diabetes was significantly poorer than that of the healthy control children in perception of

phonemic length, spelling accuracy and mathematics. Children with early-onset diabetes had learned to read later than controls, but reading performance and the incidence of dyslexia in the 3rd grade were similar in the two groups. The study confirmed that the development of academic skills can be affected by early-onset diabetes, and that difficulties in phonological processing may underlie problems in academic skills. This study also took into account the effect of familial risk for dyslexia, which was unexpectedly high in the families with diabetes, by excluding the children who had a familial risk for reading problems. This had not been considered in earlier neurocognitive studies of diabetes.

3.2.3 Study III: Verbal and Academic Skills in Children with Early-Onset Type 1 Diabetes – the Effect of Diabetes-Related Risk Factors

In order to separate the effects of early onset-age and severe hypoglycemia, the study aimed at assessing the verbal and academic skills of children with early-onset T1DM with and without a history of severe hypoglycemia (SH+ and SH-), and healthy control children, and the incidence of learning problems in these groups. In addition, the aim of the study was to assess the effects of diabetes-related risk factors (history of severe hypoglycemia, recent and long-term glycemic control), and particularly the effects of early complications (diabetic ketoacidosis at diagnosis, poor glycemic control after the 1st year of diabetes and earlier first episode of severe hypoglycemia) on the verbal and academic skills of children with early-onset diabetes.

There were significant group differences in the incidence of spelling and mathematical problems. The incidence of spelling problems was 35.1 % in SH+, 38.5 % in SH- and 10.9 % in the control group, and the incidence of mathematical problems was 18.9 % in SH+, 30.8 % in SH- and 9.8 % in the control group. There were no group differences in the incidence of reading problems. Both groups with early-onset diabetes performed poorer than the control group in perception of phonemic length and spelling accuracy, and the children without a history of severe hypoglycemia were poorer than controls in mathematics. No significant differences in any of the verbal and academic skills were found between the children with and without a history of severe hypoglycemia. Therefore, a history of severe hypoglycemia did not seem to be a risk factor for the development of verbal and academic skills in the children with early-onset diabetes. In the children with a history of severe hypoglycemia, a later age of the first episode of severe hypoglycemia was associated with poorer performance in mathematics, indicating that the concurrent development of the child's mathematical skills might be influenced by an episode of severe hypoglycemia.

Among the diabetes-related risk factors, poorer glycemic control after the first year of the disease was associated with poorer spelling skills. This suggests that good glycemic control, especially at the onset of diabetes is associated with favorable cognitive development. This study also showed that early onset-age is a risk factor for cognitive development, independently of specific disease

complications, such as episodes of severe hypoglycemia or diabetic ketoacidosis. This may also indicate that diabetes-related risk factors are not sufficiently measured by the current methodological solutions.

4 GENERAL DISCUSSION

This thesis focuses on cognitive and early academic skills in children with type 1 diabetes. It identifies the academic skills most likely to be adversely affected in children with type 1 diabetes and some of the neurocognitive processes and disease-related mechanisms underlying these possible learning problems. Although much research has been conducted on cognitive development in children with T1DM, their theoretical background has often been in disease-related models rather than in cognitive developmental theories. This thesis applies a frame of reference that combines the well-established developmental neurocognitive theory of verbal and reading skills and recent developmental models of T1DM-related brain effects.

4.1 Academic and Verbal Skills in Children with Type 1 Diabetes

Academic achievement in children with T1DM is in most cases normal, but at the group level their performance is slightly lower when compared to other students (Dahlquist & Källén, 2007). This may indicate that some children with diabetes experience problems in learning. In the present studies, children with early-onset T1DM had poorer skills in spelling and mathematics in the 3rd grade at school compared to children without diabetes. Their reading acquisition in the first grade was also slightly slower. However, in the 3rd grade their reading skills were similar to the skills of healthy children (Study II). Parents of the children with T1DM and a history of severe hypoglycemia reported more learning difficulties and need for part-time special-education services than parents of the children without a history of severe hypoglycemia or without diabetes (Study I). However, there were no group differences in the incidence of dyslexia in Study II, which indicates that the reading and spelling problems of the children with T1DM were in most cases mild. This is also in line with the results of a recent meta-analysis (Naguib et al., 2009). However, children with early-onset T1DM had a threefold incidence of spelling problems compared to

healthy children (Study III). Parent et al. (2009) also reported more problems in writing in children with T1DM than their siblings, but they attributed these problems to visuomotor and attention difficulties.

Other studies have found that children with T1DM have poorer performance in many neurocognitive domains, for example in visuospatial skills, attention and processing speed (Naguib et al., 2009). Slower speed of processing and psychomotor inefficiency are common findings in diffuse brain dysfunction and have been found to be the core deficits in adults with T1DM (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005; DCCT/EDIC, 2007). It is possible that also in children with T1DM inefficient information processing influences performance in all areas, including the development of academic skills. In order to evaluate the skills vulnerable in T1DM, a wide range of cognitive domains were assessed with a comprehensive developmental neuropsychological test (NEPSY, Korkman et al., 1997) in Study I. Contrary to expectations, findings were not of diffuse deficits but were concentrated on problems in the auditory-verbal domain in children with T1DM and especially in those with a history of severe hypoglycemia (Study I). The auditory-verbal domain had not been fully studied earlier. Therefore, Studies II and III were conducted to explore this finding. Study II confirmed that the neurocognitive mechanism underlying early learning problems is dysfunction in basic verbal skills, mainly phonological skills.

This finding accords very well with the theory of early reading development, in which phonological skills are strong predictors of reading and spelling accuracy (Vellutino et al., 2004; Lyytinen et al., 2006; Torppa et al., 2007; Pennala et al., 2010). Phonological skills develop throughout early childhood, and already at the age of 3.5 years the child's emerging skills can predict reading and spelling accuracy in the second grade (Puolakanaho et al., 2008). In Finnish, reading accuracy reaches a ceiling in the early school years (Seymour, Aro, & Erskine, 2003). Therefore, the effect of phonological skills is best shown in spelling, which requires intact perception and decoding of phonemes (Pennala et al., 2010). However, in irregular languages such as English, the influence of phonological skills on early reading is even stronger (Ziegler et al., 2010), because learning to read requires the acquisition of more grapheme-phoneme combinations. This may explain the findings of reading problems in children with T1DM in the studies conducted in English-speaking countries (Ryan et al., 1985; Kaufman et al., 1999; McCarthy et al., 2003). Phonological skills and working memory, among many other skills, are also associated with the development of mathematical skills, which were compromised in children with early-onset T1DM in Study II. Problems in mathematics have not been reported in some of the previous studies (Hagen et al., 1990; McCarthy et al., 2002), although mathematical skills can be vulnerable to diffuse insults to the brain because of the complex neurocognitive processes involved in them. Mathematical skills in children with T1DM clearly warrant further research.

The findings of a dysfunctional continuum of verbal and academic skills in children with T1DM also contribute to the research on learning disabilities.

The development of cognitive and academic skills is influenced by the interplay of many genetic and environmental factors. Environmental factors shape the genetic predispositions during childhood and thus influence brain functioning and cognitive development (Pennington, 2006). The influence of familial vulnerability on learning has been described convincingly in the JLD study (Lyytinen et al., 2004a; 2006). The effects of home literacy and the learning environment have been the most studied environmental factors in this research field (Lyytinen et al., 2004a). However, diseases, both as a genetic and as an environmental factor, also influence brain development and can therefore be one of the factors contributing to learning disabilities. This was clearly shown in Study II, in which the children with early-onset T1DM had more problems in spelling and mathematics than the control children even when the effect of familial risk for dyslexia was excluded.

4.2 The Effects of the Diabetes-Related Factors

The neurocognitive research paradigm in children with T1DM has changed over the years. This is also evident in the theoretical background of the original articles comprising this thesis. Earlier studies have concentrated on the effects of severe hypoglycemia on cognition, as noted in Study I. The findings of Study I, along with those of other studies (Rovet & Alvarez, 1997; Hershey et al., 2005; Perantie et al., 2008; Aye et al., 2011), indicate that severe hypoglycemia has an effect on brain function and cognitive skills. In particular, more complex verbal skills (Rovet & Alvarez, 1997; Rovet & Ehrlich, 1999; Northam et al., 2001; 2009; Lin et al., 2010) and memory (Kaufman et al., 1999; Northam et al., 1999; Hershey et al., 2005; Perantie et al., 2008; Lin et al., 2010) are affected in children with a history of severe hypoglycemia. It was therefore surprising that in Study III a history of severe hypoglycemia was not associated with poorer basic verbal skills or early academic skills. However, Schoenle et al. (2002), Wysocki et al., (2003) and Patiño-Fernández et al. (2010) likewise did not find an association between severe hypoglycemia and poorer cognitive skills in children with T1DM. These findings are also contrary to the hypothesis that early episodes of severe hypoglycemia are more detrimental to the developing brain than later episodes (Perantie et al., 2008). However, the effects of early severe hypoglycemia may manifest later in development, and are not yet seen in early academic skills at the age of 9 to 10 years.

Study I did not take into account other possible diabetes-related factors, and later studies have shown that severe hypoglycemia is not the only reason for cognitive dysfunction (Northam & Lin, 2010). The effects of hyperglycemia or poor metabolic control have been detected when more sensitive methods of assessing metabolic control have been used. The studies have shown that poor metabolic control is associated with poorer academic (Kaufman et al., 1999; McCarthy et al., 2003; Parent et al., 2009) and verbal skills (Perantie et al., 2008; Patiño-Fernández et al., 2010; Aye et al., 2011), and memory (Kaufman et al.,

1999; Lin et al., 2010). A weak association between poorer mean metabolic control during the years of the disease and poorer spelling accuracy was also found in Study III. However, early metabolic control, measured by metabolic control one year after diagnosis (at the age of 2 to 6), had a strong effect on spelling in the 3rd grade. This indicates that lower HbA1c levels at the beginning of the disease may be beneficial for cognitive development. An isolated episode of DKA or SH at onset or the most recently measured HbA1c level was not related to verbal and academic skills. Nevertheless, avoiding glycemic extremes is strongly advised.

The interactive effect of glycemic extremes and age can be a confounding factor in neurocognitive studies of T1DM. The onset-age of diabetes, the age when glycemic insult occured, as well as the current age and developmental phase of a person with T1DM can influence cognitive function. Early onset-age seems to have the strongest effect on cognitive development (Gaudieri et al., 2008), and this is evident also in adults with T1DM (Ferguson et al., 2005; Brismar et al., 2007). Study I was unable to differentiate the effects of severe hypoglycemia and early onset-age, but Study III revealed that early onset-age is a significant risk factor for the development of verbal and academic skills and is not dependent on a history of severe hypoglycemia. Schoenle and colleagues (2002) have reported similar findings. Glycemic insults, especially severe hypoglycemia, at an earlier age have been hypothesized to be more detrimental to brain development than the same events later in life (Desrocher & Rovet, 2004). However, the findings of this thesis only partially support this idea. Poor glycemic control at an early age seemed to affect further development, but early episodes of severe hypoglycemia did not. On the contrary, the occurrence of the first episode of severe hypoglycemia later in childhood, during the first school years, was associated with poorer mathematical skills, which is in line with the idea that currently developing skills might be affected by an episode of severe hypoglycemia (Desrocher & Rovet, 2004). The findings of this thesis lend partial support to Ryan's diathesis hypothesis (2006), according to which high levels of blood glucose at the beginning of the disease initiate detrimental changes in the central nervous system, which is why the brain is more vulnerable to later insults, for example to episodes of severe hypoglycemia. On the other hand, the children in studies II and III were relatively young and therefore the effects of severe hypoglycemia were perhaps not yet apparent in their neurocognitive functioning. Some of the effects of glycemic extremes may become evident later in life with the development of more complex skills (Åsvold, Sand, Hestad, & Bjørgaas, 2010).

The wide age ranges and the different age groups of the samples might explain some of the differences in the findings of previous neurocognitive studies, as different developmental and age-related cognitive requirements at the time of assessment influence the results. In Studies II and III, the children were of the same age and in the same grade at school, which distinguishes these studies from the previous ones. With a narrower age range, currently developing skills can be studied more reliably. The effects of diabetes and

glycemic extremes may be different in the performance of small children and teenagers, and may be more pronounced at a later age and with longer duration of the disease.

4.3 Limitations and Future Directions

The sample sizes of the original studies were relatively small, which may bias the results. The sample sizes were not large enough to detect small differences between the groups (Cohen, 1992). The samples also limit the generalizability of the results. The children in these studies were diagnosed and assessed at a relatively young age. Therefore, these findings cannot be generalized to children with later onset of diabetes or to children with a longer duration of the disease.

