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Down syndrome

Growth and endocrine impact

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Abstract
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Down syndrome (DS) is associated with psychomotor retardation, short stature and endocrine dysfunction.

Statural growth is a well-known indicator of health. The growth in DS differs markedly from that of other children and there is a 20 cm reduction of final height as compared to target height. We developed growth charts specific for Swedish children with DS, in order to facilitate early diagnosis of concomitant diseases that influence growth. The growth charts are available for paediatricians and child health care professionals in Sweden.

The mechanism underlying the impaired growth in DS is unknown. Height is influenced by parental factors, energy intake, hormone balance and general health. In DS, genetic factors deriving from the extra chromosome 21 further affect growth. Children with DS seem to have reasonable levels of growth hormone (GH), even though GH treatment for limited periods of time improves growth velocity. Within the present project, the subjects of a previous study on early GH therapy in DS were followed up regarding late effects. We found a larger adult head circumference and better psychomotor abilities in the previously treated subjects despite a lack of effect on final height.

In adult life, GH has effects on psychological well-being and metabolism. The clinical features in adults with DS might indicate impaired GH secretion. Ten young adults with DS were studied and compared with ten healthy controls. The GH secretion in the DS subjects did not differ from that in the controls. The fat body mass percentage was increased in DS, in line with the high prevalence of overweight/obesity. The finding of an increased HOMA index as well as a high relative rate of hepatic glucose production in DS indicates reduced insulin sensitivity both peripherally and in the liver.

Thyroid dysfunction is common in DS. There is a 30-fold increase in congenital hypothyroidism, and acquired hypothyroidism has been reported to be present in up to 50% of adults with DS. We collected neonatal screening results and hospital records for the first ten years of life of 68 children with DS. The mean TSH concentration was increased neonatally, indicating marginal hypothyroidism early in life in DS. However, the neonatal TSH level did not predict development of manifest hypothyroidism later in life.

Keywords: Down syndrome, growth, growth charts, body proportions, growth hormone, thyroid function, metabolism, body composition, cognition, motor development, Downs syndrom, tillväxt, tillväxtkurvor, kroppsproportioner, tillväxthormon, sköldkörtelfunktion, metabolism, kroppssammansättning, kognitiv förmåga, motorisk utveckling

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To Alvi, Lisen and Malla

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I **Myrelid**, **Å**., Gustafsson, J., Ollars, B., Annerén, G. (2002) Growth charts for Down's syndrome from birth to 18 years of age.
Archives of Disease in Childhood 87(2): 97-103

II **Myrelid**, **Å**., Jonsson, B., Guthenberg, C., von Döbeln, U., Annerén, G., Gustafsson, J. (2009) Increased neonatal thyrotropin in Down syndrome.
Acta Paediatrica 98(6): 1010-1013

III **Myrelid**, **Å**., Bergman, S., Elfvik Strömberg, M., Jonsson, B., Nyberg, F., Gustafsson, J., Annerén, G. (2009) Late effects of early growth hormone treatment in Down syndrome.
Resubmitted after revision

IV **Myrelid**, **Å**., Frisk, P., Stridsberg, M., Annerén, G., Gustafsson, J. (2009) Normal growth hormone secretion in young adults with Down syndrome.
Submitted

Contents

Abbreviations

AUC	area under the curve
BMD	bone mineral density
BMI	body mass index
BOT	Bruininks-Oseretsky test of motor proficiency
CH	congenital hypothyroidism
CNS	central nervous system
DEXA	dual-energy X-ray absorptiometry
DS	Down syndrome
GCMS	gas chromatography-mass spectrometry
GH	growth hormone
GHD	growth hormone deficiency
GHRH	growth hormone releasing hormone
HDL	high-density lipoprotein
HOMA	homeostasis model assessment
ICP	infancy-childhood-puberty
IGFBP	insulin-like growth factor binding protein
IGF-I	insulin-like growth factor-I
IQ	intelligence quotient
LDL	low-density lipoprotein
MA	mental age
PKU	phenylketonuria
PWS	Prader-Willi syndrome
SD	standard deviation
SDS	standard deviation score
SEM	standard error of the mean
SGA	small for gestational age
T3	triiodothyronine
T4	thyroxine
TH	target height
TRH	thyrotropin-releasing hormone
TS	Turner syndrome
TSH	thyroid stimulating hormone (thyrotropin)
WHO	World Health Organization
WISC	Wechsler intelligence scale for children

Introduction

Down syndrome

Down syndrome (DS) is named after John Langdon Down, the British physician who described the characteristics of individuals with the syndrome in 1866. The mechanism underlying DS was explained in 1959 when Jerome Lejeune demonstrated that people with the syndrome had an extra chromosome 21, i.e. a total of 47 chromosomes.

Down syndrome is diagnosed by chromosome analysis, but Hall's criteria may be applied while waiting for the results. The Swedish paediatrician Bertil Hall described twenty signs common in DS in 1965. With twelve or more stigmata present, the diagnosis is considered clinically certain, while with fewer than four stigmata the diagnosis is unlikely.

Down syndrome is a common chromosomal disorder,[1] with an incidence of about 1/800 live births in Sweden.[2] It is associated with mental retardation, short stature, congenital malformations, especially of the heart, and metabolic and endocrine dysfunction.[3]

Growth and growth charts

Growth is a well known indicator of health during childhood, and growth charts are important tools for the paediatrician.

In 1989 the infancy-childhood-puberty (ICP) growth model was introduced.[4] This model describes human growth from the latter half of intrauterine life to maturity, with a division into three components – the infancy, childhood and puberty phases. Each individual component reflects a different biological, and to some degree hormonal, phase of the human growth process. Growth in infancy is to a great extent dependent on nutrition. During the childhood phase growth hormone (GH) becomes important and during the pubertal growth spurt the sex steroids stimulate an increased secretion of GH.

The ICP model offers an efficient instrument to detect and understand growth failure.

Growth in Down syndrome

Statural growth is an excellent marker of health status on both the individual and the population level. This is particularly evident in a disorder such as DS, which is associated with dysfunction of several organ systems.[5,6] Short stature is a characteristic feature of DS,[7] but there is a pronounced individual variation. Final height is influenced by both the extra chromosome 21 and inherited parental factors. In addition, concomitant diseases may influence growth.

The growth retardation of children with DS commences prenatally.[8] Thus, a newborn child with DS has a birth length between -0.5 and -1.0 standard deviation scores (SDS).[9] After birth, the growth velocity is most reduced between 6 months and 3 years of age.[7,10]

Puberty in DS generally occurs somewhat early and is associated with an impaired growth spurt.[7,11] The mean peak height velocity is significantly lower in persons with DS than in controls.[12] The blunted pubertal growth spurt may be due to low levels of sex hormones, as some degree of gonadal insufficiency has been described in DS, particularly in males. Men with DS have small testes and are sterile,[11] although there are some reported cases of male fertility.[13] Women with DS are commonly fertile and their mean menarcheal age corresponds closely to that of their mothers.[11]

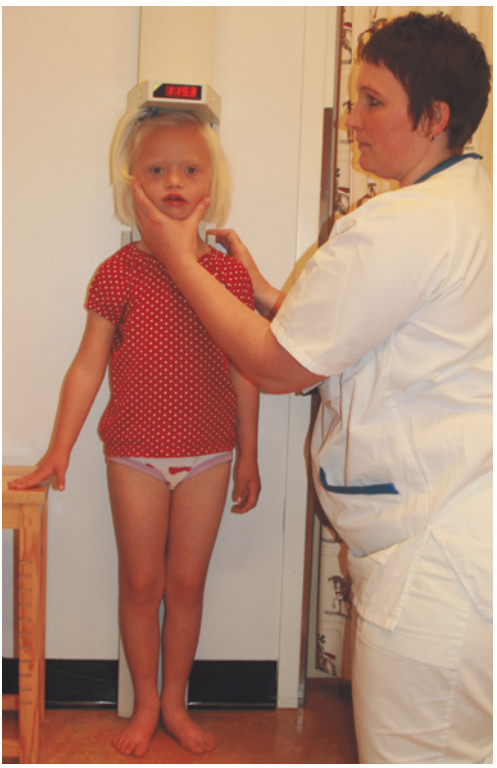

Figure 1. The body height of a young girl is examined by a nurse. Height is measured with a calibrated stadiometer, with the patient barefooted. Published with consent of the parents.

Final height in individuals with DS is approximately 20 cm lower than expected with regard to parental heights.[11] Since growth and final height differ markedly between children with DS and healthy children, standard growth charts should not be used for children with DS. If the growth of a child with DS is plotted on a standard growth chart, the effect of an additional disease, such as hypothyroidism or coeliac disease, on statural growth may be overlooked.

Syndrome-specific growth charts

Specific growth charts have been developed for several different disorders, e.g. Down syndrome,[7,14-17] Turner syndrome (TS),[18] Noonan syndrome[19] and Prader-Willi syndrome (PWS).[20]

Complicating disorders, such as coeliac disease, hypothyroidism and growth hormone deficiency (GHD), may aggravate existing growth retardation. Thus, special growth charts for children with specific disorders are important tools in the medical-follow up as well as in the monitoring of growth-promoting treatments.

Previously published growth charts for DS are based on American,[7,15] Sicilian,[14] Dutch[16] and British/Irish[17] populations. The American DS growth charts have been frequently used all over the world. It has previously been shown that the mean final height of Swedish boys with DS exceeds that of American boys with DS[11] and the difference in final height between the American DS boys and girls is reported to be low.[7] Against this background Swedish DS growth charts would facilitate the medical care of Swedish children with Down syndrome.

Growth hormone and insulin-like growth factor I

Growth hormone is produced in the anterior pituitary and has effects on several organs. Synthesis of GH is stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin, both of which are hypothalamic hormones. The secretion of GH is pulsatile and repeated measurements, providing a GH profile, can be used to evaluate the ability to produce GH. Growth hormone influences skeletal growth, by stimulating synthesis of insulin-like growth factor I (IGF-I), starting in the second half of the first year.

Insulin-like growth factor I is produced in several organs, but the major part of circulating IGF-I is produced in the liver. Since IGF-I is formed in target tissues it probably also exerts auto-/paracrine effects.

Both GH and IGF-I have metabolic effects. Direct effects of GH on metabolism include stimulation of lipolysis and glucose production.

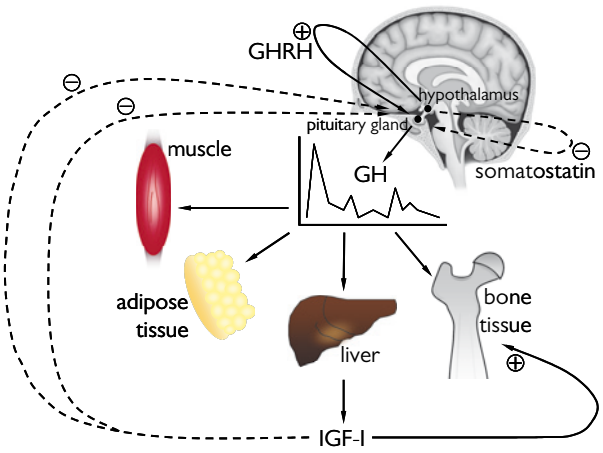

Figure 2. Illustration of the GH/IGF-I axis. The pulsatile secretion of GH is stimulated by GHRH and inhibited by somatostatin. GH affects many organs, and only the most important target tissues are shown in the figure. IGF-I is produced locally in many organs, but the liver produces the major part of circulating IGF-I.

Growth hormone and the brain

Growth hormone as well as IGFs are important brain growth promoting factors with local actions in the central nervous system (CNS).[21] Improved maturation, differentiation and growth of the CNS have been observed as secondary effects of an increase in neurotrophic factors resulting from stimulation by GH/IGF-I.[22]

It has been shown that GH reaches the cerebrospinal fluid, and specific binding sites of GH have been localised in numerous areas in the brain.[21] Hence, the reported association between intelligence and head growth during childhood[23] might be partly explained by GH.

