Chapter 4. Conclusions

Overview

In this chapter, we discuss the conclusions resulting from our evaluation of the three questions asked by the Social Security Administration (SSA). We also describe the limitations of the existing studies related to disability and short stature as well as the relationship between chronic disease and decreased growth.

This report summarizes the scientific evidence in regard to three questions attempting to determine if children with short stature are disabled because of their short stature, if children with short stature secondary to a skeletal dysplasia are disabled and if decreased growth velocity can be related to severity of chronic disease.

The results presented in Chapter 3 are based on the screening of 13,537 MEDLINE® citations and the review of 825 full articles.

Question 1. Is short stature (height less than the 5th percentile) as a result of a medically determinable impairment associated with severe functional Limitations, according to, but not limited to, SSA's definition of disability?

There were 23 studies that provided information on functional abilities among children with short stature due to medically determinable impairments. Fifteen were prospective cross-sectional studies; seven were prospective longitudinal studies; and one was a retrospective longitudinal study. Two were of good quality, eleven were of fair quality, and nine were of poor quality. One study was of fair quality in its analysis of intelligence, but of poor quality in its analysis of academic achievement.

Based on the reviewed articles, no severe functional limitations were found in children with short stature due to growth hormone deficiency, multi-hormone deficiency, Turner syndrome, Russell-Silver syndrome or isolated short stature. These specific causes of short stature were chosen because they allowed us to isolate the effect of short stature and thus enabled us to determine if there was an increased risk for disability-related problems due just to short stature. The articles focused on intelligence, academic achievement, behavior, visual-motor perception, and psychomotor development. In each of these categories, children with short stature either had testing that was not significantly different from the controls or from the population mean, or if the testing were significantly poorer it was still for the most part within 1 standard deviation (SD) of the population mean.

Academic Achievement

Eleven studies evaluated the relationship between academic achievement and short stature. Five of the studies found that children with short stature had academic achievement scores at or above the population norm. The other six studies found scores below the population norm but the great majority of subjects were still within 1 SD of the mean. These results imply that children

with short stature do not have enough difficulties with academic achievement to qualify as a disability. A major limitation in five of the studies was the exclusion of children with a low intelligence quotient (IQ). Further studies that look at academic achievement in a large unselected population of children with short stature and compares them to matched controls are needed to more clearly delineate this relationship.

Intelligence

Intelligence was evaluated in 21 studies of children with short stature. Fifteen studies found short stature children to have IQs at or above the population mean, while the remaining studies reported IQs for the most part less then 1 SD below the mean. Three of the studies that found IQs at or above the mean excluded children with low IQs. The studies were limited by the IQ exclusion and also by an absence of a control population in many of the studies. Future studies are needed to better delineate this question.

Visual-Motor Skills

Only three studies could be found that evaluated visual-motor perception in children with short stature. All three found significantly lower visual-motor skills in the evaluated children. These studies, however, were limited by their reporting of the data. Furthermore, it is not clear how a decrease in visual-motor skill can be correlated with the SSA definition of disability. Future studies are needed to evaluate disabilities caused by functional limitations in visual-motor skills.

Developmental Skills

Only one study evaluated developmental skills in a group of children with short stature. These children, who had Russell-Silver syndrome, were found to have delays in meeting their developmental landmarks. However, the value of this finding in relation to disability is questionable since the children did eventually meet their developmental landmarks (e.g., walking). Future studies are needed to determine the significance of these findings.

Behavior

Teacher-based evaluation of behavior in children with short stature was reported in seven studies. In general, behavior in the children with short stature was not significantly different from the controls. Exceptions to this were increased hyperactivity reported in one study, increased locus of control in another study, and general increased behavior problems in a third study. It is difficult to extrapolate behavior in general from these studies since they tended to use different tests, and the test results do not always overlap. In addition, sub-group results were not given for each study. Furthermore, the value of behavioral impairments for determining a child's level of disability is questionable. Further studies are needed that evaluate large groups of non-selected short stature children, use the same behavior based test, compare results to matched controls, and determine likelihood of disability.

Question 2. What is the evidence that short stature (height less than the 5th percentile) due to a skeletal dysplasia is disabling according to, but not limited to, SSA's definition of disability? If so, are children disabled by virtue of their size or other features of their conditions?