The measurement of diabetes complications and blood glucose levels across childhood development presents many methodological challenges. The original studies of this thesis clearly show that more accurate methods of measuring blood glucose and insulin levels are needed in order to study diabetes-related effects in detail. The cross-sectional design of the original studies allowed us only to observe associations between disease-related and cognitive factors, not direction of the effect. However, the T1DM-related information was collected prospectively and was reliably reported in medical records, which perhaps permits further speculations. The present and some other studies (Schoenle et al., 2002; Perantie et al., 2008; Åsvold et al., 2010) have reported that the timing of a metabolic complication can influence the cognitive outcome. Furthermore, constantly occurring glycemic fluctuations may influence the brain, although to date continuous measurement of blood glucose values in association with long-term cognitive functioning has been rare (Knight et al., 2009). However, continuous blood glucose measurements developed in connection with insulin pumps may help to clarify the associations of fluctuating blood glucose levels and cognition in the future. The interactive effects of different metabolic events and their timing constitute another obstacle that should be considered in future studies. A child may experience many episodes of hypo- and hyperglycemia during his or her development. Consequently, rather than assessing isolated risk factors or complications, research on cognitive development in children with T1DM should move towards a model that takes all aspects of metabolic aberrations and their timing and duration into consideration.

Various other important issues affecting cognitive development and learning at school were not within the scope of this thesis. For example, other neurocognitive problems previously associated with T1DM, such as deficits in visuospatial skills and attention, also contribute to the development of academic skills. These cognitive domains, however, were not assessed in studies II and III, which had larger sample sizes. Acute metabolic extremes produce dysfunction in the brain and disrupt cognition (Gonder-Frederick et al.,

2009). Children with diabetes experience them often, and therefore blood glucose fluctuations during the assessment could have affected the results. Learning in the classroom can also be inefficient. It may be disrupted by acute hypo- and hyperglycemia, and in a hypoglycemic event, the recovery of cognitive functions requires considerably longer than recovery from physical symptoms of hypoglycemia (Warren & Frier, 2005). Therefore, the disruptions in effective learning can be prolonged. Moreover, absences from school due to sick days and medical appointments can put students with T1DM at a disadvantage for learning, although this has not been associated with lower academic achievement (McCarthy et al., 2003). A chronic disease such as diabetes can also increase the risk for psychosocial problems, especially depression (Gonder-Frederick et al., 2002; Delamater, 2009). Psychosocial problems in turn might act as a confounding factor in cognitive development and learning. Some studies have reported that parenting style is associated with the child's quality of life in diabetes-related issues (Botello-Harbaum, Nansel, Haynie, Iannotti, & Simons-Morton, 2008) and with the quality of diabetes care as measured by adherence (Davis et al., 2001). Diabetes care requires continuous monitoring of the child with diabetes, and therefore parents may become overly protective of the child. This can also lead to reduced experiences and opportunities for learning in the case of a child with T1DM. There is a need to connect the findings of neurocognitive and psychosocial development and parenting styles in children with T1DM. Some of the risk factors of development may interact or accumulate, as was observed in a prospective study (Aro et al., 2009).

4.4 Practical Implications

Studies on cognitive development in children with T1DM show that at the group level their performance is lower compared to that of healthy children. However, the effect sizes are small (Gaudieri et al., 2008; Naguib et al., 2009), which indicates that the differences might not be of clinical importance. Generally, small effect size differentiates children with diabetes from controls at a group level, but not at an individual level (van Duinkerken & Brands, 2011). Although clinical significance is not the same as effect size, moderate effect sizes might be considered to be clinically significant (Gaudieri et al., 2008). Moderate effect size (Cohen's d) corresponds to a mean group difference of a half standard deviation, and it may represent an observable effect in daily life and school achievement (Cohen, 1992). There are some children with T1DM that have clinically significant problems in learning, and it is important to identify them. In addition, small, sub-clinical problems in neurocognitive functions and learning are common, especially in children with early-onset diabetes or glycemic extremes. This thesis found that these children showed a higher incidence of minor learning problems or slower acquisition of the basic academic skills. Minor problems in neurocognitive development may have

adverse consequences on learning at school (Glascoe, 2001), which in turn can influence the future possibilities of students with T1DM. Small cognitive decrements and problems in learning can also cause additional stress and worries in children with diabetes and their families. However, at the individual level, the evaluation of the risk for learning problems should also include familial, psychosocial and neurocognitive vulnerabilities, all of which can be exacerbated in association with a chronic disease that has effects on the brain.

There are many reasons to pay attention to the child's cognitive development and learning at diabetes clinics. First, learning is a major developmental task of children, and therefore diabetes care, which aims at securing the development and wellbeing of a child with T1DM, is directly connected with it. Secondly, there is increasing evidence that stable glycemic control is beneficial to cognitive development, indicating the need for good glycemic control from the onset of T1DM throughout the life course. Thirdly, intact cognitive skills are required in learning diabetes self-care. Executive skills and memory in particular are needed in the daily management of diabetes (Tarazi, Mahone, & Zabel, 2007). Diabetes education should therefore be tailored according to the child's individual learning abilities. If a child with T1DM has problems in cognitive development or learning at school, a neuropsychological assessment is recommended in order to study the different aspects of cognitive functioning and to plan support for learning.

Schools are faced with the needs of children with T1DM, which include organizing support for diabetes self-care in young children and the prevention of acute metabolic complications of diabetes during school days (Ministry of Social Affairs and Health, 2010). It is important to make these plans in collaboration with parents and school personnel before school begins. The school has also the responsibility to organize support if the child has problems in learning. Support should be given as early as possible, that is, as soon as such problems are noticed. In the best situation, parents and educators will be paying attention to the development of a child with early-onset diabetes already before school entry. Support at school can include, for example, assistance services and part-time special education. Most children with T1DM do not have problems at school and do not need special arrangements for learning. However, if the child has learning problems, diabetes may contribute to them. In this situation, intensive collaboration by the parents, teachers and medical personnel is required in order to plan effective support for the child. The number of students with diabetes in schools is large and increasing, and therefore teachers should acknowledge the risk for learning problems associated with diabetes and the relevance of stable blood glucose levels for the child's well being and learning (Taras & Potts-Datema, 2005). This is important for the early identification of problems and availability of support systems.

5 SUMMARY AND CONCLUSIONS

This thesis aimed at identifying the academic skills most likely to be affected in children with T1DM and neurocognitive processes and disease-related mechanisms underlying these possible learning problems. The main findings were:

1. The children with type 1 diabetes had poorer verbal short-term memory than the healthy children. The children with a history of severe hypoglycemia had poorer skills in phonological processing than the children without diabetes. In addition, they had more learning difficulties and more need for part-time special education than the children without diabetes or the children without a history of severe hypoglycemia.

2. The children with early-onset T1DM had poorer skills in spelling and mathematics than the healthy children. They also were poorer in perception of phonemic length, which is an important underlying process in reading, spelling and mathematics.

3. The children with early-onset T1DM had more minor learning difficulties than the healthy children. In the children with early-onset T1DM, a history of severe hypoglycemia was not associated with poorer cognitive and academic skills.

4. Poorer glycemic control one year after the diagnosis was associated with poorer spelling accuracy. Severe hypoglycemia, diabetic ketoacidosis or recent glycemic control were not associated with verbal or academic skills.

In conclusion, the development of early academic skills can be affected by T1DM. In particular, children with early-onset diabetes and glycemic extremes may be at risk for minor problems in spelling and mathematics, as well as the phonological processing underlying them. This has direct implications for diabetes care, as cognitive abilities and diabetes management are in a

multidirectional relationship with each other. In order to cope with the demands of diabetes self-care, the individual needs good cognitive abilities. On the other hand, the effective management of T1DM seems to protect from chronic physical as well as cognitive effects. Therefore, it is important to consider cognitive development in diabetes care.

This thesis attempts to combine the developmental neurocognitive model of early academic skills and the models of diabetes-related effects on brain development. Early childhood, before school age, is the period of rapid development of the brain and cognition. Therefore, the onset of diabetes and consequent metabolic changes during this period can create a risk for developmental deficits, which may become evident later at school age. This integrative perspective could lead to better understanding of developmental pathways in children with T1DM, and hence to better clinical management of T1DM.

YHTEENVETO

Tyypin 1 diabetesta sairastavien lasten kielelliset ja oppimiseen liittyvät perustaidot

Tyypin 1 diabetekseen sairastuu Suomessa enemmän lapsia kuin missään muualla maailmassa, ja erityisesti alle 5-vuotiaana diabetekseen sairastuneiden määrä kasvaa. Tämän vuoksi diabetes vaikuttaa suomalaiseen yhteiskuntaan monin tavoin – mm. koulut ja päivähoito kohtaavat yhä useammin diabetesta sairastavien lasten erityistarpeita. Diabeteksen hoidossa pyritään nykyisin aiempaa pienempään, lähellä normaalia olevaan veren glukoosipitoisuuteen, mikä saattaa lisätä vaikeiden hypoglykemioiden (liian alhaisen veren glukoosipitoisuuden) riskiä. Usein diabetesta sairastavien ongelma on kuitenkin liian korkea veren glukoosipitoisuus (hyperglykemia), mikä lisää riskiä diabeteksen pitkäaikaiskomplikaatioihin, mm. verkkokalvon, hermoston ja munuaisten vaurioihin. Diabetekseen liittyvät veren glukoosiarvojen vaihtelut ja erityisesti akuutti hypoglykemia aiheuttavat toimintahäiriön aivoissa ja saattavat siten vaikuttaa lapsen kognitiiviseen kehitykseen. Tämä tutkimus pyrki selvittämään, miten diabetesta sairastavien lasten kognitiiviset taidot, luku- ja kirjoitustaito ja matemaattiset perustaidot ovat kehittyneet.

Aiempien tutkimusten perusteella tiedetään, että diabetesta sairastavien lasten kognitiivinen kehitys on yleensä normaalikehityksen rajoissa, mutta ryhmätasolla diabetesta sairastavat suoriutuvat hieman terveitä heikommin esim. näköhahmotusta, prosessointinopeutta ja tarkkaavuutta vaativissa toiminnoissa. Myös luku- ja kirjoitustaitojen on havaittu olevan lievästi heikompia kuin terveillä lapsilla. Riskiryhmässä kognitiivisen kehityksen ja oppimisen ongelmien suhteen ovat ne lapset, jotka ovat sairastuneet diabetekseen varhain, alle 5-vuotiaana, tai joilla on ollut vaikeita hypoglykemioita, mutta myös liian korkeiden veren glukoosipitoisuuksien epäillään haittaavan kognitiivista kehitystä. Kielellisten taitojen on havaittu kehittyvän heikommin juuri niillä lapsilla, joilla on ollut vaikeita hypoglykemioita tai pitkäaikainen hyperglykemia. Diabetesta sairastavien lasten kognitiivisia taitoja käsittelevien tutkimusten vertailtavuutta haittaavat potilasaineistojen pienet koot ja laajat ikäjakaumat sekä vaikeus erottaa eri riskitekijöiden, esim. varhaisen sairastumisiän ja vaikeiden hypoglykemiakohtausten vaikutukset toisistaan. Lisäksi lapsen myöhempään kognitiiviseen kehitykseen saattaa vaikuttaa lapsen ikä vaikean hypoglykemian tai hyperglykemian aikana, mutta tällainen kehitysvaiheen vaikutus on huomioitu vasta uusimmissa diabeteksen aivovaikutuksia käsittelevissä malleissa. Aiemmat tutkimukset eivät myöskään ole hyödyntäneet kehitysneuropsykologisia teorioita eri taitojen kehityksestä ja niiden yhteyksistä toisiinsa.

Tässä väitöskirjatutkimuksessa selvitettiin tyypin 1 diabeteksen merkitystä lukemisen, kirjoittamisen ja laskemisen perustaitojen kehitykselle. Tutkimuksessa kartoitettiin kognitiivisia taitoja ja erityisesti kielellisiä perustaitoja, jotka kehittyvät ennen kouluikää ja ovat välttämättömiä lukemaan, kirjoittamaan ja laskemaan oppimiselle. Näin pyrittiin selvittämään neurokognitiivisia prosesseja, jotka häiriintyvät herkimmin varhain alkaneessa tyypin 1 diabeteksessa ja vaikeuttavat siten mahdollisesti lukemisen, kirjoittamisen ja laskemisen perustaitojen oppimista kouluiässä. Toisena tavoitteena oli selvittää diabetekseen liittyvien tekijöiden (mm. varhainen alkamisikä, hypo- ja hyperglykemia) ja näiden ajoituksen yhteyksiä kognitiivisiin taitoihin, lukemiseen, kirjoittamiseen ja laskemiseen.