Beneficial effects on cognition, energy, mood and behaviour have frequently been described in studies of GH therapy in children with PWS,[24,25] TS,[26] and GHD[26,27] as well as in children born small for gestational age (SGA).[28] When treated with GH, children born SGA have shown improvement in the intelligence quotient (IQ), and the IQ score correlates well with head growth.[28] Furthermore, it has been suggested that GH therapy might prevent retardation of mental development in PWS.[25]

Appetite and sleep are other brain functions associated with GH.[21,29]

Growth hormone in adolescence and adulthood

A marked increase in GH secretion is normally seen during puberty. Thereafter, the spontaneous GH secretion, and consequently also the production of IGF-I, progressively decrease during the life-span. Nevertheless, the GH/IGF-I axis may play a role in the level of cognitive functioning in adult life,[30] and clinical experience leaves little doubt that GH has effects on behavioural functions related to quality of life.[21] GH therapy in adult GHD

patients results in improved psychological well-being, possibly as a result of interaction with the endogenous opioid system in limbic structures.[31]

Growth hormone also influences metabolism in adult life. In adult patients with GHD there are alterations in body composition leading to overweight, increased visceral fat and decreased bone mineral density (BMD).[32,33] The deposition of intra-abdominal fat is associated with increased cardiovascular morbidity/mortality.[34]

Decreased secretion of GH may also be caused by several non-pituitary disorders, such as hypothyroidism,[35,36] coeliac disease[37] and obesity.[38,39] There is a negative association between GH secretion and body mass index (BMI), which may be explained by changes in neuroendocrine control of the somatotrophic axis as well as by metabolic alterations.[40]

Adults with GHD and adults with DS have several features in common, i.e. overweight, decreased BMD, lack of initiative, an increased risk of depression, and loss of physical capacity.

Growth hormone in Down syndrome

The mechanism responsible for the short stature in DS is as yet unclear. Much interest has been paid to GH and IGF-I, as the pronounced growth retardation in DS coincides with the time when these hormones become essential for growth. Suboptimal production of GH[41] and a selective deficiency of IGF-I[10,42] have been demonstrated in children with DS, but there is no clear evidence of a general GH deficiency.[43]

Reduced GH secretion may be caused by alterations in neural control of the somatotrophs in the hypothalamus.[44] Hypocellularity has been observed in the hypothalamic areas involved in this control in DS subjects.[45]

There are some reports on GH treatment of children with DS.[43,46,47] It has been found that GH therapy normalises the growth velocity, but "catch-down" growth was noted when the treatment was discontinued.[43,46]

Little information is available on the question of whether adults with DS have a normal capacity to produce GH.

Thyroid hormones and their function

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are essential for normal development, differentiation, growth and metabolism from early intrauterine life. Synthesis of thyroid hormones is stimulated by pituitary thyrotropin (thyroid stimulating hormone, TSH), which is formed through stimulation by thyrotropin releasing hormone (TRH) produced in the hypothalamus, and is inhibited by negative feedback of T4 and T3.

Thyroid hormones have several different actions, depending on the specific thyroid receptor expressed in the tissue. The highest concentration of thyroid receptors is found in developing neurons in the cortex and cerebellum of the foetal and neonatal brain.[48] Their actions also differ over time; for example thyroid hormones are inactive in adipose tissue and in the liver, heart, muscles and bones during foetal life, but become active in these tissues neonatally.[48]

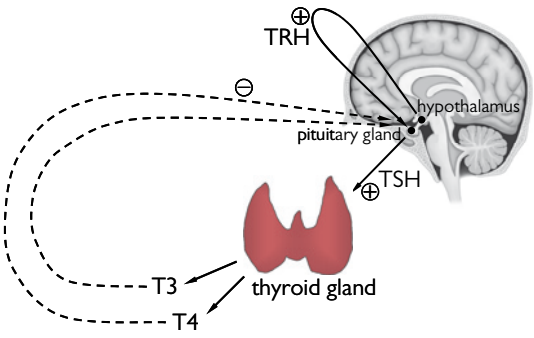

Figure 3. Illustration of the thyroid hormone axis. TSH is produced in the anterior part of the pituitary gland through stimulation by hypothalamic TRH. Circulating TSH reaches the thyroid gland, where it stimulates release of T3 and T4. The system is balanced through negative feedback of T3 and T4.

Importance of the thyroid during early life

In the first trimester foetal brain development is dependent on the passage of maternally circulating thyroid hormones through the placenta, but at 16-20 weeks of gestation the foetus is capable of producing thyroid hormones, especially T4.[49]

Several changes associated with the function of the thyroid gland occur at birth. The most dramatic change is a large increase in the infant's circulating level of TSH, which takes place during the first 30 min after birth. This rise in TSH stimulates the thyroid gland and within 24 hours there is a 50% increase in the level of T4 and a 3- to 4-fold increase in the level of T3 in the serum.[50,51] In addition, the increased TSH stimulates lipolysis of depot fat, a process which is important for the neonatal energy supply.[52] After the first days of life, there is a gradual decline in the levels of T4, T3 and TSH.

The immediate postnatal changes in the concentrations of TSH, T3 and T4 are also seen in preterm infants, but not to the same extent as in those born full term.[53] In neonates born small for gestational age there is a less marked increase in free T4 and free T3 and a moderate increase in TSH, especially in those who show a blunted "catch-up" growth.[54-56] Further, a significant reduction in the expression of thyroid hormone receptors in the CNS in such neonates has been reported, and possibly influences their psychomotor development.[57]

Hypothyroidism during childhood

Hypothyroidism in childhood can be congenital or acquired. Congenital hypothyroidism (CH) may cause irreversible CNS damage and developmental delay if untreated. The Swedish neonatal screening of CH started in 1980. Neonatal screening makes early diagnosis and replacement therapy possible and has diminished the number of persons suffering from mental retardation due to CH.

Symptoms of acquired hypothyroidism during childhood may be easily overlooked. They include growth retardation, immature body proportions, dry skin, dry hair texture, constipation, delay in dental and bone maturation, motor development delay and delayed puberty. The natural course of hypothyroidism is often so insidious that neither the child nor the parents are aware of the physical changes that have occurred.

Acquired thyroid disease may be caused by autoimmunity, and is then characterised by the presence of autoantibodies to thyroid peroxidase, thyroglobulin and/or the TSH receptor.

Hypothyroidism in Down syndrome

Hypothyroidism is common in DS.[58,59] Dysfunction of the thyroid gland may have several causes. Regarding congenital hypothyroidism, the incidence is markedly increased among newborns with DS, 28 times higher than among other newborn infants.[60] The risk of developing hypothyroidism increases with age, and in DS one may see increased levels of TSH, indicating possible thyroid dysfunction, at a young age (<3 years).[61]

There are several different mechanisms underlying development of hypothyroidism in children with DS. The growth of the thyroid gland may be disturbed, resulting in an insufficient gland size as the child grows older.[62] A possible lack of sensitivity to thyroid hormones has also been discussed.[63]

In older children and young adults with DS, development of autoimmune thyroid disorders is common.[59,61,64]

Psychomotor development in Down syndrome

Cognitive ability

Mental retardation is characterised by impaired cognitive functioning and deficits of adaptive behaviour (communication, self-help skills, social skills etc.) with onset before the age of 18 years. IQ testing goes back to 1901, when the very first test instrument was introduced by Binet and Simon.[65] At first the focus was almost entirely on cognition, but now many of the

instruments include components relating to mental functioning as well as to the individuals' functional skills in their environment.

Mental retardation is a cardinal sign in DS, but the degree shows large individual variation. The range in development of a specific skill is much greater in children with DS than in other children. The range and variability increase with age in respect to developmental milestones. Furthermore, the gradual decline in IQ score in any patient with DS, which is especially evident between the ages of 6 months and 3 years, should be regarded as a physiological phenomenon reflecting the gradual increase in the verbal and abstract contents of test materials at increasing ages.

The delay in mental development in DS is evident as early as in infancy as slow visual fixation,[66] possibly due to an impaired ability to understand and process the visual information received. Restriction in areas of verbal communication is also common during the first years of life.[67] There are several different programmes of early intervention in the care of children with DS, the most well known and widely used in Sweden being the "Karlstad model" by Professor Iréne Johansson.[68]

IQs of between 35 and 65 are common in DS,[67,69] and the mean IQ declines with increasing age.[70] Assessment of the intellectual ability in DS is mainly of interest in evaluation of interventions that may influence cognitive function. In everyday life the IQ score makes little difference, but the ability to communicate and interact socially is far more important.

Mental age (MA) is the chronological age at which a given level of performance is average or typical.[71] It may be used as a complementary parameter for describing the cognitive ability in order to facilitate understanding of intelligence test results in the general population. However, MA is a controversial concept in psychometrics, and one should not attach too much weight to absolute MAs.[71,72]

Motor proficiency

Motor development is a cerebellar process in which practice and experience result in acquisition of skills to execute specific movements. Neuronal proliferation and migration in the cerebellum are long-lasting processes. It is not until the end of the first year of life that the different layers of the cerebellum reach the structure and complexity similar to that of an adult cerebellum.[73] The size of the cerebellum is reduced in subjects with DS as a result of growth retardation and delayed maturation.[74] Further, there are reports on reduced proliferation of neural stem cells and delayed formation of synapses in DS.[75,76]

Locomotion is adjusted by the cerebellum at all times through modification of the planned movement with up-to-date information from the sensory systems; that is, the cerebellum provides a system that regulates the motor output by comparing the intention and the execution of any movement.[77]

Motor proficiency is based on performance in functional activities involving postural control, locomotion, and object manipulation.[78-80] Motor skill is commonly classified on the basis of the muscle groups and limbs involved; that is gross motor skill and fine motor skills are recognised as movements that involve large muscles and fine muscles, respectively.[78-80]

Mental retardation is associated with a reduction of strength and an earlier onset of weariness during physical activity.[81] Moreover, in assessment of motor performance, children with DS score lower than other children matched for sex and mental age.[82]

Major milestones, such as sitting, standing and grasping, are generally delayed in children with DS.[83] The altered development of motor functions may be due to the muscular hypotonia, ligamental laxity, poor balance and postural control that are commonly seen in the DS population.[84] Furthermore, individuals with DS require more time to learn movements as the movement complexity increases.[84]

The adolescent and adult with DS

Medical complications such as hypothyroidism, coeliac disease, obesity and depression are common in individuals with DS and the prevalence of these conditions increases with age.[85] DS is also associated with precocious ageing, including changes in the hair and skin, early menopause, osteoporosis, and early onset of cataract, as well as presbycusis and a markedly increased risk of Alzheimer's disease.[86] On the other hand, it has been reported that the risk of cancer and of cardiovascular and cerebrovascular disease is lower in the adult with DS than in the general population.[86]

The life expectancy is reduced compared to that in the general population, although it has improved markedly in the last decades. In the 1940s the median age at death was 12 years,[87] in 1983 it was 25 years, and in recent years the life expectancy has risen to 60 years.[88]

Body composition and obesity

The World Health Organization (WHO) has defined overweight as a BMI between 25.00 and 29.99 kg/m^2, whereas obesity is defined as BMI >30 kg/m^2.[89] BMIs between 18.50 and 24.99 kg/m^2 are considered as normal.[89]

Obesity is a common concern in the DS population,[90-95] although probably not to the same extent in Sweden as in other countries, where there are reports of prevalence rates as high as 70% and 95% in men and women, respectively.[88,90,91,95] The mechanisms behind obesity in DS are unknown, but there are several possibly contributory factors, e.g. endocrine alterations, reduced physical activity, hypotonia, and poor eating behaviour.[94]

Unfavourable changes in body composition, i.e. increased visceral fat and a decreased lean body mass, have been shown in obese subjects.[39] The body composition in DS is reported to be similar to that observed in obese subjects with the same weight to height ratio.[96] Obesity and regional fat depositions are known risk factors for development of cardiovascular disease in the general population. However, the importance of such a body composition does not seem to be so great in DS. In fact, Down syndrome has once been described as the atheroma-free syndrome,[97] and the incidence of cardiovascular manifestations is reported to be low.[98,99]

Bone mass density

Bone formation proceeds throughout childhood and adolescence, ending in early adulthood, when the peak bone mass is attained. Osteoporosis and osteopenia are characterised by a low bone mass density and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures.[100]

Measurement of bone mineral density is recognised as the most accurate and effective method of assessing the risk of osteoporotic fractures. The results of BMD measurements are commonly expressed as absolute values as well as z-scores. The z-score is a measure of standard deviation (SD) from the mean, corrected for age and gender, derived from a control population. According to WHO, osteopenia is defined as a BMD between -1 and -2.5 SD and osteoporosis as a BMD below -2.5 SD.[100]

Although there are several reports of reduced BMD in the DS population, there appears to be no increased occurrence of fractures.[101] However, there are other known skeletal alterations in DS, such as delayed ossification of secondary centres, scoliosis, and underdeveloped bones in the upper spine and neck, causing atlanto-axial instability.[102]

Energy metabolism – glucose production and lipolysis

The liver plays a central role in human energy metabolism. The ubiquitous source of energy for every living cell, glucose, is stored in and released by the liver through hormonal control. Further, glucose is synthesised from glycerol, lactate and alanine in the liver and to a small extent in the kidneys. The glucose production fluctuates to match the needs of our organ systems throughout the day.