Tutkimustulokset pohjautuvat neuropsykologisiin tutkimuksiin kahdella eri aineistolla. Ensimmäinen aineisto koostui 5-12 -vuotiaista diabetesta sairastavista ja terveistä lapsista, joiden kognitiivisia taitoja, oppimisvaikeuksia ja tukitoimien tarvetta koulussa selvitettiin laajalla neuropsykologisella tutkimuksella ja vanhempien haastattelulla. Toinen aineisto koostui diabetesta sairastavista ja terveistä lapsista, jotka olivat kolmannella luokalla koulussa ja iältään 9-10 -vuotiaita. Tämän aineiston diabetesta sairastavat lapset olivat sairastuneet alle 5-vuotiaina. Terveenä kontrolliryhmänä käytettiin Jyväskylän yliopiston ”Lapsen kielen kehitys ja suvuittain esiintyvä lukivaikeuksien riski” –tutkimushankkeen lapsia, joilla ei ollut suvussa lukivaikeutta. Lapset tutkittiin tarkoilla, osin tietokoneavusteisilla menetelmillä, jotka mittaavat lukemisen, kirjoittamisen ja laskemisen osaprosesseja sekä näiden taustalla olevia kielellisiä perustaitoja.

Väitöskirjan tulokset osoittivat, että alle 5-vuotiaana diabetekseen sairastuneilla lapsilla oli terveitä lapsia enemmän lieviä vaikeuksia oikeinkirjoituksessa ja matematiikassa. Yli 30%:lla varhain diabetekseen sairastuneista lapsista oli vaikeuksia oikeinkirjoituksessa. Lukemaan oppiminen oli hieman terveitä lapsia hitaampaa, mutta kolmannella luokalla varhain sairastuneiden lukunopeudessa tai –tarkkuudessa ei ollut eroja terveisiin lapsiin verrattuna. Varhain diabetekseen sairastuneilla oli terveitä lapsia enemmän ongelmia kielellisissä perustaidoissa – erityisesti fonologisessa prosessoinnissa. Toisaalta myös vaikeita hypoglykemioita kokeneilla lapsilla havaittiin viitteitä fonologisen prosessoinnin ongelmista. Diabetesta sairastavilla lapsilla oli myös normaalia kapeampi kielellinen lyhytkestoinen muisti. Fonologiset taidot ja kielellinen lyhytkestoinen muisti ovat lukemisen, kirjoittamisen ja laskemisen olennaisia taustaprosesseja, jotka kehittyvät ennen kouluikää. Niiden kehitys vaikuttaisi olevan altis häiriytymään varhain alkaneessa diabeteksessa.

Sairauteen liittyvistä tekijöistä varhaisella alkamisiällä vaikutti olevan suurin vaikutus oppimiseen kouluiässä, eikä yhteys riippunut vaikeiden hypoglykemioiden kokemisesta. Vaikeita hypoglykemioita kokeneiden lasten vanhemmat raportoivat kuitenkin lapsillaan olevan enemmän oppimisvaikeuksia ja tukitoimien tarvetta koulussa kuin ne vanhemmat, joiden lapset eivät olleet kokeneet vaikeita hypoglykemioita tai joiden lapsella ei ollut diabetesta. Alle 5-vuotiaana sairastuneilla

hyperglykemia sairauden alkuvaiheessa oli yhteydessä kirjoitusvaikeuksiin kouluiässä. Näiden tulosten perusteella voidaan olettaa, että veren glukoosipitoisuuden ääriarvot saattavat olla haitallisia lapsen kognitiiviselle kehitykselle. Veren glukoosipitoisuus on myös tärkeä saada lähelle normaalitasoa jo varhaisessa vaiheessa sairautta.

Vaikka kouluoppiminen sujuu normaalisti suurimmalla osalla diabetesta sairastavista lapsista, lapsen kehitykseen ja kouluoppimiseen on syytä kiinnittää huomiota. Mikäli oppimisvaikeuksia ilmenee, diabetes saattaa olla yksi vaikuttava tekijä muiden, mm. perinnöllisen oppimisvaikeusriskin, neurokognitiivisten ongelmien ja psykososiaalisen kuormituksen ohella. Tällöin on suositeltavaa tehdä neuropsykologinen tutkimus oppimisvaikeuksien selvittelemiseksi ja tukitoimien suunnittelemiseksi. Nopeasti koulussa järjestetty tuki, esim. osa-aikainen erityisopetus, ja tiivis yhteistyö vanhempien, opettajan ja hoitavan diabetes-työryhmän kesken on ensiarvoista lapsen hyvän toimintakyvyn ja oppimisen varmistamiseksi. Lasten kanssa toimivien olisi tärkeä tiedostaa diabeteksen hyvän omahoidon ja glukoositasapainon merkitys lapsen toimintakyvylle ja kehitykselle.

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ORIGINAL PAPERS

I

NEUROCOGNITIVE FUNCTIONING IN CHILDREN WITH TYPE-1 DIABETES WITH AND WITHOUT EPISODES OF SEVERE HYPOGLYCAEMIA

by

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Neurocognitive functioning in children with type-1 diabetes with and without episodes of severe hypoglycaemia

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Previous studies have shown that recurrent severe hypoglycaemia can cause long-term cognitive impairment in children with type-1 diabetes, but the results are controversial, possibly due to the heterogeneity of samples and lack of comprehensive neuropsychological assessments of children. The aim of this study was to assess the effects of diabetes and severe hypoglycaemia on the neurocognitive functioning of children with a standardized, wide age-range neuropsychological test battery designed for the assessment of children. Eleven children with diabetes and a history of severe hypoglycaemia, 10 children with diabetes without a history of severe hypoglycaemia, and 10 healthy control children (a total of 31 children: 14 males and 17 females, age range 5 years 6 months to 11 years 11 months, mean 9 years 4 months, SD 1 year 11 months) were studied using the Wechsler Intelligence Scale for Children–Revised (WISC-R) and the NEPSY, a Developmental Neuropsychological Assessment. The NEPSY assessed development in attention and executive functions, language, sensorimotor functions, visuospatial processing, and learning and memory. Children with a history of severe hypoglycaemia had more neuropsychological impairments, more learning difficulties (as reported by parents), and needed more part-time special education than those in the other groups. Significant differences were found in verbal short-term memory and phonological processing. Results suggest that severe hypoglycaemia is a risk factor for learning due to deficits in auditory–verbal functioning.

Type-1 (insulin-dependent) diabetes mellitus is a chronic metabolic disorder caused by an autoimmune destructive process of the pancreatic beta cells, leading to hyperglycaemia and to the need for insulin replacement therapy. The geographical incidence varies considerably throughout the world, with highest rate in Finland (45 per 100 000 children below 15 years of age per year; Tuomilehto et al. 1999).

One of the main goals of diabetes management is to achieve near-normoglycaemia to prevent or to minimize the long-term complications of diabetes (retinopathy, nephropathy, and neuropathy). However, attempts towards near-normoglycaemia can lead to an increasing incidence of hypoglycemic episodes, which are the most common acute complications of insulin therapy.

For descriptive and clinical purposes, hypoglycaemia in children can be divided into four categories: (1) asymptomatic (biochemical), (2) mild symptomatic, (3) moderate symptomatic, and (4) severe hypoglycaemia. In mild symptomatic hypoglycaemia, the patients are able to detect and treat the hypoglycaemia by themselves. In moderate hypoglycaemia, the aid of another person is needed. Hypoglycaemia is severe when the patient is unconscious, and/or has convulsions. Virtually no hypoglycaemia occurring in children under 6 years can be classified as mild as young children are rarely able to treat themselves. Annually, 5–10% of children with type-1 diabetes mellitus experience severe hypoglycaemia leading to unconsciousness. They may experience mild symptomatic or asymptomatic hypoglycaemic episodes weekly (Åman et al. 1989, Barkai et al. 1998).

It has been noticed that recurrent severe hypoglycaemia can cause long-term cognitive impairment in children with type-1 diabetes (Rovet et al. 1987, Bjørgaas et al. 1997, Rovet and Ehrlich 1999), but valid reports in which such correlations have not been found also exist (Ryan et al. 1985, Northam et al. 1992). Deficits in verbal abilities (Rovet and Alvarez 1997), spatial abilities (Rovet 2000), attention (Bjørgaas et al. 1997, Rovet and Alvarez 1997), and short-term memory (Rovet and Ehrlich 1999) have been reported in connection with episodes of severe hypoglycaemia. The vast majority of the evidence with regard to the long-term effects of hypoglycaemia on neurocognitive performance is based on adults with long-standing diabetes and the results are controversial (Rovet 2000).

Studies on the effects of severe hypoglycaemia in children with diabetes have been made using small sample sizes (Rovet et al. 1987, Bjørgaas et al. 1997, Kaufman et al. 1999). Recently, Northam and coworkers (1999, 2001) published a prospective study with a large and representative cohort. The variety of tests used to assess different neurocognitive domains make it difficult to compare results between studies. Wide age-ranges within studies have also led to problems in test selection. Many of the neuropsychological tests used have either been originally developed for adults (e.g. Wisconsin Card Sorting Test; Berg 1948) or are experimental tests, thereby rendering evaluation of the clinical relevance of the results difficult.

In this controlled study we assessed the effects of diabetes and severe hypoglycaemia on neurocognitive functioning in children with a comprehensive neuropsychological test battery, including standardized normative values for every age group.

Method

PARTICIPANTS

The study population consisted of 21 children with type-1 diabetes mellitus and 10 healthy children (Table I). The ages of the children ranged from 5 years 6 months to 11 years 11 months and the duration of diabetes ranged from 1 year 9 months to 9 years 7 months. The children with diabetes were outpatients at Kymenlaakso Central Hospital in Finland. Of the children with diabetes, 11 had experienced at least one episode of severe hypoglycaemia (D+H group), defined as unconsciousness and/or convulsions associated with blood glucose concentration <3mmol/L or with prompt response to the administration of glucagon or intravenous glucose. The other 10 children with diabetes had never experienced severe hypoglycaemia (D–H group). The unaffected children served as controls (C group). They consisted of volunteers from the children of hospital staff and children from a local sports club.

All children at Kymenlaakso Central Hospital outpatient clinic who had experienced severe hypoglycaemia and met the criteria for prepubescence (Tanner Stage 1; Tanner 1962) and had normal milestones in psychomotor development (evaluated at well-child clinic and by a paediatrician at the hospital) were included in the study. The D+H group was matched with the D–H and C groups for sex, age, and parents' educational level. Parents' educational level was categorized as 1, compulsory 9-year education only; 2, vocational education or similar; 3, college education or similar; and 4, university education. The clinical data on severe hypoglycaemia were confirmed both by interviewing children and their families and by reviewing hospital records. Of the children with hypoglycaemia, four had experienced 1 episode, four had 2 episodes, two had 3 episodes, and one child had 4 episodes of severe hypoglycaemia. The episodes had occurred 9 months to 7 years (median 4 years) before the study. The two diabetic groups did not differ in recent metabolic control, defined as HbA1c-value, or in prevalence and severity of initial ketoacidosis, defined as serum pH<7.3 (see Table I). None had been unconscious during ketoacidosis, and none of the children had experienced later ketoacidosis. The two diabetes groups differed in age at diagnosis and duration of illness. Age at diagnosis was younger and duration of diabetes was longer in the D+H group than in the D–H group (see Table I). All the children had normal psychomotor development and had no history of intrauterine or perinatal problems, other neurological disorders, nor trauma. No one had experienced any psychological crises. All children were in ordinary elementary schools except for four who were in preschool.

NEUROPSYCHOLOGICAL ASSESSMENT

The Finnish version of the Wechsler Intelligence Scale for Children–Revised (WISC-R; Wechsler 1984) was used to assess general intelligence in the children aged 6 years and older. A 5-year-old child in the D–H group received the Finnish version of the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler 1995). All the verbal subtests (Information, Similarities, Arithmetic, Vocabulary, and Comprehension) were administered and they formed the Verbal IQ score. Performance IQ was formed from the Picture Completion, Block Design, Object Assembly, and Coding subtests (Picture Completion, Block Design, and Object Assembly in WPPSI-R). The IQ scores (Full-Scale, Verbal, and Performance IQ) have a mean of 100 (SD 15) and for the individual subtests the mean is 10 (SD 3). The Digit span forward assessed verbal short-term memory and was included in the neuropsychological domain of Memory and learning.

The NEPSY, a Developmental Neuropsychological Assessment (Korkman et al. 1997) is a neuropsychological test for children 3 to 12 years of age. The Finnish version consists of 30 neuropsychological subtests designed to assess neuropsychological development in five functional domains: Attention/Executive functions, Language, Sensorimotor functions, Visuospatial processing, and Memory and learning. The subtests of the Finnish version correspond to the English version of the NEPSY (Korkman et al. 1998). The subtests have been standardized on a single sample of children (Korkman 2000). Each age group has its own standardized normative values where the mean standard score is 10 (SD 3). Of the 30 NEPSY subtests, 16 were administered (Table II). The selected subtests

Table I: Characteristics of diabetes and hypoglycaemia (D+H), diabetes without hypoglycaemia (D–H), and control groups

Characteristics	*Groups*			*Significant group differences*
	D+H (n=11)	*D–H (n=10)*	*Control (n=10)*	
Sex, *n*	5 M, 6 F	4 M, 6 F	5 M, 5 F	
Age, y; mean (SD)	9.55 (2.19)	9.10 (1.92)	9.23 (1.79)	
Parents' education[a], mean (SD)	2.09 (0.83)	2.40 (0.84)	2.90 (0.99)	
Age at diagnosis, y; mean (SD)	3.32 (1.45)	5.40 (2.38)		$t=-2.45(18)$[f]
Duration of diabetes, y; mean (SD)	6.16 (2.52)	3.70 (1.63)		$t=2.67(18)$[f]
HbA1c, %[b]; mean (SD)	8.3 (1.9)	8.4 (2.0)		
Initial ketoacidosis, *n*	2	3		
Learning difficulties[c], *n*	5[e]	2[e]	0[e]	$\chi^2=7.33(2)$[f]
Special education, *n*	5[e]	2[e]	0[e]	$\chi^2=7.33(2)$[f]
Neuropsychological impairment[d], *n*	7	3	0	$\chi^2=9.74(2)$[f]

[a]Parents' education was categorized as: 1, compulsory 9-year education only; 2, vocational education or similar; 3, college education or similar; and 4, university education; [b]DCA 2000 Analyzer (Bayer Corporation, Elkhart, IN, USA), reference limit 4–6.2%; [c]Learning difficulties as reported by parents; [d]Indicated as standard score <4 in any of the NEPSY subtests (Korkman et al. 1997); [e]$n=9$; [f]$p<0.05$.

were mainly core subtests of the domains. Picture perception and Picture recognition subtests were used in order to obtain information about the visuospatial memory of the children with diabetes. The tests were administered in the same order to all the children.

PROCEDURE

All the children were assessed by the same psychologist over two or three sessions, with each session lasting 45 to 60 minutes. Between sessions there was a break. According to the wishes of the child and the parents, the sessions were scheduled for the same day or for different days within a 2-week period. The examiner was not informed which of the two diabetes groups the child belonged to. After the evaluation of the children with diabetes the control group was assessed. The blood glucose level of the children with diabetes was measured before each assessment session. None of the children had symptoms of hypoglycaemia or blood glucose value <3mmol/L at the time of assessment.

At the beginning of the assessment a structured interview on the child's cognitive development, learning, and social relationships was administered to the parents. The parents were asked if the child had learning difficulties in reading, spelling, or mathematics or had received part-time special education at school. Informed consent was obtained from the parents. The ethics committee of the hospital approved the study.

Table II: Description of NEPSY subtests (Finnish version; Korkman et al. 1997)

Domain	*Subtest*	*Description*
Attention/Executive functions	Tower	Assesses planning, monitoring, and problem solving. The child has to arrange 3 balls on 3 pegs in a prescribed number of moves and time limit.
	Auditory attention and Response set	Assesses vigilance, selective auditory attention, and ability to shift set. The child learns to respond to certain word in Part A, and has to shift set and respond to contrasting stimuli in Part B.
	Visual attention	Assesses the speed and accuracy of visual search.
Language	Phonological processing	Assesses the ability to process the phonology of words. The child has to identify words from segments or create a new word by omitting a word segment.
	Comprehension of instructions	Assesses the ability to process and respond to verbal instructions. Requires understanding of concepts and syntactic features.
	Speeded naming	Assesses the ability to access and produce familiar words rapidly. The child has to name quickly the size, color and shape of the object. Time and errors are recorded.
	Verbal fluency	Assesses the ability to generate words according to semantic and phonemic categories.
Sensorimotor functions	Fingertip tapping	Assesses finger dexterity and psychomotor speed. The child taps the index finger against the thumb 30 times. In the second part the child taps the fingers sequentially against the thumb. The score measures the time taken.
	Visuomotor precision	Assesses fine motor skills and hand-eye coordination. The child draws a line inside a track without crossing over the boundaries. The score measures both errors and the time taken.
	Finger discrimination	Assesses tactile perception. Without the aid of vision, the child identifies which of his fingers the examiner touches.
Visuospatial processing	Design copying	Assesses visuomotor integration and visuospatial skills. The child copies two-dimensional figures.
	Arrows	Assesses the ability to judge the direction, angularity and orientation of lines. The child is asked which two of eight arrows hit the target.
	Picture perception	Assesses visual recognition. The child is presented with three photos of an object, with 3s for each photo. The first photo is not sharply focused, the second is sharper and the third is the sharpest. The child is asked to name the object as soon as s/he recognizes it. (This test is not in the English version of NEPSY.)
Memory and learning	Picture recognition	Assesses visual and visuospatial memory. The child is asked to select the photo he has seen in the previous subtest from among four photos of similar objects. (This test is not in the English version of NEPSY).
	Memory for names	Assesses pair-associative memory for visual and verbal information. The child learns the names of the children seen in eight pictures. The pictures are presented three times, and 30min after the last presentation the child is asked to name the children in the pictures again.
	List learning	Assesses verbal learning. A 15-item word list is presented over five trials. An interference list is administered and recalled once, and the child is then asked to repeat the first list. Delayed recall time is after 30min. (This subtest was administered only to children who were 7 years and older.)

STATISTICAL ANALYSIS

Multivariate analysis of variance was used to determine group effects on general intelligence and on the neuropsychological domains. Parents' education was entered as a covariate. The data of the two diabetes groups were analyzed using parents' education, age at diagnosis, and duration of diabetes as covariates. Univariate ANOVA models were used to determine group differences in the IQ measures and in the individual subtests. Pairwise comparisons were further analyzed by Tukey's HSD test. Cross-tabulations with the χ^2 test were used to determine differences between the groups in the dichotomous variables (e.g. learning difficulties, need for special education).

Results

Significant differences were found in the learning difficulties reported by parents ($\chi^2=7.33(2), p<0.05$) and need for part-time special education ($\chi^2=7.33(2), p<0.05$). Most learning difficulties and special education needs were reported in the D+H group, indicating that the children who had experienced severe hypoglycaemia had more learning difficulties in reading, spelling, and mathematics (see Table I).

Because previous studies have not found conclusive evidence on the clinical significance and quality of neurocognitive impairments in children with diabetes, we took the evaluation of clinically significant neurocognitive impairments as our first task. A significant neuropsychological

Table III: Test scores in diabetes and hypoglycaemia (D+H), diabetes without hypoglycaemia (D–H), and control groups. Values are mean standard scores (SD)

Tests/subtests	*Groups*			*Significant group differences*
	D+H (n=11)	*D–H (n=10)*	*Control (n=10)*	
WISC-R				
Information	7.36 (2.34)	9.60 (3.44)	8.50 (2.01)	
Similarities	9.45 (1.81)	9.80 (3.29)	9.50 (1.65)	
Arithmetic	9.18 (2.32)	10.40 (1.58)	10.80 (1.93)	
Vocabulary	6.36 (2.98)	8.90 (3.84)	9.30 (2.87)	
Comprehension	7.91 (2.43)	8.80 (2.82)	8.60 (2.59)	
Picture completion	8.45 (2.46)	10.00 (3.20)	9.80 (2.82)	
Block design	11.18 (1.94)	11.50 (2.80)	12.40 (3.27)	
Object assembly	10.55 (2.38)	11.10 (3.38)	11.20 (2.04)	
Coding	11.18 (2.23)	10.56 (3.13)	11.00 (2.75)	
Verbal IQ[a]	87.91 (10.05)	96.30 (14.93)	95.40 (9.86)	
Performance IQ[a]	102.09 (12.73)	106.10 (16.58)	107.20 (14.36)	
Full-scale IQ[a]	93.55 (10.13)	101.00 (15.58)	101.00 (10.58)	
NEPSY				
Attention/Executive functions				
Tower	12.27 (1.90)	10.60 (2.84)	13.50 (2.07)	D–H<C[c]
Auditory attention	9.27 (4.27)	11.80 (2.57)	11.10 (2.33)	
Visual attention	10.82 (1.25)	10.90 (3.70)	10.90 (2.42)	
Language				
Phonological processes	7.45 (3.70)	9.00 (2.62)	11.10 (2.38)	D+H<C[c]
Comprehension	7.00 (2.61)	8.90 (4.09)	8.80 (3.26)	
Speeded naming	9.18 (2.86)	11.30 (2.11)	10.10 (2.13)	
Verbal fluency	8.36 (3.91)	7.90 (4.84)	11.90 (2.73)	
Sensorimotor functions				
Fingertip tapping	12.09 (1.81)	12.80 (1.14)	12.60 (1.58)	
Visuomotor precision	11.00 (2.65)	10.90 (3.78)	11.60 (4.33)	
Finger discrimination	10.09 (2.63)	10.30 (2.98)	11.40 (1.84)	
Visuospatial processing				
Design copying	11.45 (2.21)	11.70 (2.63)	11.70 (1.89)	
Arrows	11.18 (2.71)	11.20 (1.23)	12.00 (2.49)	
Picture perception	9.73 (3.00)	12.40 (2.07)	11.00 (2.87)	
Memory and learning				
Picture recognition	11.09 (3.18)	10.40 (3.03)	10.90 (2.42)	
Memory for names	8.82 (2.86)	9.70 (3.27)	11.00 (3.30)	
List learning	9.44 (2.46)	10.22 (3.35)	11.57 (4.69)	
Digit span forward[b]	4.73 (0.79)	4.60 (0.52)	5.80 (0.92)	D+H<C[d] D–H<C[d]

[a]Mean 100, SD 15, in subtests, standard score mean 10, SD 3; [b]raw score; [c]$p<0.05$; [d]$p<0.01$.

impairment is considered to exist when a person scores 2SD below the neuropsychological test mean (standard score <4). On the basis of the volume of neuropsychological impairment in the groups, we counted as having impairment those children who had at least one standard score <4. In the D+H group seven of 11 and in the D–H group three of 10 had significant neuropsychological impairments in at least one area of functioning, mainly in language and executive functions. None of the children in the control group had any neuropsychological deficits (see Table I). The between-group difference was significant (χ^2=9.74(2), p<0.05).

The test scores in the D+H, D–H, and C groups are displayed in Table III. The data were analyzed with multivariate analyses of variance within the Wechsler tests and neuropsychological domains. Due to the small size of the sample, the power of the analysis was not sufficient to detect small differences. There were almost significant group effects in the neuropsychological domains of Memory and learning (p=0.09), Attention/Executive functions (p=0.12), and Language (p=0.15). Parents' education was not a significant covariate in any of the analyses.

In the neuropsychological subtests assessing Memory and learning a significant difference was found in the Digit span forward (F=7.6 (2, 28), p<0.01). Digit span forward was exceptionally short in both diabetes groups (D+H mean 4.73 digits [SD 0.79, p<0.01] and D–H mean 4.6 [SD 0.52, p<0.01]) when compared with the control group (mean 5.80 [SD 0.92]). In the neuropsychological subtests assessing language functions a significant difference was found in Phonological processes (F=3.92 (2, 28), p<0.05). The D+H group had lower standard scores than control children (p<0.05). In the neuropsychological subtests assessing Attention/Executive functions, Visuospatial and Sensorimotor functions, all three groups scored near or over the standard means of the subtests, indicating high-level abilities. Group differences were found in the Tower subtest assessing planning and executive processes (F=4.04 (2, 28), p<0.05). A significant difference was found between the D–H and C groups (p<0.05). No statistical difference was found in the Wechsler subtests. Verbal IQ in the D+H group was 87.9, in the D–H group 96.3, and in the control group 95.4, but the differences did not reach statistical significance.

Because the two diabetes groups differed in age at diagnosis and duration of illness, comparison within the diabetes groups were made using these variables and parents' education as covariates. A significant group effect (F=4.43 (3, 14), p<0.05) was found in attention and executive functions. Pairwise comparisons revealed significant differences in the Tower subtest (p<0.05), where the D–H group had lower scores than the D+H group, and in Auditive attention (p<0.05), where the D+H group performed more poorly than the D–H group. Age at diagnosis (p<0.05) and duration of diabetes (p<0.01) were significant covariates in the Auditive attention subtest. There was no significant group effect in any of the other neuropsychological domains nor in intelligence.

Discussion

The aim of the study was to assess the effects of diabetes and severe hypoglycaemia on neurocognitive functioning in children. We used a comprehensive, well standardized, and validated, wide age-range neuropsychological test in order to assess a variety of cognitive domains. By means of the NEPSY, it is possible to study both basic and complex aspects of neurocognitive functioning with subtests appropriate across wide age groups, thereby obtaining information on the clinical relevance of neurocognitive deficits when compared with age expectations (Korkman et al. 1998). A comprehensive neuropsychological assessment can explain a behavioural outcome (e.g. learning difficulty) by showing the deficits in basic function (e.g. phonological processing).

In this study, the children with diabetes who had experienced severe hypoglycaemia had significantly more neuropsychological deficits and learning difficulty, and they needed more special education than the healthy children or the children with diabetes but without a history of severe hypoglycaemia. The clinical significance of cognitive impairments in children with diabetes has not been fully recognized in previous studies. Significant differences were found in verbal short-term memory and phonological processing skills between the children who had experienced severe hypoglycaemia and the healthy children. Other studies have also reported a relation between poorer short-term memory and severe hypoglycaemia (Kaufman et al. 1999, Northam et al. 1999, Rovet and Ehrlich 1999). Phonological processing skills have not been assessed comprehensively in previous studies. Deficits in auditory–verbal functions, as found in our study, have an influence on the development of verbal skills. They may partly explain the lower verbal intelligence in children with a history of severe hypoglycaemia found in the prospective studies by Rovet and Ehrlich (1999) and Northam and colleagues (2001).