Lipolysis is the metabolic process whereby lipids in depot fat are hydrolysed into free fatty acids and glycerol. Thus, the production of glycerol reflects lipolysis. The glycerol is released into the blood and then absorbed by the liver or kidney, where it may be used as a substrate for glucose.

Stable isotope technique and gas chromatography-mass spectrometry

The most frequently used method for measuring energy substrate production (i.e. lipolysis and production of glucose) is the isotope dilution technique using a tracer. The tracers of choice are compounds labelled with stable (non-radioactive) isotopes. Isotopes of an element have different atomic weights, due to differences in the number of neutrons in the nucleus.

The rate of production of energy substrates can be calculated from isotopic enrichments of glucose and glycerol obtained during constant rate infusion of trace amounts of the corresponding isotope labelled compounds.[103] The production rates of glucose and glycerol are calculated as follows:

(production rate = i * 100/IR)

where i is the infusion rate of the tracer and IR is the isotopic ratio of the tracer in plasma (given as labelled/unlabelled substrate in per cent).[103]

Ethical approval

The Regional Ethical Review Board of Uppsala has approved these studies.

Aims of the studies

The aims of the studies were as follows:

to create growth charts specific for Swedish children with Down syndrome from birth to 18 years of age and to compare these with the DS growth charts of Cronk et al[7] and the Swedish standard growth charts of Karlberg et al.[104] (Study I)

to determine whether newborn children with Down syndrome showed increased TSH concentrations at neonatal metabolic screening compared with other newborn infants. (Study II)

to investigate whether an increased TSH concentration at neonatal screening in children with Down syndrome could predict thyroid disease during the first ten years of childhood. (Study II)

to investigate late effects of early growth hormone treatment on growth and psychomotor development in Down syndrome. (Study III)

to determine whether GH secretion was impaired in young adults with Down syndrome. (Study IV)

to study the body composition in young adults with Down syndrome. (Study IV)

to estimate insulin sensitivity and rates of glucose production and lipolysis in young adults with Down syndrome. (Study IV)

Material and methods

Study I

Patients

The study was based on data from 4 832 examinations of 354 (151 F) children and young adolescents with DS born in 1970-97 (Table 1). Of these, data for 203 individuals (83 F) with DS were found in hospital records of four paediatric units in Sweden (Uppsala University Children's Hospital, Danderyd Central Hospital, Eskilstuna Central Hospital and the Halmstad County Hospital). Data of the remaining 151 (68 F) children and young adolescents were obtained through an appeal in "FUB Kontakt", a journal for parents of mentally handicapped children.

Ten of the 354 children were excluded because of earlier treatment with growth hormone within a study. The remaining 344 children were included irrespective of the presence or absence of complicating diseases such as congenital heart defect and hypothyroidism.

The great majority of the children were of Caucasian origin and born in Sweden.

Table 1. *The numbers of male and female children with DS and the numbers of observations on which the growth charts are based, distributed between two groups: group 1 consisting of the children from the four paediatric units, and group 2 comprising the children recruited through the appeal in the journal "FUB Kontakt".*

	group 1	group 2	total
Males			
Number of children	120	83	203
Number of observations	1 363	540	1 903
Females			
Number of children	83	68	151
Number of observations	956	571	1 527

Study design

The data were sorted according to gender and divided into 44 age groups. The first two years of life were split into one-month intervals, the follow-

ing year into three-month intervals, and from the age of three one-year intervals were used. Each child contributed with a single set of data per age group. If more than one observation of a child was available within an age group, the first observation recorded was used.

The growth charts cover the period from birth to 18 years of age, except those for head circumference, which cover the first four years of life.

Data for weight and BMI were transformed into logarithms prior to the statistical analysis in order to obtain normal distributions. Our growth charts are based on means and standard deviations, using the weighted regression fitness system distributed by Jandel. The software used was Microsoft Excel 97 SR-1 (Microsoft Corporation®, Redmond, WA, USA) and SigmaPlot, Scientific Graph System, version 3 for Windows (Jandel Scientific Software®, San Rafael, CA, USA).

The final version of the growth charts that are used within the Swedish health system were produced by PC PAL AB (Stockholm, Sweden).

Study II

Patients

Thyrotropin levels obtained at neonatal screening of 73 children (34 F) with DS born in 1986-1996 and who on some occasion during childhood had received care at Uppsala University Children's Hospital were analysed retrospectively.

Five children were excluded from the study, two children (1 F) as they were not born in Sweden and three (2 F) because the results of their TSH analysis could not be retrieved from the archives of the PKU laboratory.

The remaining 68 children were followed up by means of their hospital records regarding the occurrence of thyroid disease. Five children (4 F) died before reaching the age of ten years (age range at death 1-6 years). None of the deceased children had developed hypothyroidism. One child (female) emigrated before the age of ten years.

Hospital records covering at least the first ten years of life were available for all the remaining children, giving a study group of 62 subjects with DS (26 F) with complete data.

Study design

Data from analysis of dried filter paper blood were obtained from the PKU laboratory at the Centre for Inherited Metabolic Diseases, Karolinska University Hospital, Huddinge, Sweden. The laboratory performs all neonatal metabolic screening in Sweden and analyses approximately 500 samples daily in sets of up to 251.

A TSH value of 0.01 mU/L was used when the obtained level was below the limit of detection, both for infants with DS and control subjects. Mean and standard deviation values for TSH were calculated for each set (median number of samples per set = 234, range 78-251) in which a sample from a DS child was analysed. These values were used as controls. No information regarding the gender of the control subjects was available. Standard deviation scores were calculated for each DS patient as:

$(TSH_{observed} - TSH_{mean}$ for controls in set)/SD of TSH for controls

Descriptive central statistics are given as means and medians, and dispersion is given as SDs and ranges. As the data did not have a normal distribution, non-parametric statistics of the Wilcoxon type were used for analyses. Four-field tables were tested with Fisher's exact test. P values of less than 0.05 were considered statistically significant. Pearson correlation was used when analysing data from hospital records and linking these data to the neonatal screening results.

Study III

Patients

Fifteen adolescents (3 F) with DS, treated with daily injections of GH in early childhood (at approximately 7 months – 3½ years of age), and 15 age matched controls (9 F) with DS from a prior study[46] were followed up in this study. Twenty-five DS adolescents (83%) agreed to participate, but three (2 previously treated males, 1 female control) of these were excluded because of severe behavioural problems.

Auxiological data of an additional 15 subjects (6 F) with DS examined in the out-patient clinic during the same time period were used in order to obtain a larger DS control group (Figure 4). There were no differences in any growth parameters between these additional control subjects and the original controls. The two groups were therefore combined to form an extended group of controls for analyses of anthropometric parameters.

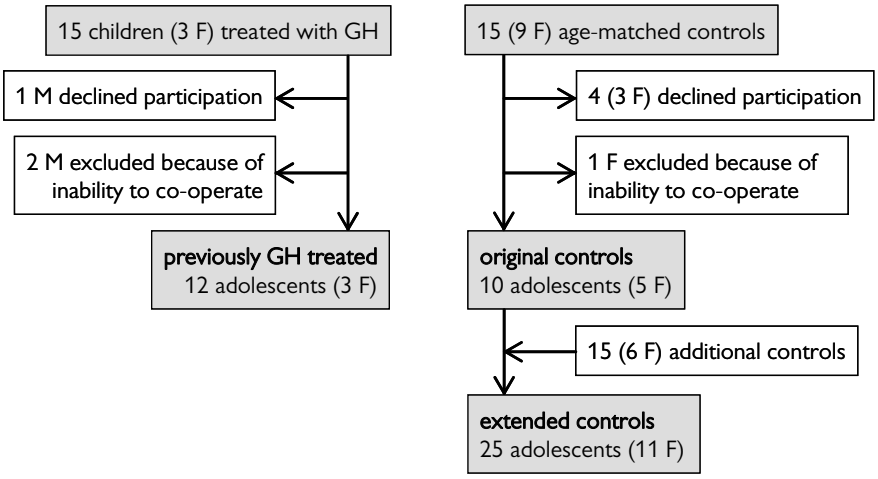

Figure 4. Study population. The number of adolescents with DS included and the reasons for exclusion.

Methods

Physical examination included measurements of body weight, body height, sitting height, arm span and head circumference. From these data, BMI, relative sitting height and the ratio between arm span and body height were calculated.

The Leiter international performance scale – revised (Leiter-R), a test of non-verbal cognitive ability at ages 2:0-20:11 years, was used to assess cognitive ability. Further, two subtests of the Wechsler intelligence scale for children – third edition (WISC-III), Block design and Vocabulary, were chosen because of their high g-factor loadings. All patients were assessed by the same psychologist with both tests on the same occasion.

Bruininks-Oseretsky test of motor proficiency, second edition (BOT-2) is a standardised test of gross and fine motor skills for individuals aged 4:0-21:11 years and was used in assessment of general motor ability. The test was administered individually by the same physical therapist on a single occasion.

Figure 5. One of the studied adolescents performing the subtest Block design of WISC-III. Published with consent of the adolescent and his guardians.

Figure 6. An adolescent in the study during assessment of motor proficiency with BOT-2. Consent to publication was obtained from this young male and his guardians.

Study design

Anthropometric data were adjusted for age and sex on the basis of growth charts commonly used in paediatric medicine in Sweden and expressed as SDS. Target height (TH) was calculated as $(H_{father} + H_{mother} \pm 13)/2$, with subtraction of another 20 cm to compensate for the short stature occurring in DS.[11]

The scoring process is similar in Leiter-R and BOT-2. Raw point scores, based on the number of items passed, are converted to scaled scores, i.e. Brief IQ standard score and Total motor composite score, respectively. The scaled scores are standardised on a normal population without psychomotor delays. However, the standardisation results in loss of substantial variability in performance in lower functioning individuals.[105,106] When the psychomotor performance of the previously treated adolescents was compared with that of the controls, both raw point scores and scaled scores were used.

Non-parametric statistical tests were applied. The Mann-Whitney exact U-test was used when comparing the groups. A binomial test was applied for comparison of mean raw point scores between the groups, where superiority of the GH treated adolescents in any variable was set to "1" and otherwise "0".

Study IV

Patients

Ten young adults (5 F) with DS, aged 24-32 years, constituted the population of study IV. Half of the patients (3 F) were reared at home with their parents and the other half were living in sheltered housing. All patients were receiving medical care at the University Children's Hospital, Uppsala, Sweden. Five patients (3 F) were receiving thyroid hormone replacement therapy for hypothyroidism and one female patient had a history of mild depression and was having ongoing low dose antidepressive treatment. In addition, one male patient had undergone neonatal surgery for an atrioventricular septal defect and had since been considered to be in a good state of health.