The frontal and temporal regions, particularly in the left hemisphere, are involved in language, memory, and attentional processes. Auer and Siesjo (1988) and Chalmers and colleagues (1991) found that abnormal blood glucose levels in particular affect the frontal and temporal regions of the brain, especially the hippocampus (Auer 1986). In cerebral blood flow studies hypoglycaemia has been shown to have an asymmetrical effect with a greater reduction of left- versus right-hemisphere profusion (Jarjour et al. 1995).

The brains of infants appear to have an increased vulnerability to hypoglycaemia (Harwoth and Coodin 1960). Preterm infants born small for gestational age (Lucas et al. 1988), infants of mothers with diabetes (Schwartz and Teramo 2000), and infants with persistent hyperinsulinemic hypoglycaemia (Cresto et al. 1998) are most at risk. An adverse neurodevelopmental outcome can be seen even after moderate neonatal hypoglycaemia (Lucas et al. 1988), and prolonged or repeated episodes of profound neonatal hypoglycaemia may lead to severe learning disability* and epilepsy (Menni et al. 2001). In contrast to these patients, children with diabetes are usually older and recover from severe hypoglycaemic attacks without permanent major neurological deficits (Tupola et al. 1998). However, transient hemiplegia after severe hypoglycaemia has been described in children with diabetes (Lala et al. 1989, Wayne et al. 1990). The mechanism of this neurological deficit remains unclear.

In our study, the neurocognitive functioning of the children with diabetes and without an experience of severe hypoglycaemia was less affected than that of those with recurrent severe hypoglycaemia. However, they too had slightly poorer auditory–verbal skills than the unaffected

*US usage: mental retardation.

children. In addition, they differed in a task requiring executive processes. Thus, diabetes can be associated with subtle, diffuse deficits in the child's performance. The explanation could lie in the mild symptomatic or asymptomatic hypoglycaemic episodes which all children with diabetes experience. Such episodes cause transient cognitive deficits, especially in planning and cognitive flexibility, sustained attention, and reaction time (Ryan et al. 1990) and, cumulatively, may have a negative effect on the child's performance.

Minor problems in neurocognitive functioning may cause learning difficulties at school. Ryan (1988) reported poorer school achievement among children with diabetes, especially in reading and spelling. In our study, the children with diabetes and especially those who had experienced severe hypoglycaemia had more learning difficulties reported by parents and needed more part-time special education than the unaffected children. A limitation of the study is that teachers' reports were not obtained. In the literature, there is no consensus regarding the link between specific learning disorders and diabetes. When compared with other groups of children with chronic illnesses, children with diabetes perform more poorly at school and surpass only those children with a neurological illness e.g. epilepsy (Fowler et al. 1985). Deficits in neurocognitive functioning apart, other reasons can be adduced to explain the poorer school achievement of children with diabetes. They may be more frequently absent from school, which can affect school performance. Mild hypoglycaemic episodes have an influence on attention (Ryan et al. 1990, Gschwend et al. 1995), psychomotor speed and memory (Reich et al. 1990), and learning in the classroom is not always effective. It is likely that teachers are not always aware of hypoglycaemia-induced cognitive deficits, and this may also influence performance at school.

The limitations of the current study are acknowledged. We have used a small sample, and this restricts the generalizability of the results. Nevertheless, some significant differences in neurocognitive functioning between the groups were found. Most of the previous studies on the effects of diabetes on cognitive functioning have found that the critical factors affecting cognitive development in children are early onset of diabetes (Ryan et al. 1985, Rovet et al. 1988, Hagen et al. 1990) and prevalence of severe hypoglycaemia (Rovet et al. 1987, Bjørgaas et al. 1997). However, according to Kaufman and colleagues (1999) age of diagnosis is not related to neurocognitive test results. In our study, the children who had had severe hypoglycaemia were diagnosed at a younger age than the other children with diabetes. This is quite often the case, as young children have a higher incidence of severe hypoglycaemia (Ternand et al. 1982). It remains doubtful, however, whether the onset age of diabetes or the occurrence of severe hypoglycaemia at a certain age affects cognitive development. Because of the small size of the sample, the present study cannot fully differentiate the effects of the age at onset of illness and severe hypoglycaemia.

In children with diabetes, neurocognitive functioning is in most cases normally developed, but diffuse deficits may also exist. Clinically significant impairments are associated with severe hypoglycaemia. Deficits in cognitive functioning in turn have an important effect on the child's performance, on school achievement as well as on the child's ability to manage diabetes. This study suggests that neuropsychological assessments should be administered to children with diabetes in order to identify possible deficits in neurocognitive functioning.

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II

VERBAL AND ACADEMIC SKILLS IN CHILDREN WITH EARLY-ONSET TYPE 1 DIABETES

by

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Verbal and academic skills in children with early-onset type 1 diabetes

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AIM Basic verbal and academic skills can be adversely affected by early-onset diabetes, although these skills have been studied less than other cognitive functions. This study aimed to explore the mechanism of learning deficits in children with diabetes by assessing basic verbal and academic skills in children with early-onset diabetes and in comparison children. In addition, the incidence of dyslexia (≤10th centile in reading speed or reading–spelling accuracy) was studied.
METHOD The performance of 51 children with early-onset diabetes (25 females, 26 males; mean age 9y 11mo, SD 4mo; range 9–10y) was compared with that of 92 children without diabetes (40 females, 52 males; mean age 9y 10mo, SD 3mo; range 9–10y) in the tasks of phonological processing, short-term memory, rapid automatized naming, reading, spelling, and mathematics.
RESULTS The performance of children with diabetes was poorer than that of the comparison children in phonological processing (p=0.001), spelling accuracy (p<0.001), and mathematics (p=0.024). They learned to read later (p=0.013), but reading performance and the incidence of dyslexia in the third grade (aged 9–10y) were similar in the two groups.
INTERPRETATION Children with early-onset diabetes are prone to minor learning difficulties in their early school years as a result of deficits in phonological processing.

Cognitive development may be affected in children with type 1 diabetes. Among the variables related to this illness, early age at onset shows the strongest effect on cognitive development, whereas the role of severe hypoglycaemia and other complications is more controversial.[1] It has been proposed that developing skills are vulnerable to brain insults, for example as a result of extreme fluctuations in blood glucose.[2] For this reason, basic cognitive functions that develop during early childhood, and the emerging skills dependent on them, are prone to be affected in early-onset diabetes. Research on the basic cognitive functions should, therefore, add essential information about the possible mechanism of learning deficits in children with diabetes.

Previous research into the cognitive functions of children with diabetes has focused on intelligence, learning and memory, processing speed, and attention.[1] Among verbal skills, the focus has been on complex skills such as verbal intelligence[3,4] and verbal learning and memory.[4,5] Prospective studies have shown problems in the development of verbal intelligence as a function of severe hypoglycaemia,[3,4] which increase with the duration of illness, whereas the findings of cross-sectional studies have been more inconclusive, probably because of large differences in the age of the sample populations and different methods of assessment.

Basic verbal skills have been assessed in only a few studies, and deficits in auditory short-term memory[6–9] and phonological processing[9] have been reported in some children with diabetes. Rapid automatized naming has not been assessed in children with diabetes, although it is an important measure of language processing and is closely associated with reading.[10,11] Phonological processes, auditory short-term memory, and automatized retrieval from the long-term memory (rapid automatized naming) are required to develop fluent skills in reading and spelling.[12,13] These basic processes develop rapidly during childhood, before school age, and are, therefore, prone to be affected in early-onset diabetes.

Hannonen et al.[9] have suggested that deficits in basic verbal skills in some children with diabetes might be linked to an increased need for special education in learning to read and spell. As achievement in mathematics is associated with reading,[14] it is surprising that mathematical learning difficulties have not been reported in previous studies.[6–8,15] Although the evidence for the overall influence of diabetes on school achievement is weak,[7,8,15,16] children who have acquired diabetes at an early age[7,16] and children with longer disease duration,[6] with a history of severe hypoglycaemia,[9] or with poor glycaemic control[8] have a higher risk for poorer achievement or learning difficulties, and they are, therefore, more likely to

need extra support at school. In addition to diabetes, other factors affect development and achievement. For example, familial risk is a well-documented predictor of reading difficulties[10,12] and can also affect the development of children with diabetes. This study assesses academic skills with sensitive, partly computerized, tasks of reading, spelling, and mathematics to identify which processes are affected in early-onset diabetes. In addition, the severity of reading disability in children with diabetes is studied using the criteria for dyslexia.

The aim of this study was to compare children with early-onset type 1 diabetes and age-matched comparison children without diabetes in terms of (1) basic verbal and academic skills in the third grade at school (at the age of 9–10y), (2) time of reading acquisition at the beginning of education, and (3) the incidence of dyslexia in the third grade at school.

What this paper adds

- The development of academic skills can be affected by early-onset diabetes.
- Children with early-onset diabetes may have minor learning difficulties in spelling and mathematics.
- Difficulties in phonological processing underlie problems in academic skills.

METHOD

Participants

Sixty-three children with type 1 diabetes, screened by the paediatric diabetes clinics of the four special care hospitals in Finland, participated in the study. Children with type 1 diabetes who had been diagnosed before 5 years of age and who were 9 to 10 years of age at the time of the study were eligible for inclusion. Exclusion criteria were native language other than Finnish and a diagnosed neurological disorder that affects cognitive development (e.g. learning disability* and autism). The nurse or the doctor of the paediatric diabetes clinic identified children who fulfilled the criteria and contacted their parents. The data were collected over 3 consecutive years from 2006 to 2008. Seventy-nine children and their parents were asked to participate in the study. Sixteen refused to participate, mainly because of time constraints. Background information on refusals was not available. Sixty-three (79.7%) children with diabetes participated in the study. Of the children with diabetes, 19% had a familial risk of dyslexia, as reported by the parent, and defined as at least one parent and one other close relative who had problems with reading and spelling. None of the children in the comparison group had a familial risk of dyslexia, as their selection for this group was based on this requirement. Thus, the children with diabetes and familial risk of dyslexia were excluded from the statistical analyses, leaving 51 children in the diabetes group.

The comparison group used in the Jyväskylä Longitudinal Study of Dyslexia (n=92) was selected as the comparison group of this study. The children in this group had neither familial risk of dyslexia nor diabetes. The comparison children had been followed from birth in order to study their language development and the predictors and precursors of dyslexia. Originally, they were screened over 4 consecutive years from families attending maternity clinics in central Finland. The comparison group was assessed with the same tests as the diabetes group during the years 2003 to 2006. (For a detailed description of the comparison group, see Lyytinen et al.[12])

The children in the two groups were assessed at the same age: in the spring semester of the third grade (in Finland, children enter school at the age of 7) or during the following summer. There were no differences between the groups in sex, age, IQ, or parents' education (Table I). More treatment for neonatal complications (preterm birth, asphyxia, infection, neonatal hypoglycaemia, exchange transfusion, neonatal hyperbilirubinaemia) were recorded in the comparison group than in the diabetes group (32.6% and 15.7% respectively, $\chi^2[1]=4.76$, $p=0.029$), whereas both groups had normal developmental milestones in speaking and walking.

*North American usage: mental retardation.

Procedure

At the beginning of the psychological assessment, written informed consent was provided by the parent and verbal assent was given by the child. The mother filled in a structured questionnaire on her child's development, school history, and the time of reading acquisition, her own and the child's father's education and profession, type of family, and familial risk for dyslexia (parents, siblings, close relatives). The birth and illness history of the children was obtained from the hospital medical records. The protocol was approved by the Kymenlaakso Central Hospital's Ethics Committee.

Children were assessed by experienced psychologists. The two groups were assessed separately. The assessment lasted 2 hours, with a break after 1 hour. Before and after the assessment, the children with diabetes measured their plasma glucose level. If plasma glucose was less than 4mmol/l, a 10g carbohydrate snack was given and the assessment delayed until the plasma glucose value was more than 4mmol/l. If plasma glucose was more than 18mmol/l, the assessment was delayed

Table I: Participant characteristics

	Diabetes group	Comparison group
n	51	92
Female/Male, *n*	25/26	40/52
Mean age (SD)	9y 11mo (4mo)	9y 10mo (3mo)
Mother's education,[a] mean (SD)	4.34 (1.35)	4.66 (1.39)
Father's education,[a] mean (SD)	3.61 (1.43)	3.99 (1.34)
Mean Verbal IQ (SD)	99.76 (16.42)	102.03 (14.69)
Mean Performance IQ (SD)	98.53 (20.60)	101.56 (15.67)
Mean Full-scale IQ (SD)	98.84 (16.24)	101.30 (12.38)
Mean age at diabetes onset (SD)	3y (1y 4mo)	–
Mean HbA_{1c} (%), mean (SD)	8.2 (0.6)	–
Latest HbA_{1c} (%), mean (SD)	8.3 (0.8)	–
Occurrence of severe hypoglycaemia (%)	60.8	–

[a]Parents' education was classified using a seven-point scale constructed by combining general education, secondary vocational education, and tertiary education; –, data not available.

until the value was 4 to 18mmol/l. All the tests were administered in a fixed order.

Cognitive measures

IQ was assessed with the Wechsler Intelligence Scale for Children – Third Edition.[17] The subtests of Vocabulary, Comprehension, and Similarities were used to form Verbal IQ. Similarly, the subtests of Picture Completion, Block Design, and Object Assembly constituted Performance IQ.

The other cognitive and academic measures are presented in Table S1[18–21] (available online only). The cognitive and academic skill variables were computed using standardized *z*-scores from the individual tasks (standardization was based on the mean and SD of the comparison group). The speed measures were transformed so that the high *z*-scores corresponded to fast performance.

Reading accuracy was composed of the measures of the accuracy of oral text reading, oral pseudo-word text reading, and single non-word reading. Reading speed was composed of the measures of the speed of oral text reading, oral pseudo-word text reading, single non-word reading, reading rapid words, and oral word list reading. Spelling accuracy was composed of spelling words and non-words. Mathematics assessment was composed of the five series of measures of the speed of verbal counting and measures of the accuracy of verbal counting and arithmetic. Cronbach's alpha was 0.81 for reading accuracy, 0.92 for reading speed, 0.65 for spelling accuracy, and 0.84 for mathematics. To normalize the distributions of the composite variables, a logarithmic transformation was used for the skewed distributions (reading accuracy and mathematics), and extreme values were moved next to the second lowest value of the distribution of the whole sample (reading speed and rapid automatized naming).

The time of reading acquisition (grouped as before first grade, autumn first grade, spring first grade, second grade) and the occurrence of dyslexia were also used as dependent variables. The criterion for a diagnosis of dyslexia was performance at or below the 10th centile of the comparison group's performance in at least three out of the four measures of reading–spelling accuracy (single non-word reading, text reading, pseudo-word text reading, word and non-word spelling) or three out of the four measures of reading speed (single non-word reading, text reading, pseudo-word text reading, oral word list reading). In addition, children who fell below the criterion in two of the accuracy and two of the speed measures were also considered to have dyslexia. The criterion for dyslexia was strict and similar to that of Hutzler and Wimmer.[22]

Illness measures

Data for age at onset of diabetes, metabolic control (latest HbA_{1c} [glycosylated haemoglobin] measurement and mean HbA_{1c} level during illness), and history of severe hypoglycaemia were acquired from the patient records. HbA_{1c} levels were measured at visits to the clinic on a 3-monthly basis. If there was a period when measurements were made more often than once every 3 months, the mean of the measurements during that period was counted. Severe hypoglycaemia was defined as seizures or a remarkably lowered level of consciousness observed by parents or other adults, and was associated with measured subnormal blood glucose level or with response to administration of glucagon or intravenous glucose. The illness variables of the diabetes group are presented in Table I.

Statistical analyses

Group differences in verbal (perception of phonemic length, non-word repetition, verbal short-term memory, and rapid automatized naming) and academic (reading accuracy, reading speed, spelling accuracy, and mathematics) skills were analysed by multiple analyses of covariance (MANCOVA) and differences in the performances of individual tasks by ANCOVA. Mother's and father's education were entered as covariates in the analyses. Cohen's *d* (with pooled SD) was used as a measure of effect size. Group differences in the time of reading acquisition and the incidence of dyslexia were analysed by χ^2 tests.

RESULTS

The diabetes and comparison groups differed in verbal processes ($F_{4,125}$=4.52; p=0.002) and academic skills ($F_{4,127}$=5.15; p=0.001). Mother's and father's education were not statistically significant covariates in the MANCOVAs. The group means and standard deviations for verbal and academic skills are presented in Table II. The children with diabetes performed significantly worse than the comparison children in perception of phonemic length ($F_{1,128}$=12.08; p=0.001), spelling accuracy

Table II: Verbal and academic skills in the diabetes group and comparison group, statistical significance of group differences, and effect sizes

	Diabetes group, mean (SD)	Comparison group, mean (SD)	*F*	*p* value	Effect size	95% confidence interval
Verbal skills						
Perception of phonemic length	−0.66 (1.18)	−0.00 (1.01)	12.08	0.001	−0.59	−0.84 to −0.31
Non-word repetition	0.13 (1.19)	0.06 (0.98)	0.22	0.639	0.06	−0.19 to 0.35
Verbal short-term memory	−0.25 (1.13)	0.07 (0.96)	2.37	0.126	−0.30	−0.54 to −0.02
Rapid automatized naming	0.02 (0.63)	0.05 (0.79)	0.09	0.759	−0.04	−0.18 to 0.18
Academic skills						
Reading accuracy	0.05 (0.67)	0.08 (0.61)	0.07	0.797	−0.05	−0.19 to 0.12
Reading speed	0.02 (0.63)	0.06 (0.71)	0.20	0.659	−0.02	−0.19 to 0.14
Spelling accuracy	−0.62 (1.00)	0.00 (0.83)	14.70	<0.001	−0.66	−0.87 to −0.43
Mathematics	−0.30 (0.50)	−0.06 (0.66)	5.19	0.024	−0.43	−0.54 to −0.25

($F_{1,130}$=14.70; p<0.001), and mathematics ($F_{1,130}$=5.19; p=0.024). The effect sizes were moderate for spelling accuracy (−0.66) and perception of phonemic length (−0.59) and small for mathematics (−0.43) and short-term memory (−0.30).

Group differences were found in the time of reading acquisition (χ^2(3)=10.85, p=0.013). The children with diabetes learned to read later than the comparison children. Nine children (17.6%) with diabetes and 10 children (10.9%) in the comparison group fulfilled the dyslexia criteria, but the difference was not statistically significant (χ^2[1]=1.31, p=0.253).

DISCUSSION

The aim of the study was to investigate basic verbal and academic skills in children with early-onset diabetes and in a comparison group. In the third grade (at the age of 9–10y), the children with early-onset diabetes had more difficulties in phonological processing, spelling, and mathematics. Reading performance was not affected in the third grade, although the children with diabetes had learned to read later than the comparison children. Further, the incidence of severe reading disability (i.e. dyslexia) was not significantly higher in the children with diabetes.

The early onset of diabetes seems to have the strongest influence on cognitive skills.[1] Basic verbal skills have been studied less than other cognitive functions, but in this and in our previous study[9] problems were found in phonological processing in some children with diabetes. Children with early-onset diabetes have a disadvantage in academic achievement,[1] and Dahlquist et al.[16] found that the early-onset effect lasts throughout compulsory education. Because of the greater age variation in the samples used, previous studies[6-8] have not been able to assess the developing academic skills. As the present children were all at the same level of education, this study was able to show that early-onset diabetes is associated with difficulty in processing phonemic length, which results in less accurate spelling in Finnish and other regular orthographies;[12] it is also closely associated with reading and spelling in irregular orthographies (e.g. English).[13]

In this study, mathematics skill was also compromised in children with early-onset diabetes. Previous studies[6-8,15] have not found evidence of mathematical learning problems, which is unexpected because mathematical skills involve complex cognitive processes[14] and are, therefore, vulnerable to diffuse insults to the brain. Among these processes, short-term memory,[6-9] attention,[1,4] phonological processing,[9] and non-verbal skills[6,7] have been shown to be vulnerable in some children with diabetes. The processes involved in mathematical skills warrant further research in children with diabetes.

Ryan[23] has proposed that neurodevelopment can be affected by metabolic changes in diabetes, especially during rapid brain maturation in young children. Early onset of diabetes has been associated with structural changes in the brain,[24] suggesting that learning difficulties in children with early-onset diabetes are associated with brain dysfunction. On the other hand, learning and school achievement can also be compromised by school absence and the psychosocial burden of the chronic illness.

One purpose of this study was to assess the significance of learning deficits in children with early-onset diabetes. The effect sizes for separate academic skills varied from nominal to moderate in this study. Similarly, in a recent meta-analysis,[1] the effect of early-onset diabetes on overall academic achievement was small to moderate, which can be clinically meaningful at a group level. In this study, there were more children with dyslexia in the diabetes group than in the comparison group. However, the difference was not statistically significant, indicating that the reading and spelling difficulties in children with diabetes are seldom at the level of dyslexia but rather within a subclinical range. Children with minor learning difficulties also have lower school achievement and may need support services at school.[25]

To our knowledge, the role of familial dyslexia has not been addressed in previous studies. In this study, 19% of the parents reported a history of reading and spelling problems. The high incidence of familial dyslexia in the families with diabetes was unexpected, but can be explained, in part, by the fact that parents reported minor as well as more serious deficits. The reading skills of the parents in the diabetes group were not assessed. However, the genetic linkage between diabetes and dyslexia might also be a topic of research in the future.

Limitations

There were some differences in the early development of the diabetes and comparison groups, but both groups showed normal developmental milestones. The differences in when the developmental data were collected (retrospective in the diabetes group, prospective in the comparison group) may have influenced the results. Although the early age at onset seems to have the strongest effect on cognitive development, the role of diabetes complications can also be relevant. The effect of disease complications on learning was beyond the scope of this article, the purpose of which was to explore the mechanism of learning deficits in children with early onset diabetes. However, the interactive effects of early onset diabetes and extreme levels of plasma glucose merit further research.

CONCLUSION

Early-onset diabetes affects the development of verbal and academic skills. Slower or deficient development continues to be evident in spelling and mathematics at 9 years of age. It seems that early-onset diabetes is not related to a higher risk of dyslexia. However, even minor learning problems may have an influence on school achievement, motivation, and self-esteem, and, together with a chronic and difficult to manage illness, they can affect the quality of life of the child and the family. It is important, therefore, to discuss learning at the visits to the clinic. The presence of additional risk factors, for example familial or psychosocial, should also be considered with each child.

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ONLINE MATERIAL

Additional material and supporting information may be found in the online version of this article.

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Table S1. Description of the cognitive and academic tests and tasks.

Domain, *Test / Task*	Description
Verbal Skills *Perception of phonemic length*	Assesses discrimination of phonemic length (essential in Finnish spelling: a change in the duration of a phoneme changes the meaning of a word, e.g. kuka (who) – kukka (flower)). A same-different judgement task, administered by a computer (Cognitive Workshop program, developed by the Universities of Dundee and Jyväskylä). The child listens to a pair of non-words via headphones and has to decide if the second non-word is similar to the first heard or not. Twelve out of the 22 non-word pairs differ in phoneme duration (e.g. [simpu] / [simpuu]). Number of correct answers out of 22 items is used as the measure.
Non-word Repetition (subtest of the NEPSY[18])	Assesses phonological processing and repetition of the phonology of non-words. The child hears each non-word once via headphones and has to repeat that word immediately. The number of correct repetitions out of 16 items is used as the measure.
Verbal short-term memory (digit span forward)	The child has to repeat a series of spoken digits of gradually increasing length, starting with two digits. The number of correctly repeated series is used as the measure.
Rapid automatized naming (the Rapid Automatized Naming Test; Finnish version[19]).	The standard procedure with the subtests of objects and letters (see Denckla and Rudel[20]) is used. The child is asked to name a series of visual stimuli as rapidly as possible. Total matrix completion time (seconds) is used as the measure. The speed of naming is composed of the average time of the two subtests.
Academic Skills Reading *Oral text reading*	The child reads aloud a text in Finnish comprising four paragraphs with a total of 189 words. Reading performance is recorded. The number of words read in one minute (speed measure) and the percentage of correctly read words (accuracy measure) is counted from the recording.
Oral pseudo-word text reading	The child reads aloud a short text made up of pseudo-words resembling real Finnish words but having no meaning (a total of 38 words). Reading is recorded and the number of words read in one minute is used as the speed measure and the percentage of correctly read words is used as the accuracy measure.
Single non-word reading	Two separate sets (3- and 4-syllable non-words) of 10 items are presented in a fixed order on a computer screen (Cognitive Workshop program). The task is to read aloud the target item as quickly and accurately as possible. The number of correctly read non-words is used as the accuracy measure. Two response time variables (ms.) are extracted: reaction time (the time between the presentation of the target and initiation of the child's vocalisation) and production time (the time taken by the child to

	articulate the target). The mean of the response times (reaction time + production time) is used as the measure of reading speed.
Reading rapidly presented words	Assesses the level of automatization in word decoding, administered by a computer (Cognitive Workshop program). Eighteen Finnish words are presented on a computer screen for 80 ms one at a time after which a mask of similar length is presented. The task is to read the target word. the number of correct answers is used as the measure.
Oral word list reading (in the standardized reading test of Lukilasse[21])	The child has two minutes to read aloud as many words as possible from a 105-item word list. The standard score is based on the number of correctly read words.
Spelling *Spelling words and non-words*	 The child is asked to write with a pencil 10 Finnish words and 12 four-syllable non-words presented by a computer via headphones (Cognitive Workshop program). The sum of correctly spelled words and non-words is calculated.
Mathematics *Verbal Counting*	 The child is asked to count a series of numbers in a prescribed set (e.g. even numbers from 2 to 30) as fast as possible. If the child makes a mistake, he has to correct it in order to continue. The accuracy of the series as well as the time taken to count is measured.
Arithmetic	The child is asked to solve as many basic arithmetic tasks as he can in 5 min. The tasks are presented on a task sheet and the child writes down the answers with a pencil. The number of correct answers is counted.