Ten controls, matched for age and sex, served for comparison regarding secretion of GH and measurements of body composition.

Methods

Body weight, body height and sitting height were measured at a physical examination. Relative sitting height and BMI were then calculated.

Growth hormone in serum was determined by fluoroimmunometry (Immulite®2000, Siemens, Munich, Germany and AutoDelfia hGH, Wallac OY, Turku, Finland; the former results were multiplied by a factor of 1.45 to correspond to the Wallac method).

The concentrations of insulin and IGF-I in serum were measured by electrochemiluminescence immunoassays (Modular, Roche Diagnostics, Basel, Switzerland, and Immulite®2500, Siemens, Munich, Germany, respectively).

Certified laboratory methods were used to measure glucose, triglycerides, cholesterol and high- and low-density lipoprotein cholesterols (HDL and LDL, respectively).

Stable isotope labelled compounds, [6,6-$^2H_2$]glucose and [1,1,2,3,3-$^2H_5$]glycerol (Cambridge Isotope Laboratories, Woburn, MA, USA) were used to assess production of glucose and glycerol. The [6,6-$^2H_2$]glucose and [1,1,2,3,3-$^2H_5$]glycerol were dissolved in 0.9% saline solution. The solutions were sterile in microbiological cultures and pyrogen-free when tested by the Limulus lysate method.[107]

The isotopic enrichments of [6,6-$^2H_2$]glucose and [1,1,2,3,3-$^2H_5$]-glycerol were determined by gas chromatography-mass spectrometry (GCMS). A Finnigan SSQ 70 mass spectrometer (Finnigan MAT, San José, CA, USA) equipped with a Varian 3400 gas chromatograph (Varian Associates Inc, Sunnyvale, CA, USA) with a non-polar capillary column was used. Chemical ionisation was performed with methane, and ions were selectively monitored. The ions monitored for glucose were mass

over charge ratio (m/z) 331 and 333, reflecting unlabelled and dideuterated glucose, and those for glycerol were m/z 159 for unlabelled glycerol and 164 for the 5-deuterated compound.

Insulin resistance, based on fasting levels of blood glucose and plasma insulin, was evaluated using the HOMA (homeostasis model assessment) Calculator 2.2.2 (Diabetes Research Laboratory, Oxford, United Kingdom).

Bone mineral density and body composition were assessed by dual-energy X-ray absorptiometry (DEXA; Lunar Radiation, Madison, WI, USA).

Study design

A 12 h nocturnal GH profile was assessed by continuous venous blood sampling at 30 min intervals using a withdrawal pump. The Pulsar program[108] was used to process the GH profiles.

On discontinuation of GH measurement, productions of glucose and glycerol were assessed in the DS subjects by means of stable isotope tracers after an overnight fast. Bolus doses of the tracers were given in the first 5 minutes, followed by a constant rate infusion. Two separate peripheral vein catheters were used, one for infusion of the tracers and one for collection of blood samples. The blood samples were obtained before the bolus doses and every 10 minutes in the second hour of the infusion. Immediately after withdrawal, the samples were centrifuged and frozen until analysed.

Descriptive central statistics are presented as mean±SD unless otherwise stated. Statistical analyses were performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). For the analyses, non-parametric statistical tests were used: the Mann-Whitney exact U-test in comparison of the groups, and Spearman rank correlation in correlation analyses. Statistical significance was set at $p<0.05$.

Results

Study I

The mean birth length both of girls and of boys with DS was 48±2.3cm, corresponding to -1 SD and -1.5 SD, respectively, on growth charts for healthy Swedish children.[104]

The mean final height of females with DS was 147.5±5.7cm (-2.5 SD, Swedish standard[104]) and that of males with DS was 161.5±6.2cm (-2.5 SD[104]); thus there was a difference of 14 cm between the genders. When plotted on the growth charts of American children with DS,[7] these mean final heights were slightly above the 50th and on the 95th percentile, respectively. The children with DS reached their final height at relatively young ages, girls at 15 years and boys at 16 years.

The girls had a mean birth weight of 2.9±0.3 kg, corresponding to -1.5 SD.[104] The mean weight at 18 years of age was 54±7.5 kg, corresponding to -0.5 SD according to the Swedish standard[104] and to the 25th percentile of American DS growth charts.[7] The corresponding figures for the boys with DS were 3.0±0.6 kg (-1.2 SD[104]), and 61±8.3 kg (-0.4 SD[104], and the 55th percentile[7]), respectively.

At birth, the boys had a mean head circumference of 33.0±1.7 cm, corresponding to -0.5 SD, whereas at 4 years of age it was 48±1.4 cm, -2.0 SD, Swedish standard.[104] The head circumference of the girls with DS developed in a similar way with a mean of 32.5±1.6 cm at birth and of 47.5±1.2 cm at 4 years of age, corresponding to -0.7 SD and -2.0 SD,[104] respectively.

The body mass index was above 25 kg/m^2 in 31% of the boys and 36% of the girls at 18 years of age.

The final version of the growth charts also includes a comparison with the growth data of Albertsson Wikland et al[109] from 2002 (see pp 40-41).

Study II

None of the studied children with DS was diagnosed with congenital hypothyroidism at neonatal screening. The mean plasma level of TSH in the DS subjects (n=68) was higher, 7.0±7.45 mU/L, than that in the controls, 3.9±2.43 mU/L ($p<0.010$). Further, the infants with DS had an

elevated TSH-SDS at birth, 1.1±2.67 (p<0.012). The differences between DS infants and controls were mainly due to a marked increase in mean TSH and TSH-SDS in the DS males (n=37) (p<0.003). The male DS neonates had a higher TSH-SDS, 1.9±3.31, than the DS females, 0.19±1.11 (p<0.009), whereas the difference between the male and female TSH levels, 9.1±9.0 and 4.5±3.88 respectively, was only borderline significant (p<0.058).

Table 2. *Mean TSH concentration and calculated TSH-SDS in the infants with DS at neonatal metabolic screening.*

		n	mean±SD	DS vs. controls	females vs. males
TSH (mU/L)	females	31	4.5±3.88	NS	p<0.058
	males	37	9.1±9.01	p<0.003	
	total	68	7.0±7.45	p<0.010	
TSH-SDS	females	31	0.2±1.11	NS	p<0.009
	males	37	1.9±3.31	p<0.003	
	total	68	1.1±2.67	p<0.012	

According to the hospital records, 22 children (35%) (11 F) developed hypothyroidism during their first decade; four of these (3 F) were positive for autoantibodies at diagnosis or later in the follow-up period. Seven children (10%) (3 F) were diagnosed with hypothyroidism before the age of two years. None of these were antibody positive.

No significant correlation was found between the screening level of TSH or TSH-SDS and the occurrence of hypothyroidism during childhood, although there was a tendency for the DS children diagnosed with hypothyroidism to have a higher neonatal TSH level (p<0.089). Neither was there any correlation between the TSH level or TSH-SDS at neonatal screening and the age at diagnosis of childhood hypothyroidism. The results did not change when the genders were analysed separately.

There were no differences between the DS subjects who developed and those who did not develop hypothyroidism during childhood with respect to birth length, birth weight, Apgar score, gestational age, infant age at screening, or maternal age. The infants with DS were also divided into two groups based on the neonatal TSH level, i.e. those with levels above and those with levels at or below the mean level of the controls. When the above parameters were analysed, the neonates with elevated TSH were found to have a lower birth weight than those with normal TSH (p<0.03).

Study III

There were no differences between the GH treated subjects and the extended group of controls regarding final height[92] and adult weight.[92]

The adolescents previously treated with GH had a larger head circumference SDS[110] than the extended group of controls, -1.6 SDS and -2.2 SDS respectively (p<0.016).

Table 3. *Details of height, weight and head circumference expressed as SDS (with reference to Myrelid et al[92] and Fredriks et al[110]) of the subjects included in the present study prior to and immediately at the end of growth hormone treatment in the study by Annerén et al.[46] Data are given as mean±SD unless otherwise stated.*

characteristics	GH-treated subjects (n=12)	original controls (n=10)	p value
Prior to GH treatment			
Mean age (months)	7.7	6.0	
Height SDS[92]	0.1±1.29	0.6±1.48	NS
Weight SDS[92]	0.9±0.86	0.5±0.91	NS
Head circumference SDS[110]	-1.3±0.78	-1.5±0.88	NS
At the end of GH treatment			
Mean age (months)	44.1	43.9	
Height SDS[92]	1.4±1.32	-0.01±0.85	<0.007
Weight SDS[92]	1.4±0.80	1.2±2.50	<0.050
Head circumference SDS[110]	-1.1±0.52	-1.6±0.76	NS

The body proportions, i.e. the ratio between arm span and height and the relative sitting height (absolute values as well as SDS[111]) were similar in the two groups after adjustment for sex and age. The relative sitting height was increased (median 54.5%, range 49.3-59.5%) and the relative sitting height SDS[111] was 1.6±1.56 for all DS subjects (including the additional controls).

Table 4. *Anthropometric data (mean±SD, unless stated otherwise) of previously treated subjects and the extended group of controls (separated into original and additional controls), all with DS. The p values are calculated from comparisons of the previously treated group and the extended control group.*

characteristics	GH-treated subjects (n=12)	original controls (n=10)	additional controls (n=15)	extended controls (n=25)	p value
Age range (years:months)	17:3-20:2	17:0-19:10	16:0-30:0	16:0-30:0	NS
Final height SDS[92]	-0.39±1.128	-0.21±1.062	0.37±1.128	0.13±1.117	NS
Adult weight SDS[92]	1.08±1.376	0.98±1.015	0.71±1.437	0.82±1.268	NS
Head circumference SDS[110]	-1.6±0.64	-2.1±0.80	-2.2±0.61	-2.2±0.68	<0.016
Sitting height SDS[111]	-2.2±1.23	-2.1±0.90	-2.2±1.18	-2.2±1.06	NS
Relative sitting height (%)	54.5±1.37	54.8±2.22	53.4±2.53	53.9±2.47	NS
Relative sitting height SDS[111]	1.9±1.07	2.0±1.45	1.0±1.86	1.9±1.07	NS
Arm span SDS[112]	-3.9±1.27	-4.4±1.79	-3.9±1.37	-4.1±1.58	NS
Arm span/height ratio (%)	97.7±2.65	97.1±3.12	95.6±3.13	96.3±3.14	NS

When using scaled scores, standardised on a population without intellectual impairment, no differences were found between the groups in assessed cognitive performance on Leiter-R or WISC-III. However, the mean raw point scores of the previously GH treated adolescents were consistently higher than those of the controls ($p<0.03$) in all subtests of both Leiter-R and WISC-III (Table 5, Figure 7).

All adolescents obtained Total motor composite scores below -2 SD for their age on the BOT-2. The mean raw point scores of the previously treated adolescents were above the mean score of the controls in all but one subtest ($p<0.07$) of BOT-2 (Figure 8). A significant difference between the groups was also shown in the composite motor area of Strength and agility, where the previously treated adolescents performed better than the controls ($p<0.043$) (Table 6).

Table 5. *Performance on Leiter-R and WISC-III (mean±SD) and the estimated age equivalents (years:months) in each subtest of Leiter-R as well as the overall mental age, given as means and ranges. Statistical analyses were not performed regarding age equivalents.*

	GH-treated (n=12)	controls (n=10)	p value
Figure ground, item raw point	13.3±2.74	12.6±1.96	NS
Figure ground, age equivalent	5:4 (4:3-7:1)	5:2 (3:11-6:0)	
Form completion, item raw point	21.4±4.48	20.7±3.83	NS
Form completion, age equivalent	6:0 (4:0-7:4)	5:11 (4:7-7:4)	
Sequential order, item raw point	11.1±4.46	10.7±5.03	NS
Sequential order, age equivalent	4:9 (4:2-7:1)	4:7 (3:7-6:7)	
Repeated patterns, item raw point	8.9±3.70	8.2±2.90	NS
Repeated patterns, age equivalent	4:6 (3:3-6:6)	4:5 (3:3-5:9)	
Brief IQ composite score	38.7±3.94	38.4±2.95	NS
Mental age	5:2 (4:0-6:11)	5:0 (4:1-6:0)	
WISC-III block design	7.1±7.06	6.7±4.90	NS
WISC-III vocabulary	11.3±4.33	11.0±5.75	NS

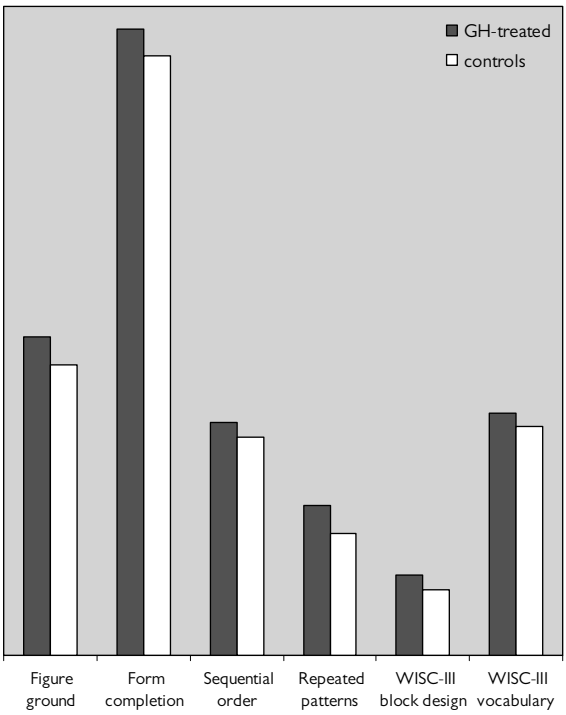

Figure 7. Illustrations of the mean raw point score of performance on Leiter-R and WISC-III in the previously treated adolescents and the original controls. The scores were slightly but consistently higher in the group previously treated with GH.

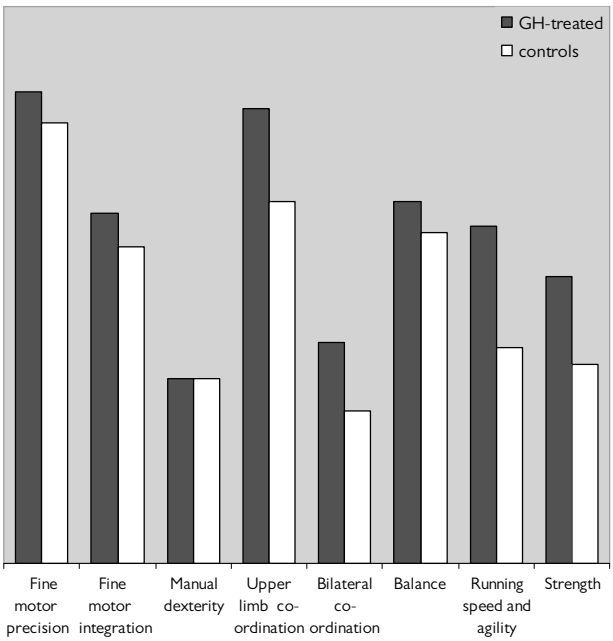

Figure 8. The mean raw point score of performance on BOT-2 in the previously treated adolescents and the original controls.

Table 6. *Performance on BOT-2 (divided into subtest raw point score, motor area composite standard score and standard deviation scores, SDS) given as means and standard deviations. A low score indicates poor performance.*

	GH-treated (n=12)	controls (n=10)	p value
Fine motor precision	29.7±4.14	27.7±7.67	NS
Fine motor integration	22.0±7.98	19.9±9.83	NS
Fine manual control	27.4±2.39	26.9±4.38	NS
Fine manual control SDS	-2.3±0.24	-2.3±0.46	NS
Manual dexterity	11.6±6.08	11.6±3.44	NS
Upper-limb co-ordination	28.6±4.80	22.7±7.89	<0.085
Manual co-ordination	26.3±3.60	24.7±2.21	NS
Manual co-ordination SDS	-2.4±0.36	-2.5±0.23	NS
Bilateral co-ordination	13.9±5.33	9.6±5.36	<0.074
Balance	22.8±5.31	20.8±6.91	NS
Body co-ordination	27.3±2.73	25.6±2.76	NS
Body co-ordination SDS	-2.3±0.27	-2.4±0.29	NS
Running speed and agility	21.2±8.50	13.6±6.02	<0.032
Strength	18.0±5.86	12.5±6.19	<0.037
Strength and agility	29.7±3.60	26.4±3.95	<0.043
Strength and agility SDS	-2.0±0.36	-2.4±0.40	<0.043
Total motor composite	25±3.0	24±3.2	NS
Age equivalent (years:months)	6:1	5:6	NS
Total motor composite SDS	-2.5±0.30	-2.6±0.32	NS

Study IV

The subjects with DS were shorter than the controls, but had a similar sitting height. Consequently, the relative sitting height was increased in the DS subjects, corresponding to 2.2±1.10 SDS[111] when corrected for age and sex. There was no difference in weight between the adults with and without DS and thus, the former had a higher BMI (29.5±4.00 vs. 24.2±3.60 kg/m^2; p<0.015). All, but one (female) of the DS subjects were overweight (1 F, 4 M) or obese (3 F, 1 M).

Table 7. *Data on anthropometry and body composition (mean±SD) in ten young adults with DS and ten non-DS controls matched for age and sex.*

characteristics	DS subjects	controls	p value
Height SDS[109]	-3.1±0.94	-0.1±0.85	<0.0001
DS-specific height SDS[92]	-0.01±0.98	not applicable	
Relative sitting height SDS[111]	2.2±1.10	0.6±1.06	<0.006
BMI (kg/m^2)	29.5±4.00	24.2±3.60	<0.015
Lean body mass (kg)	44.1±11.39	51.5±11.22	NS
Lean body mass percentage	62.2±10.16	70.9±8.18	<0.043
Fat body mass (kg)	23.8±7.17	17.9±7.17	NS
Fat body mass percentage	34.0±9.56	24.5±8.00	<0.035

There were no differences in the 12 h GH profile, i.e. number of peaks, peak height, peak amplitude and area under the curve, between the DS subjects and controls (Figure 9). The mean serum IGF-I level of the DS population was in the lower end of the reference interval.

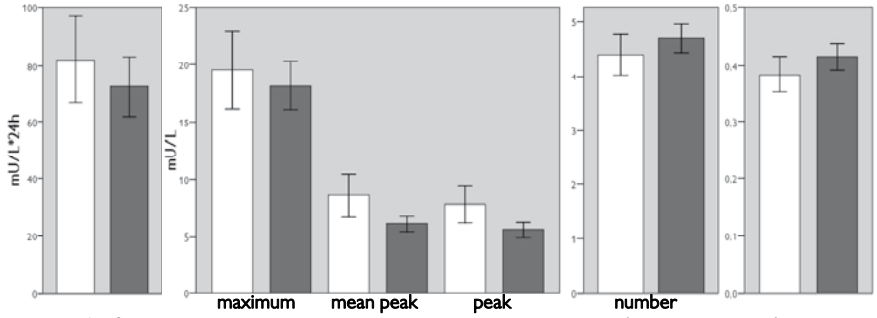

Figure 9. Characteristics of the nocturnal GH profile in DS subjects and controls illustrated in bar charts and given as numbers (mean±standard error of the mean [SEM]) below.

Table 8. *Energy metabolism and endocrine data (mean±SD) in DS subjects and age- and sex-matched controls.*

characteristics	DS subjects	controls	p value
IGF-I (µg/L)	214±60.4	229±56.0	NS
IGF-I (SDS)	-0.76±1.16	-0.45±1.01	NS
Insulin (mU/L)	10.5±4.66	7.1±2.38	<0.063
Glucose (mmol/L)	5.2±0.58	4.6±0.36	<0.011
HOMA* index	1.4±0.62	0.8±0.25	<0.004
Total cholesterol (mmol/L)	4.4±0.76	4.1±0.51	NS
LDL cholesterol (mmol/L)	2.8±0.65	2.6±0.44	NS
HDL cholesterol (mmol/L)	1.1±0.22	1.1±0.26	NS
Triglycerides (mmol/L)	1.1±0.34	0.9±0.35	NS
Relative rate of lipolysis (µmol/kg/min)	3.5±1.68	not available	
Relative rate of glucose production (µmol/kg/min)	15.5±5.07	not available	

*HOMA=homeostasis model assessment

The mean relative rate of total body glycerol production was 3.5±1.68 µmol/kg/min. Lipolysis did not correlate to percentage body fat in the DS subjects. The mean rate of glucose production in the DS adults was 15.5±5.07 µmol/kg/min.

Examination with DEXA demonstrated a higher percentage body fat in the DS subjects in comparison with the controls: 34.0±9.56 and

24.5±8.00, respectively ($p<0.035$). The percentage lean body mass was 62.2±10.16 in the DS subjects, which was significantly lower ($p<0.043$) than that of the controls, 70.9±8.18. Furthermore, both the assessed BMD and z-scores were lower in the adults with DS than in the controls ($p<0.015$ and $p<0.007$, respectively). Two DS subjects (both male) were osteoporotic, and two other DS subjects (1 F) were osteopenic, whereas none of the controls had a subnormal BMD.

Table 9. *Data on bone mineral density (BMD; mean±SD) for the young adults with DS and the controls.*

	DS subjects	controls	p value
z-score femoral region	-0.85±0.946	0.28±1.209	<0.033
z-score vertebral region	-1.04±0.766	0.17±1.040	<0.009
z-score total body	-0.86±1.186	0.71±1.130	<0.007
BMD total body	1.10±0.109	1.23±0.122	<0.015

Discussion

Growth as index of health

Growth parameters are used worldwide as indicators of health during childhood and with use of growth charts the paediatrician can screen for conditions resulting in impaired or accelerated growth.

Children with DS are overrepresented with regard to congenital and acquired disorders that may affect growth, i.e. congenital heart defects,[113] hypothyroidism[62,114,115] and coeliac disease.[6] In our study no children were excluded by reason of any additional disorder. Treated hypothyroidism and coeliac disease should not affect growth to any significant extent, and congenital heart defect is part of the syndrome in 50% of the DS population.[116] A comparison between children with no or mild congenital heart disease and children with moderate or severe heart disease has shown that the difference in height is less than 2 cm up to the age of eight years and that there is a difference in weight corresponding to 0.5-2 kg.[7]

Designing growth charts

It might be considered that optimally the creation of growth charts should be based on a longitudinal and prospective study with repeated examinations of a large and representative group. However, drawbacks regarding time constraints and logistics make this a less attractive model.

In our study repeated data for each child were used, as in a longitudinal study, as well as several examinations of different children in the same age group, as in a cross-sectional study. The design is commonly used when growth in specific groups with relatively few subjects is analysed.[7,16,117,118]

To eliminate bias in the selection of the children in the study, mean scores and standard deviations of all parameters were calculated and compared between the two groups of children recruited. There were no differences in any of the parameters related to growth.

To facilitate a comparison with the general population a shaded area corresponding to ±3 SD of the present Swedish standard growth chart[109] is seen in the final version of the DS specific growth charts (Figs. 10-12).

Anthropometry in Down syndrome

Birth length and final height

In comparison with healthy boys, boys with DS had a mean birth length and a mean final height at 18 years of age corresponding to -1.5 and -2.5 SD,[104] respectively. Compared with the American DS growth charts for males,[7] the final height of the male DS subjects in the present study corresponds to the 95th percentile. The rather marked difference in final height between Swedish and American males with DS may be due to factors such as ethnic diversity and differences in the size of the study groups.

The girls with DS had a mean birth length of -1 SD and a mean final height at the age of 18 years corresponding to -2.5 SD according to the Swedish standard.[104] The mean final height of the girls with DS was slightly greater than that of the American girls.[7]

The birth lengths of our children with DS could not be compared with those of the American children, since the latter growth charts start at 1 month of age. In contrast to the American data,[7] our subjects with DS showed the same difference in mean final height between the genders as that of healthy individuals.