III

VERBAL AND ACADEMIC SKILLS IN CHILDREN WITH EARLY-ONSET TYPE 1 DIABETES – THE EFFECTS OF DIABETES-RELATED RISK FACTORS

by

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Verbal and Academic Skills in Children with Early Onset Type 1 Diabetes - The Effects of Diabetes-related Risk Factors

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Abstract

Early onset age is associated with cognitive dysfunction in children with type 1 diabetes mellitus (T1DM), but the role of abnormal glucose levels in cognitive development remains ambiguous. The study aimed at assessing the effects of diabetes-related risk factors on verbal and academic skills in children with early-onset T1DM. The study comprised 63 children with T1DM diagnosed before five years of age and 92 control children without diabetes, aged 9 to 10 years. In the T1DM group, 37 had experienced severe hypoglycemia (SH+ group) and 26 had avoided it (SH- group). Severe hypoglycemia (SH), diabetic ketoacidosis (DKA) and glycemic control (HbA1c) were used as diabetes-related factors. Task performance in phonological processing, verbal short-term memory, rapid automatized naming, reading, spelling and mathematics, and the incidence of learning problems were compared between the SH+, SH- and control groups, and the effects of the diabetes-related risk factors were analyzed with GLMs. The SH+ and SH- groups showed poorer performance than controls in phonological processing and spelling accuracy, and the SH- group poorer performance than controls in mathematics. The SH+ and SH- groups had a threefold risk for spelling problems compared to controls. SH, DKA and recent HbA1c were not linearly associated with poorer skills, but poorer first year glycemic control was associated with poorer spelling accuracy. *Conclusion:* Early onset of T1DM can increase the risk for learning problems in early academic skills, independently of the history of SH or DKA. Early good glycemic control seems to be associated with favorable cognitive development.

Key words: cognition, academic skills, T1DM, hypoglycemia, glycemic control, children

Introduction

An association between type 1 diabetes mellitus (T1DM) and cognitive and neural dysfunction has been demonstrated [24]. However, the mechanism underlying deficient neurodevelopment remains unclear. Hypotheses have been proposed concerning the effect of extreme or fluctuating levels of plasma glucose on the brain metabolism and neural functioning. Northam and Lin [24] and Desrocher and Rovet [7] have suggested that the timing of the metabolic insult in the child's development is an important predictor of the outcome. Generally, earlier brain damage has a worse cognitive outcome than insults sustained later in childhood [2]. This has also been shown in children with T1DM: those with earlier onset of the disease have lower cognitive and academic skills than those with later onset of T1DM or healthy children [10].

Besides early onset of diabetes, several risk factors, in particular severe hypoglycemia and prolonged hyperglycemia have been shown to affect cognitive development. The interaction of early onset-age of T1DM and extreme levels of plasma glucose at an early age is proposed to have the most detrimental effect on cognitive development [7, 24, 33]. According to the neurodevelopmental model of Desrocher and Rovet [7], severe hypoglycemias occurring at different ages may have different effects on cognitive development, while severe hypoglycemias in early childhood might in particular be harmful for cognitive development [3]. Ryan [33] has proposed that hyperglycemia in a young child affects brain structure and function, thereby rendering the brain more vulnerable to later insults, for example severe hypoglycemia. Diabetic ketoacidosis (DKA) has been associated with deficient memory [11, 35] and verbal [35] functions. However, it is debatable, whether a single episode of DKA can have long-term effects on cognition. Diabetes-related factors may also have interactive effects [24], and may be different in boys and girls [9, 11, 34]. However, only a few studies assessing these interactions [11, 29, 34] or synergy [19] have been published so far.

Verbal skills develop during early childhood and have been shown to be at risk for deficient development in early onset T1DM [13, 34]. Among metabolic complications, hyperglycemia [27, 29] and history of severe hypoglycemia [3, 14, 16, 19, 25, 31, 32] have been associated with poorer verbal skills. However, conflicting results have also been found [4], suggesting that the associations between diabetes-related events and cognition are complicated. Previously, we have demonstrated a neurocognitive mechanism underlying deficient development of early academic skills in children with early onset T1DM [13]; children with early onset disease had poorer skills in phonological perception, which is an important underlying process in spelling and mathematics. However, a history of severe hypoglycemia [14] has also been associated with less adequate phonological processing. In addition, T1DM [14] and severe hypoglycemia [16, 23] has been associated with dysfunctional verbal short-term memory, which also influences reading and spelling processes [28, 37]. Deficits in basic verbal functions may therefore lead to poorer learning and academic achievement in children with T1DM, as previously reported [5]. These same risk

factors - longer duration of diabetes [18], poor metabolic control [16, 21, 26] and a history of severe hypoglycemia [14, 16, 21] - may also increase the risk for poorer academic achievement or learning problems.

Prior studies have found that early onset of T1DM and plasma glucose extremes may influence brain function and cognition; however, it has been difficult to separate these effects. This study aimed at assessing the interactive effects of early onset-age and diabetes-related risk factors on verbal and academic skills. The aims of this study were twofold: first, to compare verbal and academic skills and the incidence of learning problems of children with early-onset T1DM with and without a history of severe hypoglycemia with the same skills of healthy controls; and second, among all the children with early-onset T1DM, to assess the effects of diabetes-related risk factors (history of severe hypoglycemia, recent and long-term glycemic control), and particularly the effects of early complications (diabetic ketoacidosis at onset, poor glycemic control after the 1st year of diabetes and early severe hypoglycemia), on their verbal and academic skills.

Materials and methods

Subjects

Sixty-three children with T1DM, screened by the pediatric diabetes clinics of four special care hospitals in Finland, participated in the study. Children with T1DM who had been diagnosed before five years of age and who were 9 to 10 years of age at the time of the study were eligible for inclusion. Exclusion criteria were native language other than Finnish and a diagnosed neurological disorder that affects cognitive development. The nurse or the doctor of the pediatric diabetes clinic identified children who fulfilled the criteria and contacted their parents. Seventy-nine children and their parents were asked to participate in the study. Sixteen refused to participate. Thus sixty-three (79.7 %) children with T1DM participated in the study. The children with T1DM were assigned into two groups according to whether or not they had a history of severe hypoglycemia (SH), as ascertained from their medical records. Children who had experienced severe hypoglycemia formed the SH+ group (N=37) and children who had avoided SH formed the SH- group (N=26).

The children forming the control group in the Jyväskylä Longitudinal Study of Dyslexia (n=92) were also selected for the control group of this study (for a detailed description of the control group, see Lyytinen et al. [20]). The children in this group had neither diabetes nor familial risk for dyslexia. The control children had been followed from birth in order to study their language development and the predictors and precursors of dyslexia. Originally, they were drawn from families attending maternity clinics and screened over four consecutive years.

The children in the three groups were assessed at the same age: in the spring semester of the 3rd grade or during the following summer. No differences were observed between the groups in gender, age, parents' education or IQ (Table 1). The children in the control group did not have familial risk for dyslexia, as this was an exclusion criterion for selection into this group. Group differences were therefore found in familial risk for dyslexia, with 16.2 % of the SH+ group and 23.1 % of the SH- group having familial risk for dyslexia (χ^2 (2) = 20.00, $p < .001$) as reported by the parent and defined as at least one parent and one other close relative with dyslexia. Therefore, familial risk for dyslexia was used as a covariate in the statistical analyses.[7]

Protocol

At the beginning of the cognitive assessment, the parent signed a written informed consent and the child gave a verbal assent. The mother filled in a structured questionnaire on her child's development, school history, her own and the child's father's education, and familial risk for dyslexia (parents, siblings, close relatives). The medical history of the children was obtained from the hospital medical records. The protocol was approved by the Kymenlaakso Hospital District's Ethics Committee and is in accordance with the Declaration of Helsinki. The cognitive

[7] The analyses were also made without children with familial risk for dyslexia, and the main results remained similar.

assessment lasted two hours, with a break after one hour. Before and after the assessment, the children with T1DM measured their blood glucose (BG) level. The BG level was required to be between 4 and 18 mmol / l during the assessment. All the tests were administered in a fixed order.

Cognitive measures

The cognitive measures used have been reported in detail in Hannonen et al. [13]. IQ was assessed with the subtests of Vocabulary, Comprehension, Similarities, Picture Completion, Block Design and Object Assembly of the Wechsler Intelligence Scale for Children – Third Version [38].

Verbal measures: Perception of Phonemic Length (a same-different judgment task of non-words, administered by a computer via headphones; Cognitive Workshop program, developed by the Universities of Dundee and Jyväskylä) assessed phonological processing. Non-word Repetition, a subtest from the NEPSY [17], assessed phonological processing and repetition of the phonology of non-words. Digit span forward assessed verbal short-term memory. The Rapid Automatized Naming Test (Finnish version) [1] assessed rapid serial naming. Standard procedure with the subtests of objects and letters [6] was used.

Academic skills: Reading accuracy comprised the measures of the accuracy of oral text reading, oral pseudo word text reading and single non-word reading. Reading speed was composed of the measures of the speed of oral text reading, oral pseudo-word text reading, single non-word reading, reading rapid words and Word List Reading [15]. Spelling accuracy was composed of spelling words and nonwords. Mathematics assessment comprised measures of the speed of verbal counting and measures of the accuracy of verbal counting and arithmetic.

The verbal and academic skill variables were computed using the standardized z-scores of the individual tasks (standardization was based on the mean and SD of the control group). The children whose performance was below the 10^{th} percentile of the control group's performance in reading speed, reading accuracy, spelling accuracy or mathematics were considered to have learning problems in that skill.

T1DM-related measures

Data on age at onset of T1DM; diabetic ketoacidosis (DKA; pH < 7.30) at onset of T1DM; glycemic control during the early stage of diabetes (HbA1c one year after onset of T1DM), currently (latest HbA1c measurement), and during the disease (mean HbA1c level during the disease); history of severe hypoglycemia (SH); age at first SH episode; and insulin treatment regimen at the time of the assessment were obtained from the medical records of the child. This information was recorded prospectively in the child's medical records at the visits to the clinic on a 3-monthly basis. Severe hypoglycemia was defined as seizures or a markedly lowered level of consciousness, as observed by adults, associated with measured subnormal blood glucose level or with a response to administration of glucagon or intravenous glucose. The disease-related variables of the T1DM groups are presented in Table 1.

There were no statistically significant differences in any of the disease measures (besides SH) between the SH+ and SH- groups.

Statistical analyses

Group differences (SH+, SH- and control group) in verbal skills (perception of phonemic length, non-word repetition, verbal short-term memory and rapid automatized naming) and academic skills (reading accuracy, reading speed, spelling accuracy and mathematics) were analyzed with general linear models (GLM) with gender, familial risk for dyslexia and parents' education as covariates. Pair-wise post hoc comparisons of the groups were analyzed by LSD tests. Group differences in the incidence of learning problems in academic skills were analyzed by χ^2 tests.

To study the effects of T1DM-related factors (diabetic ketoacidosis at onset of T1DM, glycemic control after the 1st year of T1DM, long-term glycemic control, recent glycemic control and history of severe hypoglycemia), GLMs were performed with one disease factor at a time as a predictor and verbal and academic skills as dependent variables. Gender, familial risk for dyslexia and parents' education were used as covariates in all GLMs. The association of the age of the first SH and verbal and academic skills were analyzed with nonparametric correlations.

Results

The SH+, SH- and control groups differed in verbal skills ($F(8, 268) = 2.40$, $p = .016$) and academic skills ($F(8, 272) = 3.61$, $p = .001$). In verbal skills, the only difference was found in the perception of phonemic length ($F(2,136) = 5.28$, $p = .006$), in which the control group outperformed both the SH+ ($p = .023$) and SH- ($p = .004$) groups. In academic skills mean differences were found in spelling accuracy ($F(2,138) = 8.12$, $p < .001$), in which SH+ ($p < .001$) and SH- ($p = .009$) performed worse than the control group, and in mathematics ($F(2,138) = 4.00$, $p = .020$), in which SH- performed worse than the control group ($p = .005$). No significant differences were found in the post hoc analyses between the SH+ and SH- groups in any of the skills. The group means and standard deviations in verbal and academic skills are presented in Table 2. Familial risk for dyslexia and parents' education were not significantly associated with any of the verbal or academic skills. Gender was significantly associated with verbal skills ($F(4, 133) = 2.86$, $p = .026$). Girls performed better than boys in non-word repetition ($F(1, 136) = 8.09$, $p = .005$) and in verbal short-term memory ($F(1, 136) = 5.24$, $p = .024$).