The individuals with DS reached their final height at relatively young ages, males at 16 years and females at 15 years, in agreement with the findings of an early onset of puberty.[7,10,11] Our results also show that both boys and girls with DS have a reduced pubertal growth spurt, contributing to the low final height.

Target height calculated as previously described, with subtraction of 20 cm to compensate for the short stature seen in DS, was shown to be valid.[11] All DS subjects in study III were close to their separately modified TH, with a mean of 100% for both the previously treated (range 94.4-104.2%) and for the controls (range 93.7-104.8%).

The short stature in DS is to a great extent due to relatively short legs.[119] The marked increase in relative sitting height and in the relative sitting height SDS seen in studies III and IV confirms the occurrence of abnormal body proportions in DS.

The ratio between arm span and height varies with ethnicity and gender.[120] The subjects with DS in study III were all of Caucasian origin, and hence the expected arm span/height ratio would be close to one, with no difference between the genders.[120] The studied subjects did not differ in this respect. Thus, the relatively short legs in DS are matched by equally short arms.

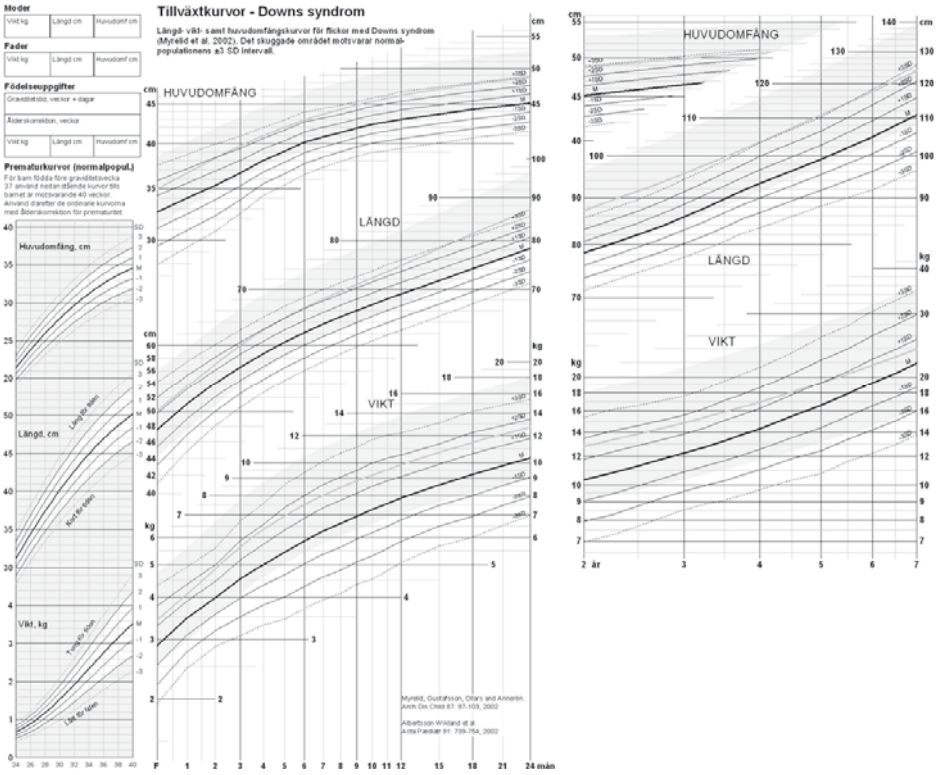

Figure 10. Growth charts for height, weight and head circumference (mean±3 SD) of Swedish girls with Down syndrome from birth to 7 years of age.

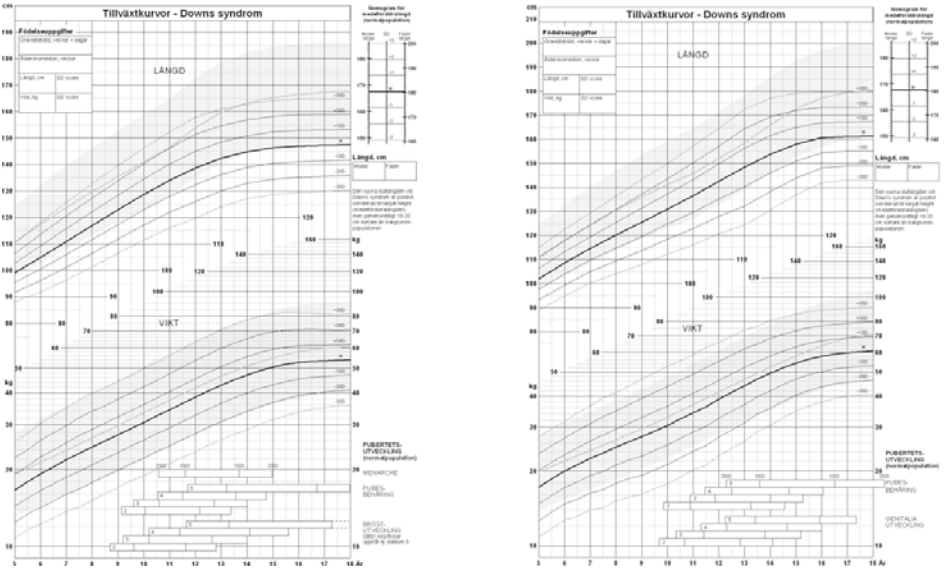

Figure 11. Growth charts for height, weight and head circumference (mean±3 SD) of girls and boys with Down syndrome, respectively, from 5 to 18 years of age.

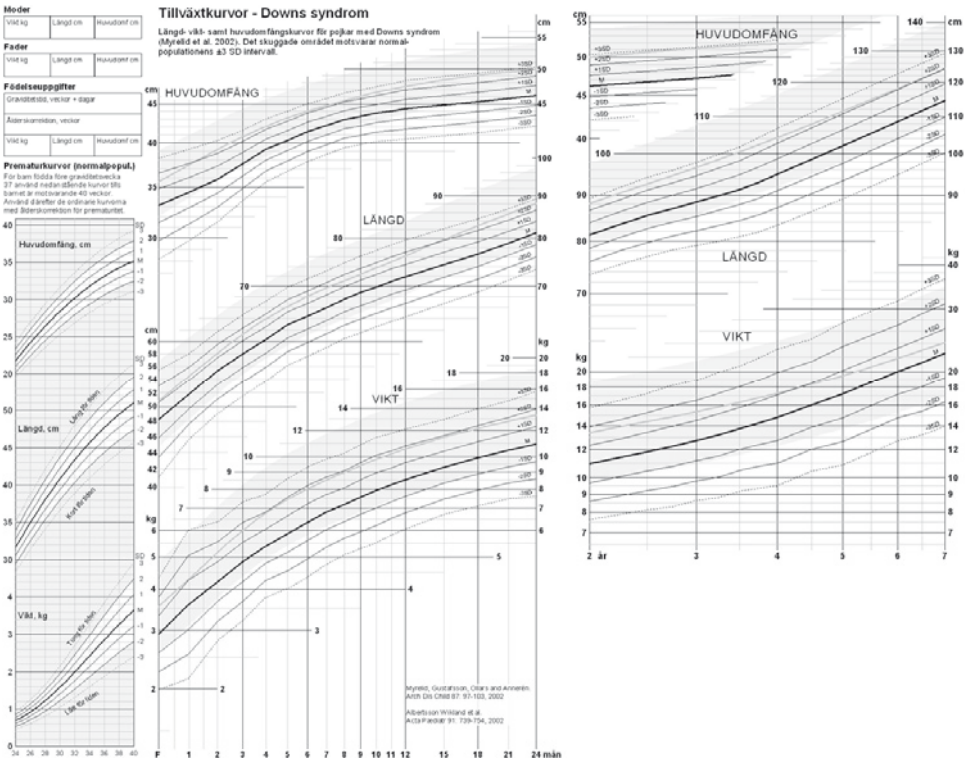

Figure 12. Growth charts for height, weight and head circumference (mean±3 SD) of Swedish boys with Down syndrome from birth to 7 years of age.

Weight and body mass index

Although the Swedish males with DS had a greater mean final height than their American counterparts, their mean weight at 18 years was close to the 50th percentile of the corresponding American males.[7] The mean weight of Swedish girls with DS was at the 25th percentile of the American growth charts at the age of 18 years.[7]

One-third of the individuals with DS were overweight (BMI >25kg/m^2), as defined by WHO,[89] at the age of 18 years in our study. A comparison with the weight and height data of the American individuals with DS indicates that overweight is a greater problem in the latter group.

Overweight and obesity, as based on BMI, is common in DS. An altered body proportion is reported to influence BMI, which is slightly elevated in association with relatively short lower limbs.[121] This effect might to some extent explain the high prevalence of increased BMI seen in individuals with DS.[90-95]

In study IV, where all but one of the young DS adults had an increased BMI, the high prevalence of overweight/obesity could be confirmed in

assessment of the body composition; the subjects with DS showing an increased body fat percentage and a decreased percentage lean body mass.

The cause of obesity in DS is unknown, but is probably multifactorial, with contributions of endocrine abnormalities, reduced exercise, hypotonia, a depressed metabolic rate and poor eating behaviour.[94]

Head circumference

In view of the mental retardation associated with DS, the growth of the head is of great interest. Our results showed that the mean head circumference of the children with DS was smaller than that of healthy Swedish children,[104] but slightly larger than that of American children with DS.[15] The deviation of growth of the head in children with DS increases with age, with a total decrease of approximately 1.5 SD from birth to the age of four years when compared to Swedish standard.[104]

In agreement with previous studies, there was a gender difference in head circumference, the male head tending to be larger than the female.[14,15]

Bone mineral density

The bone mineral density in the DS group was below that of the controls. Four of the young adults with DS were diagnosed with osteoporosis (2 M) or osteopenia (1 M/1 F).

Bone mineral density has previously been shown to be decreased in DS subjects,[122,123] especially in males, where the skeletal mass normally exceeds that of females.[124,125] Several factors are known to be associated both with low BMD and with DS, such as a small body size, a sedentary lifestyle, poor nutrition, hypotonia, reduced physical activity and both thyroid and gonadal dysfunction.[122,123,126] The latter may explain the altered difference in BMD between the genders, as gonadal dysfunction is more common in male than in female subjects with DS.

Short stature may lead to underestimation of BMD, whereas obesity tends to cause the opposite,[127] but the influence of body composition on BMD is unclear.[122] Further, a decreased peak bone mass in DS has been postulated, and may possibly be due to low muscle strength and delayed gross motor development. [101,126] Peak bone mass correlates well to the establishment and degree of osteoporosis.[128] Hence, a marginal drop in BMD may be of substantial importance in DS. Additionally, Tümer et al[129] suggested an association between osteoporosis and the distal region of chromosome 21.

Growth hormone secretion

Little is known about growth hormone secretion in DS. The few available studies concern children with DS,[43,130] who seem to have reasonable endogenous growth hormone concentrations.[43] In the adult DS population a poor stimulated GH response has been reported,[45] but continuous and spontaneous GH secretion has not previously been studied in DS. Study IV showed that young adults with DS have a normal capacity to produce and release GH spontaneously.

The synthesis of IGF-I is stimulated by GH and the levels of IGF-I in the subjects with DS were also normal, although in the lower end of the reference interval. Similar results have been reported previously,[131] but it has been difficult to show a significant correlation between the concentrations of GH and IGF-I.[132] We found that the level of IGF-I correlated positively to the area under the curve (AUC) for spontaneous secretion of GH both in the total study population and in the DS subjects alone.

There is some controversy regarding the impact of body composition on the GH and IGF-I levels in overweight subjects. GH secretion is negatively associated with BMI,[133] and the GH response in obese subjects has been reported to be as impaired as that in hypopituitary patients with severe GHD.[40] The common occurrence of insulin resistance and hyperinsulinism in obesity may allow normal IGF-I synthesis and secretion despite altered somatotroph function. There are reports of increased as well as decreased concentrations of IGF-I in obese subjects.[134,135] Landin-Wilhelmsen et al[135] suggested that low levels of IGF-I may be related to increased adipose tissue and decreased lean body mass,[135] whereas Ghigo et al[40] proposed that the increased levels of IGF-I might be a result of an increased GH sensitivity in obesity. Nevertheless, despite increased BMIs, no correlation between IGF-I and BMI was seen in the DS subjects of our study or in those of a previous study.[42]

Growth hormone and cognitive function

Very few investigations have been made on GH treatment in children with DS.[43,46,47] However, from studies of the GH effect in other conditions, it may be concluded that GH has beneficial effects on cognition, energy, mood and behaviour in children with PWS,[24,25] TS[26] and GHD,[26,27] as well as in children born SGA.[28]

The assumed effect of GH on cognitive function and mood is plausible, as GH has been shown to reach the cerebrospinal fluid and affect the central nervous system directly.[21] In addition, GH may exert a local growth promoting effect on the brain.[23] An association between intelligence and head growth during childhood has been reported,[23] and the IQ score correlates positively with increasing head circumference during GH therapy

in SGA children.[28] GH receptors have been found in several regions of the brain,[21,29,136] of which the receptors in the hippocampal area are particularly interesting, as they may mediate the actions of GH on memory and cognition.[21]

Microencephaly is considered to be the main cause of mental retardation in DS,[75] but there is also a delay in central myelination which correlates well with the extent of developmental delay.[137] Impaired neurogenesis during critical phases of brain building has been demonstrated in infants with DS and results in severe hypocellularity. Chakrabarti et al[76] demonstrated that the reduced neural proliferation further correlated with the delayed synapse formation in the cortex and hippocampus in DS.

Intelligence per se is often questioned, particularly in assessment of cognitive functions in mentally retarded populations. Being mentally retarded implies having limitations in cognitive areas including abstract thinking, but also lacking necessary adaptive skills to deal with everyday life and being dependent on others. Many individuals with DS are described as being socially quite alert, a strength that helps them to communicate and take part in social settings, but with no relation to their level of intelligence. Assessment of adaptive functioning is a way of broadening the concept of intellectual ability, and such data would have given interesting complementary information in the investigation of the cognitive effects of GH treatment.

Growth hormone and motor performance

Growth hormone has an anabolic effect on skeletal muscle.[138] The muscle mass is reported to increase within the first year of GH therapy in individuals with GHD as well as in children born SGA and children with PWS.[138-142] Exogenous GH also improves muscular function,[140] and improvements of strength and agility are reported to occur during GH therapy in children with PWS.[142]

The improved motor performance of the previously GH-treated adolescents in study III may be related to a direct effect on skeletal muscle mass and function. However, in view of the differences in fine motor skills described in the original study of these subjects,[46] the improved motor proficiency might also be derived from a CNS effect.

It has been postulated that the motor problems in DS may be related to the delayed cerebellar maturation and the relatively small cerebellum.[83,143,144] Thus, previous findings of improved fine motor skill[46] and an increased head circumference[47] could theoretically be an effect of improved cerebellar maturation and growth during GH treatment, as a high density of IGF-I receptors in the cerebellum has been reported.[145] The presence of GH receptors has been confirmed in the human putamen[21] and in the rat and rabbit cerebellum.[146] It has further been demon-

strated that GH replacement in GHD patients, by increasing the circulating IGF-I, yields a faster working memory performance and recruitment of task-associated prefrontal regions.[147]

Growth hormone therapy

Study III was a follow-up of children with DS who had been treated with daily injections of GH for three years during early childhood.[46] Their growth velocity was normalised during the GH treatment.[46] Further, some improvement of their fine motor skill was observed at the end of treatment, although there was no significant effect on head circumference.[46] Torrado et al[47] reported increased growth velocity, height SDS and weight SDS, and also an increase in head circumference SDS during GH treatment in children with DS. No information on psychomotor function was given in that report.

The available data on GH therapy in DS are unanimous, with the reported effects entirely beneficial.[43,46,47] There is a marked response to exogenous GH treatment in DS,[43,46,47] despite the previous findings of reasonable GH concentrations in DS children[43] and the present observations of normal GH secretion in young adults with DS. Against this background, it may be suggested that in DS the effect of endogenous GH is reduced and that the bioactivity of circulating endogenous GH in this syndrome may be questioned.[42]

The diabetic and leukaemogenic potential of GH therapy has been discussed in the literature.[148,149] In view of the intrinsic predisposition to diabetes and leukaemia in the DS population,[150] GH treatment might further increase the risk of these diseases, a possibility which should be taken into account when GH treatment in persons with DS is discussed. None of the adolescents with DS were being or had been treated for diabetes or leukaemia. Neither were any other adverse effects, early or late, of the GH treatment observed in these subjects.

Reduced proliferation of neural stem cells during early brain development has been observed in infants with DS[75] and correlates with delayed synapse formation in the cortex and hippocampus.[76] Further, the cerebral, cerebellar and hippocampal volumes are decreased in DS.[74] These defects are likely to have a continuous impact on brain function in DS.[76]

Earlier studies have shown that GH promotes proliferation of neural precursors, neurogenesis and gliogenesis during early brain development,[151] presumably through local production of IGF-I. Further, IGF-I has been shown to be essential for hippocampal neurogenesis.[152] Thus, the rationale for early GH treatment in DS is the neuronal growth-promoting and protective effects of GH and IGF-I.[21,153,154] In fact, a recent study of the effects of thyroxine treatment in young children with DS[155] has shown it possible to improve early development and growth. It must be empha-

sised that even a small change in psychomotor attainment can be of substantial importance in a developmentally delayed population.

Energy metabolism

Energy substrate production and insulin sensitivity

The rate of hepatic glucose production during fasting was increased in the young adults with DS in comparison with data from studies of normal adults.[156,157] Further, the DS subjects had both higher fasting plasma glucose and serum insulin levels and a higher HOMA index than the controls. Altogether, these findings indicate a relative reduction in hepatic and peripheral insulin sensitivity in DS.

The subjects with DS showed increased lipolysis as compared with previously reported data from healthy individuals.[157,158] This is in line with the increased proportion of fat mass found in the DS subjects, although no statistical correlation was found between lipolysis and body fat mass or body fat mass percentage. However, the high rate of lipolysis increases the circulating free fatty acids and may thus have a negative influence on insulin sensitivity.

The calculated measure of insulin resistance (HOMA index) correlated to fat body mass in both groups, DS subjects and controls, separately. The slope of the regression lines differed, indicating that body fat has a more marked effect on insulin sensitivity in the DS individuals.

Neonatal metabolic screening

Neonatal metabolic screening in Sweden was established in 1965. The screening is commonly called the PKU test. The name is derived from phenylketonuria (PKU), the first disease for which screening was performed. New metabolic disorders have been added to the screening programme with time. Today, children are also screened for galactosaemia, congenital hypothyroidism, congenital adrenal hyperplasia, and biotinidase deficiency.

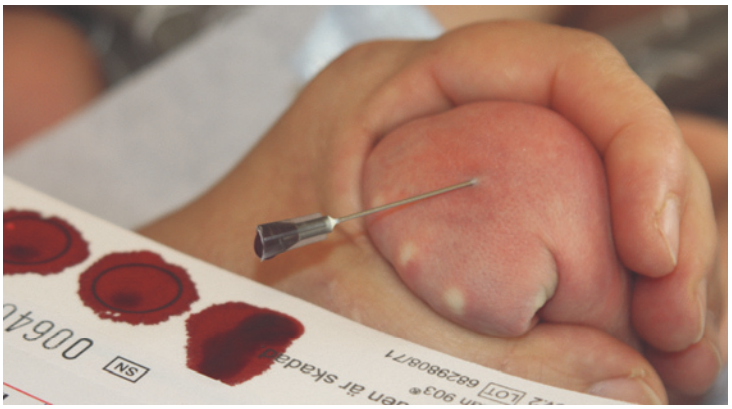

Figure 13. Blood sampling for neonatal metabolic screening. A dorsal vein of the hand is punctured >48 hours after birth and the blood is collected on a filter paper. Published with the consent of the parents.

In study II the results from neonatal screening for CH, by analysis of the TSH concentration in dried filter paper blood in children with DS were compared with those of controls. The results show an increase in the TSH concentration as well as in TSH-SDS in the infants with DS. The data support the notion that DS infants are mildly hypothyroid at birth, and the findings are in agreement with the report by Trotsenburg et al[159] of a "left-shifted" Gaussian T4 concentration frequency distribution in DS neonates.

Thyroid disorders

Thyroid disorders, hypothyroidism in particular, are common in individuals with DS, as mentioned earlier. Congenital hypothyroidism is increased almost 30-fold in children with DS, and hypothyroidism acquired later in life has been reported to affect 30-50% of the DS population.[64,160]

One of the aims of study II was to investigate a possible correlation between an increased TSH concentration at neonatal screening and thyroid disease during childhood. The possibility of predicting later development of hypothyroidism on the basis of the neonatal screening result would be helpful in routine follow-up of children with DS.

There was a tendency towards a higher neonatal TSH level in the infants who became hypothyroid during the first ten years of life, but no significant correlation was found between screening levels of TSH and occurrence of hypothyroidism during childhood.

Subclinical hypothyroidism

Subclinical hypothyroidism is defined as elevated TSH but normal T3 and T4 in individuals with no clinical signs of hypothyroidism. Numerous studies have led to the conclusion that subclinical hypothyroidism is common in DS, with as many as half of the DS population being affected.[161]

The subclinical hypothyroidism in DS is concluded to be of thyroidal origin, as the bioactivity of TSH has been proven normal by Konings et al,[162] and it might possibly be explained by a need for a higher "TSH pressure" to produce sufficient thyroid hormones.[162]

In people with subclinical hypothyroidism in the general population, there is a yearly progression to overt hypothyroidism of approximately 2-5%,[163] a rate proportional to the TSH concentration and even higher in the presence of thyroid antibodies.

Infants with neonatal hyperthyrotropinaemia have been found to be at risk for development of subclinical hypothyroidism in early childhood.[163] In a follow-up of infants with false positive results at neonatal TSH screening, all showed normal clinical conditions and statural growth at 16-44 months of age, but 25% were positive for thyroid antibodies and 20% were shown to have thyroid abnormalities.[163] The authors concluded that elevation of TSH in the newborn may represent a true clinical condition with mild thyroid dysfunction persisting or reappearing after the neonatal period.[163]

Manifest hypothyroidism

Primary hypothyroidism is usually diagnosed from a combination of an elevated serum TSH level and a low level of T4, with or without the presence of clinical symptoms associated with hypothyroidism.

When caring medically for children with DS, it may be difficult to discriminate symptoms and signs related to hypothyroidism, such as constipation, decreased growth velocity and slow cerebration, from syndrome-specific characteristics. Thus, it is possible that hypothyroidism may be missed in some DS subjects, whereas others may erroneously be diagnosed with apparent hypothyroidism.