The incidence of spelling problems was 35.1 % in SH+, 38.5 % in SH- and 10.9 % in the control group ($\chi^2(2) = 14.77$, $p = .001$), and the incidence of mathematical problems was 18.9 % in SH+, 30.8 % in SH- and 9.8 % in the control group ($\chi^2(2) = 7.26$, $p = .027$). There were no significant group differences in the incidence of reading problems (reading speed: 8.1 % in SH+, 15.4 % in SH-, 9.9 % in the control group, and reading accuracy: 10.8 % in SH+, 19.2 % in SH- and 9.8 % in the control group).

The effects of the T1DM-related risk factors are shown in Table 3 (Verbal skills) and 4 (Academic skills). The disease factors had no significant effect on the verbal skills. HbA1c one year after diagnosis (HbA1c 1yr) was a significant predictor of academic skills ($F(4, 50) = 3.92$, $p = .008$). Further, lower HbA1c 1 yr predicted better spelling accuracy ($F(1, 53) = 8.85$, $p = .004$). Also, the mean HbA1c during the disease (HbA1c mean) had a close to significant main effect on academic skills ($p = .072$), and a significant effect on spelling accuracy ($F(1, 53) = 5.03$, $p = .029$), with lower mean HbA1c predicting better spelling skills. None of the covariates had significant effects in the analyses.

In the children with a history of SH, age at the first SH was negatively associated with performance in mathematics (Spearman's Rho = -.35, $p = .032$), indicating worse performance in mathematics in the children whose first SH episode occurred later in childhood. Age of the first SH was not associated with the performance in verbal skills, reading or spelling.

Discussion

The aim of this study was to assess the effects of diabetes-related risk factors on verbal and academic skills in children with early-onset T1DM. This study shows that early-onset T1DM can increase the risk for deficient academic skills, independently of the history of severe hypoglycemia. In most of the previous studies, the effects of these two risk factors have not been separated. The effect of early age of onset on cognition has been acknowledged earlier [10]. In this study, the children with early-onset T1DM had poorer performance than the healthy children only in a few skills - phonological perception and spelling. These skills are highly correlated both theoretically [28, 37] as well as statistically ($r = .296$, $p < .001$). In addition, the incidence of spelling difficulties in the children with early onset T1DM was more than triple the incidence in the control children indicating the clinical significance of this finding. Although most children with T1DM do not have concerns regarding academic achievement [21], poorer verbal and academic skills can have long-term effects on the school achievement and future possibilities of some children with T1DM, as also reported in previous studies [5, 25]. In this study, as also previously reported by Schoenle et al. [34], gender differences were found in the verbal skills among the children with T1DM. Boys diagnosed at a young age seem to be more vulnerable to verbal deficits than girls.

Among children with early-onset T1DM, history of severe hypoglycemia did not have an effect on verbal or academic skills. No significant differences in any of the verbal and academic skills between the children with and without a history of severe hypoglycemia were found. In mathematics, however, only the children who had avoided severe hypoglycemia were significantly poorer than the healthy control children. Similarly, Schoenle et al. [34], Patiño-Fernández et al. [27], Wysocki et al. [39], and Strudwick et al. [36] have not found effects of severe hypoglycemia on cognitive function, and in a meta-analysis [10] severe hypoglycemia had nominal to small effect on cognition. Some studies have found an association between verbal problems and severe hypoglycemia [14, 22], but it was not possible to differentiate this association from the effect of early disease onset. However, recent reports on a large follow-up study describe an association between severe hypoglycemia and lower verbal intelligence [25] and verbal skills [19], which indicates that avoiding severe hypoglycemias is warranted. In our study, with a relatively small sample size, the effect size would have needed to be large in order to yield significant group differences. Therefore, the effect of severe hypoglycemia was not detected; however, smaller effects on cognition cannot be ruled out. Besides, the children in this study were young, 9 to 10 years old, and the effects of severe hypoglycemia may become apparent at an older age [3].

Poor glycemic control after the first year of disease was the only disease-related risk factor, which seemed to have an effect on spelling. This indicates the importance of good metabolic control on cognitive development. A negative association between high plasma glucose values, especially prolonged hyperglycemia, and verbal [27, 29, 34] and academic [21, 26] skills has been reported earlier in some, but not all studies

[19, 22]. The timing of poor glycemic control can influence the results. In this study, the effect of recent metabolic control was not detected. According to Ryan [33], hyperglycemia in the early years of development can initiate a chain of adverse functional and structural changes in the brain. This study provides some support for Ryan's hypothesis. Other early metabolic complications, e.g. ketoacidosis at the disease onset or early severe hypoglycemia did not influence cognitive skills. The association between severe hypoglycemia at a later age and poorer performance in mathematics supports the hypothesis that severe hypoglycemia can disturb currently developing skills. DKA has been studied very little in association of cognitive skills, but recently an association with cognitive and memory problems have been reported [11, 35]. The effect of DKA on cognitive development warrants further research.

Both early-onset T1DM and extreme plasma glucose values can adversely affect brain structure and function. Ferguson et al [8] reported larger lateral ventricles in people with early-onset T1DM than in people with later onset of diabetes. Perantie et al. [30] found diffuse changes in regional brain volumes in youth with T1DM differentially associated with either severe hypoglycemia or hyperglycemia. Northam et al. [25] also described several changes in the brain metabolism and structure associated with T1DM, severe hypoglycemia and hyperglycemia, and the frontal and temporal lobes seem to be especially vulnerable [25, 30]. These brain areas are also involved in verbal processes. In children with early-onset T1DM, disturbances in the brain metabolism owing to frequent events of hyper- and hypoglycemia cannot be avoided. Therefore, it seems likely that the interactive effects of young age at diagnosis of T1DM and the continuous metabolic changes occurring during the rapid period of brain development influence brain function.

The effects of diabetes-related factors on cognition might not be comprehensively measured by the current methodological solutions, because it is methodologically difficult to separate individual metabolic events from each other. Therefore, the interactive effects of hypo- and hyperglycemia and their timing in the developing brain need further research. Also fluctuations in plasma glucose cause methodological difficulties in measuring the effects of metabolic complications. Moreover, fluctuating blood glucose values may also cause acute disruptions in learning at school [12], which in turn may affect the development of academic skills.

Development of verbal and academic skills has a strong genetic involvement [20]. Because children with familial risk for dyslexia were present only in the T1DM groups genetic risk for dyslexia could have influenced the results. However, when the analyses were conducted without the children with familial risk for dyslexia, the significance of the group differences remained the same except in mathematics, where the significance of the group differences changed to .053. Therefore, the results could not be attributed to familial but rather to the unique effects of early onset of the disease.

Since this study involved only children with T1DM diagnosed under the age of five, these findings cannot be generalized to children with later onset T1DM. However, with this design, it was possible to separate the effects of early age of onset and metabolic complications, which has been problematic in some other studies. Metabolic complications in children with later onset T1DM may nevertheless cause difficulties in cognitive development [10].

In conclusion, early-onset T1DM affects the development of phonological processing, spelling and mathematics in the early school years. Poor metabolic control in the first year of disease has an effect on spelling accuracy. Episodes of severe hypoglycemia do not seem to influence academic skills directly; however, good metabolic balance should remain a target.

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

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Table1. Demographic and diabetes-related characteristics across the severe hypoglycemia group (SH+), no severe hypoglycemia group (SH-) and control group.

	T1DM groups		control group
	SH+ group	SH- group	
n	37	26	92
Female / Male, n	21/16	10/16	40/52
Age, mean (SD)	9.89 (0.30)	9.84 (0.33)	9.79 (0.28)
Mother's education,[a] mean (SD)	4.36 (1.38)	4.24 (1.20)	4.66 (1.39)
Father's education,[a] mean (SD)	3.80 (1.32)	3.40 (1.56)	3.99 (1.34)
Verbal IQ, mean (SD)	99.62 (14.07)	98.31 (19.88)	102.03 (14.69)
Performance IQ, mean (SD)	100.65 (20.24)	96.85 (19.10)	101.56 (15.67)
Full Scale IQ, mean (SD)	99.62 (14.64)	97.42 (18.18)	101.30 (12.38)
Age at onset of T1DM, mean (SD)	2.72 (1.27)	3.24 (1.21)	-
Ketoacidosis at onset (%)	29.7	29.2	-
HbA1c after 1 yr of illness (%)	8.01 (0.94)	8.00 (0.82)	-
Mean HbA1c (%)	8.21 (0.67)	8.21 (0.64)	-
Latest HbA1c (%)	8.31 (0.80)	8.23 (0.63)	-
Age at the first severe hypoglycemia, mean (SD)	4.67 (2.19)	-	-
Insulin treatment regimen (%):			
Two daily injections	2.7	0.0	-
Three daily injections	16.2	23.1	-
Basal-bolus treatment	64.9	57.7	-
Insulin pump	16.2	19.2	-

[a] Parents' education was classified using a seven-point scale constructed by combining general education, secondary vocational education, and tertiary education.

Table 2. Academic and verbal skills in the SH+ group, SH- group and control group.

	SH+ group	SH- group	control group				
	mean (SD) n=35[a]	mean (SD) n=25[a]	mean (SD) n=83[a]	F	p-value	η^2_p	Significant differences
Verbal skills				2.40	.016	.07	
Perception of phonemic length	-0.59 (1.27)	-0.87 (1.45)	-0.00 (1.01)	5.28	.006	.07	SH+ < C* SH- < C**
Non-word repetition	-0.03 (0.88)	0.16 (1.57)	0.06 (0.98)	0.64	.531	.01	
Verbal short-term memory	-0.08 (1.18)	-0.51 (1.20)	0.07 (0.96)	2.26	.108	.03	
Rapid automatized naming	-0.04 (0.61)	-0.04 (0.90)	0.05 (0.79)	0.11	.895	.00	
Academic Skills				3.61	.001	.10	
Reading accuracy	0.09 (0.68)	-0.05 (0.74)	0.08 (0.61)	0.27	.761	.00	
Reading speed	-0.04 (0.61)	0.01 (0.76)	0.06 (0.71)	0.26	.773	.00	
Spelling accuracy	-0.67 (0.95)	-0.59 (1.06)	0.00 (0.83)	8.12	< .001	.11	SH+ < C*** SH- < C**
Mathematics	-0.20 (0.49)	-0.49 (0.59)	-0.06 (0.66)	4.00	.020	.06	SH- < C**

[a] group sizes were reduced due to missing data in some children.

η^2_p = Effect Size

* p < .05, ** p < .01, *** p < .001

Table 3. The effects of diabetes-related factors on verbal skills.

	Verbal Skills, All			Perception of phonemic length			Non-word repetition			Verbal short-term memory			Rapid automatized naming		
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
DKA	0.87	.488	.07	0.07	.789	.00	0.31	.583	.01	0.78	.383	.02	2.41	.126	.04
HbA1c 1yr	2.24	.078	.15	2.85	.097	.05	1.44	.235	.03	0.00	.954	.00	2.93	.093	.05
mean HbA1c	2.32	.069	.16	3.85	.055	.07	2.26	.139	.04	0.34	.565	.01	1.43	.238	.03
latest HbA1c	1.06	.386	.08	1.74	.193	.03	0.02	.895	.00	0.58	.451	.01	1.26	.267	.02
SH	1.28	.292	.09	0.60	.441	.01	1.09	.300	.02	0.91	.345	.02	0.12	.726	.00

DKA = diabetic ketoacidosis, HbA1c 1yr = HbA1c 1 year after diagnosis, mean HbA1c = HbA1c mean during the disease, latest HbA1c = the most recent HbA1c, SH = history of severe hypoglycemia,

η_p^2 = Effect Size

Table 4. The effects of diabetes-related factors on academic skills.

	Academic Skills, All			Reading Accuracy			Reading Speed			Spelling Accuracy			Mathematics		
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
DKA	0.93	.455	.07	0.47	.497	.01	2.59	.113	.05	0.19	.664	.00	0.70	.407	.01
HbA1c 1yr	3.92	.008**	.24	1.58	.214	.03	2.88	.095	.05	8.85	.004**	.14	0.01	.915	.00
mean HbA1c	2.29	.072	.16	0.80	.376	.02	1.59	.214	.03	5.03	.029*	.09	0.06	.806	.00
latest HbA1c	1.44	.236	.10	0.27	.607	.01	1.07	.306	.02	2.07	.156	.04	0.54	.464	.01
SH	1.92	.121	.13	0.24	.628	.00	0.30	.584	.01	0.24	.628	.00	3.34	.073	.06

DKA = diabetic ketoacidosis, HbA1c 1yr = HbA1c 1 year after diagnosis, mean HbA1c = HbA1c mean during the disease, latest HbA1c = the most recent HbA1c, SH = history of severe hypoglycemia,

η_p^2 = Effect Size,

* $p < .05$, ** $p < .01$

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