When hospital records at diagnosis for the 22 thyroxine-treated children in Study II were analysed in detail, three subgroups were formed based on laboratory findings and the presence of clinical signs. Seven children (3 F) with manifest hypothyroidism (increased TSH and decreased T4); six children (3 F) with subclinical hypothyroidism (elevated TSH and T4 on the lower reference limit) and symptoms of hypothyroidism; and nine children (5 F) with normal TSH levels and T4 levels close to the lower reference limit, but still instituted on thyroxine due to clinical signs

which could be related to hypothyroidism constituted groups A, B and C, respectively. Our findings of manifest hypothyroidism in seven children (group A, 9.6%) is in agreement with earlier reported incidences of approximately 10% among schoolchildren with DS.[164,165]

There are several possible mechanisms underlying the development of hypothyroidism over time in DS. Defective embryological migration and differentiation of thyroid cells and/or foetal failure to form the thyroid gland, resulting in agenesis or hypoplasia, respectively, have been postulated.[62] A DS-specific thyroid (regulation) disorder caused by a genomic dosage imbalance has recently been suggested as yet another mechanism.[3,166] Data that may support the occurrence of reduced thyroid hormone sensitivity in DS have also been produced,[63] and it is well known that children and adults with DS are prone to develop autoimmune thyroid disease, which may result both in subclinical and in manifest hypothyroidism.[59,64]

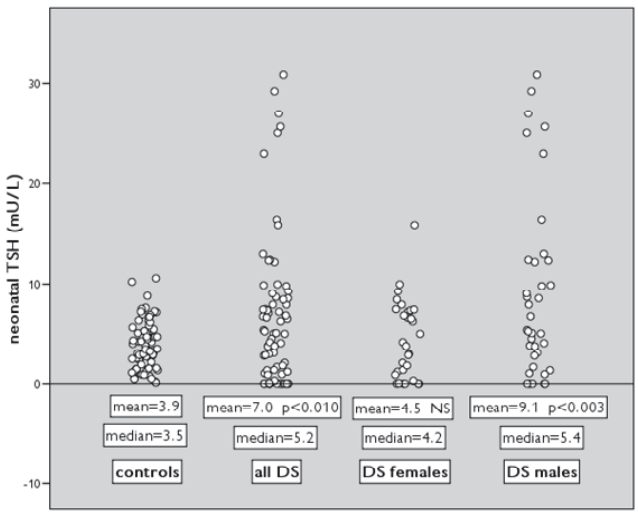

Figure 14. Distribution of TSH levels observed at the neonatal screening of controls and DS infants. The control markers represent means from 78-251 samples analysed in the same set as each child with DS. The p values are calculated in comparison with controls.

Differences between the genders

Females are generally overrepresented among patients with thyroid disease,[167,168] but available data do not indicate such a gender difference among people with DS.[61] Our data on the occurrence of manifest hypothyroidism in children with DS during the first decade of life did not differ in this respect.

Although congenital hypothyroidism, detected at neonatal screening, is generally more common in girls than in boys,[169,170] male infants have been shown to have elevated TSH levels in cord blood.[171] Furthermore, an association between low Apgar score and elevated cord blood TSH has

been reported[172] and it is known that male foetuses are associated with higher incidence rates of unfavourable perinatal outcome in general.[173,174] With these associations borne in mind, the difference in neonatal TSH between the genders could be due to higher foetal stress during labour in the male infants. However, among the DS children there was no difference in Apgar score either between the males and females or between subgroups with different TSH levels. The results of study II are compatible with the previously reported occurrence of mild hypothyroidism in DS infants.[60,159,175,176]

Thyroxine therapy

The attitude towards thyroxine treatment of DS children with evidence of subclinical hypothyroidism is usually liberal. Thyroxine replacement is easy to carry out and no adverse effects have been reported in children with DS and subclinical hypothyroidism.[61,177] In addition, beneficial effects of thyroxine on growth and mental development have been observed in DS during the first two years of life.[155]

Conclusions

Diagnosis-specific growth charts for Swedish children with Down syndrome have been established, facilitating diagnosis of any concomitant disease that may influence growth. The growth charts are available for child health care workers throughout Sweden, and are included in several of the hospital record software systems used in Sweden.

Infants with DS, boys in particular, have an increased mean TSH concentration at neonatal metabolic screening, indicating marginal hypothyroidism. The TSH level does not predict development of manifest hypothyroidism during childhood.

Early growth hormone treatment (for three years) in children with Down syndrome seems to have some late beneficial effects. The early treatment had no effect on final height, but the treated subjects had an increased adult head circumference and showed some improvement in cognition and motor development.

Young adults with Down syndrome have a normal capacity to produce growth hormone.

When target height is calculated in individuals with Down syndrome, 20 cm should be subtracted to compensate for the short stature in DS.

Body proportions are altered in Down syndrome. That is, the relative sitting height is increased, indicating short legs in relation to the trunk. The short legs are matched by equally short arms.

Overweight and obesity are common in DS, and as many as one-third of the population are overweight at the age of 18. The high prevalence of overweight/obesity is in line with the findings of an increased proportion of fat body mass and a decreased lean body mass percentage in assessment of body composition.

Young adults with Down syndrome show increased rates of glucose production and lipolysis when compared with reported data on individuals without DS. Further, there is a relative reduction of peripheral and hepatic insulin sensitivity in subjects with DS.

Summary in Swedish – Tillväxt och hormonbalans vid Downs syndrom

Downs syndrom (DS) är en vanlig kromosomavvikelse med ett fall på 800 födda barn i Sverige. Syndromet beskrevs 1866 av den brittiske läkaren John Langdon Down och fick därmed sitt namn. Först hundra år senare, 1959, kunde man visa att DS orsakas av en extra kromosom 21, dvs. trisomi 21.

Individer med Downs syndrom har flera yttre gemensamma drag vilka beskrevs av den svenska barnläkaren Bertil Hall 1965. Halls tecken används än idag som stöd vid diagnos, ju fler tecken desto högre sannolikhet att det undersökta barnet har DS. Säker diagnos ställs dock med hjälp av kromosomanalys.

Kortvuxenhet och utvecklingsstörning är kardinaltecken vid DS, men det finns stor individuell variation. Personer med DS har dessutom ökad risk för andra tillstånd och sjukdomar, till exempel medfödda hjärtfel, glutenintolerans, ämnesomsättnings- och hormonrubbningar. Studierna som ingår i avhandlingen behandlar tillväxt och hormoner som påverkar tillväxten.

Studie I: Tillväxtkurvor för svenska barn med Downs syndrom

Fysisk tillväxt är en god indikator på barns hälsa, på både individuell nivå och befolkningsnivå. Tillväxtkurvor är ett viktigt instrument inom barnhälsovård då de möjliggör tidig upptäckt av sjukdom som påverkar tillväxten, till exempel sköldkörtelhormonbrist och glutenintolerans. Barn med Downs syndrom är redan från födseln mindre än andra barn och då är det lätt att förbise ytterligare försämrad tillväxt. Eftersom dessa barn dessutom i hög grad drabbas av sådana sjukdomar finns ett behov av diagnosspecifika tillväxtkurvor.

Kurvorna är baserade på 4 832 undersökningar av totalt 354 svenska barn med DS födda mellan 1970-1997 och illustrerar tillväxt från födelse till 18 års ålder. I studien görs också en jämförelse mellan svenska och amerikanska barn med DS samt mellan svenska barn med respektive utan DS. Svenska barn med DS är längre än jämnåriga amerikanska barn med DS, men fortfarande avsevärt kortare än svenska barn utan DS. Inom stu-

dien kunde vi även påvisa att var tredje individ med DS vid 18 års ålder är överviktig (BMI >25 kg/m^2).

Tillväxtkurvorna för svenska barn med DS är ett användbart redskap för att upptäcka ytterligare tillväxtrubbning tidigt inom denna patientkategori och de finns idag tillgängliga för alla som arbetar med barnsjukvård eller barnhälsovård.

Studie II: Sköldkörtelhormon hos nyfödda med Downs syndrom förutsäger inte senare sjukdom

Sköldkörtelhormon har flera viktiga funktioner i kroppen, från fosterstadiet och livet ut. Brist på sköldkörtelhormon, som uppkommer under barndomen, orsakar bland annat minskad längdtillväxt, trötthet och förstoppning. Medfödd brist på sköldkörtelhormon är ovanlig, men kan obehandlad leda till svår utvecklingsstörning. Alla barn som föds i Sverige undersöks avseende medfödd brist på sköldkörtelhormon i samband med PKU-provtagningen. Barn med DS har en nästan 30-faldigt förhöjd risk för medfödd brist på sköldkörtelhormon och det är dessutom vanligt att de utvecklar sköldkörtelhormonbrist senare i livet.

Vi undersökte, i samarbete med PKU-laboratoriet, nivåerna av sköldkörtelhormon i nyföddhetsperioden hos 68 barn med DS. Dessutom utreddes om dessa nivåer kan förutsäga en sköldkörtelhormonbrist senare under barndomen. Studien kunde påvisa att barn, i synnerhet pojkar, med DS har höjda TSH-nivåer som nyfödda, vilket indikerar mild brist på sköldkörtelhormon. TSH-nivåerna kunde dock inte prediktera utveckling av sköldkörtelhormonbrist senare under barndomen.

Studie III: Seneffekter av tillväxthormonbehandling vid Downs syndrom

Längdtillväxt under spädbarnsperioden är i stor utsträckning beroende av nutrition, men från sex månaders ålder blir betydelsen av tillväxthormon (GH) allt större. GH stimulerar tillväxt genom ökad produktion av tillväxtfaktorn IGF-I. Mekanismen bakom kortvuxenheten vid DS är alltjämt okänd, men man har kunnat påvisa låga nivåer av IGF-I, trots relativt normala nivåer av GH, hos barn med DS.

I en tidigare studie då 15 barn med DS behandlades med GH från 6 månaders ålder och tre år framåt kunde man se tydlig effekt på längdtillväxten. Dessutom påvisades en något förbättrad finmotorisk utveckling, men ingen effekt på huvudomfång, mental utveckling eller grovmotorik, vid jämförelse med 15 andra jämngamla barn med DS. Både de ungdomar som behandlades för ca 15 år sedan och kontrollungdomarna

erbjöds delta i denna uppföljningsstudie med syfte att undersöka eventuella seneffekter av behandlingen.

Det fanns inga skillnader mellan grupperna gällande slutlängd eller vikt, men de GH-behandlade ungdomarna hade ett större huvudomfång än kontrollerna. Båda grupperna presterade snarlika resultat vid de psykomotoriska bedömningarna, men då i relation till normalvärden baserade på jämnåriga individer utan utvecklingsstörning. Om man i stället analyserade hur många uppgifter de egentligen klarade, dvs. råpoängen, i varje delmoment av undersökningen, så presterade ungdomarna som behandlats med GH bättre än kontrollerna på samtliga delmoment utom ett där poängen var identiska.

Det större huvudomfånget i kombination med bättre prestation vid de psykomotoriska bedömningarna indikerar att individer med DS kan ha nytta av tillväxthormon med avseende på psykomotorisk utveckling.

Studie IV: Insöndring av tillväxthormon hos unga vuxna med Downs syndrom

Tillväxthormon har välkända effekter på barns tillväxt, och i vuxenlivet vet man att hormonet påverkar ämnesomsättning och psykologiskt välbefinnande. Insöndringen av GH sjunker normalt med stigande ålder, men en bristsituation kan alltjämt uppstå. De symtom man ser hos vuxna individer med GH-brist, till exempel övervikt med ökad fettmassa, beteendeavvikelser med minskad initiativförmåga och försämrad fysisk prestationsförmåga, återfinns även hos vuxna med DS. Mot denna bakgrund har man ifrågasatt förmågan att insöndra GH hos vuxna individer med DS.

Tio unga vuxna med DS och tio köns- och åldersmatchade kontroller har studerats avseende GH insöndring och kroppssammansättning. Dessutom undersöktes fettomsättning samt glukosproduktion hos individerna med DS.

Inga skillnader kunde påvisas avseende GH-nivåer mellan grupperna, dvs. unga vuxna med DS har en normal förmåga att insöndra GH. BMI var högre i DS-gruppen än i kontrollgruppen, bara en av individerna med DS hade normalt BMI. Vid undersökning av kroppssammansättning kunde man påvisa ökad andel fettvävnad. Dessutom förelåg minskad bentäthet vid DS jämfört med kontrollerna.

Individerna med DS hade högre fasteblodsocker och insulinnivåer än kontrollerna samtidigt som deras leverproduktion av glukos under fasta var högre än det normalmaterial som finns publicerat. Därutöver var även lipolysen, dvs. omsättningen av depåfett, förhöjd i DS-gruppen i jämförelse med publicerat normalmaterial. Resultaten talar för att unga vuxna med Downs syndrom har en nedsatt insulinkänslighet både perifert och på levernivå i jämförelse med friska individer.

Acknowledgements

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