There were 31 papers from 25 study groups that provided information on functional abilities among children with short stature due to skeletal dysplasia. Of the studies, 22 were prospective cross-sectional studies; five were prospective longitudinal studies; two were retrospective longitudinal; and two were retrospective cross-sectional. One was of good quality, 16 were of fair quality, and 12 were of poor quality. One study was of good quality in its analysis of academic achievement, but of fair quality in its analysis of ambulation and mobility. One study was of fair quality in its analysis of neuromuscular function and range of motion, but of poor quality in its analysis of ambulation and mobility.

Based on the articles reviewed, children with skeletal dysplasias were not at increased risk of having severe impairments in intelligence, academic achievement, or psychological outcome. There was an increased risk for delay in achievement of motor skills in children with achondroplasia and osteogenesis imperfecta, and decreased ambulation, range of motion and mobility in children with more severe forms of osteogenesis imperfecta. The results for hearing impairment, respiratory dysfunction and spinal curvature appear to indicate an increased risk for impairment in these three areas, but the studies were limited in the number of children evaluated and how the samples were selected, thus making it difficult to arrive at a definitive conclusion in these areas.

Academic Achievement

Three studies examined academic achievement among children with achondroplasia or osteogenesis imperfecta. In two studies, achondroplasia patients scored lower than control groups, yet remained in the normal range. Further studies on this issue are needed to evaluate a larger population of children with achondroplasia, osteogenesis imperfecta and other types of skeletal dysplasias.

Intelligence

Five studies evaluated intelligence in children with achondroplasia, osteogenesis imperfecta and other skeletal dysplasias. No evidence of significantly impaired intelligence was found in any of the skeletal dysplasias by intelligence testing with all scores either above the population norm or within 0.5 SD of the norm. These studies were generally small for the comparisons made. Further studies on this issue are needed to evaluate a larger population with skeletal-dysplasias clearly defined by up-to-date standards.

Psychomotor Development

Six studies found generally delayed achievement of psychomotor abilities or development in children with achondroplasia and osteogenesis imperfecta. Each group evaluated was small, used different testing instruments, and had varying ages of subjects. Furthermore, none was followed longitudinally. Clinically useful conclusions about ultimate motor function in children with

skeletal dysplasias cannot be made from these studies. Larger, longitudinal studies are needed that test psychomotor functional abilities.

Neuromuscular

From review of the available literature, children with short stature due to various skeletal dysplasias appear to be at risk for neuromuscular abnormalities. Six studies evaluated neuromuscular function in children with skeletal dysplasias. The four studies that looked solely at children with achondroplasia found varied abnormalities. The three that measured strength found substantial weakness and hypotonia. Asymmetry, sensory deficits, poor coordination, and seizures were found in frequencies higher than controls or than are expected in the healthy population. All studies highlighted the significant risk of often occult cervical cord compression in these young children. The one paper that evaluated osteogenesis imperfecta found substantial muscle weakness in children who are moderately to severely affected their disease. The one paper that reviewed other skeletal dysplasias found cervical cord complications in children with Morquio disease. Further studies of children with skeletal dysplasias, especially achondroplasia, are needed to better delineate the extent of neuromuscular impairment.

Ambulation and Mobility

Of the eight papers considering ambulation and mobility in children with short stature due to skeletal dysplasia, all considered children with osteogenesis imperfecta. All found significant impairment in ambulation, with greater impairment, as expected, in patients with more severe disease. Children with the less severe types of osteogenesis imperfecta (tarda, Type I, Type IV) were more likely to attain some walking capability, although a substantial proportion of these children did require assistance. Orthopedic abnormalities such as scoliosis, decreased range of motion, decreased muscle strength and fracture contribute to limitations of ambulation. All of the studies were of small size; although given the rarity of osteogenesis imperfecta, the studies were of reasonable size. Definitions of levels of ambulation were consistent and fairly objective. Studies of ambulation and mobility disabilities are necessary for children with skeletal dysplasias other than osteogenesis imperfecta.

Limb Range of Motion

Two studies evaluated upper and lower range of motion (ROM) abnormalities in children with various types of osteogenesis imperfecta and with achondroplasia. Decreased ROM was found in children with osteogenesis imperfecta, but no such correlation was seen in children with achondroplasia. Decreased lower extremity ROM may impact on ability to independently ambulate. Decreased upper extremity ROM may limit an individual’s independence by reducing his or her ability to engage in self-care. Further studies are necessary to better delineate the connection between limb ROM and various skeletal dysplasias.

Spinal Curvature

Four papers assessed spinal deformities in children with short stature due to skeletal dysplasia. Three studied children with osteogenesis imperfecta, and one studied children with

diastrophic dysplasia. A high prevalence of scoliosis was found in children with both conditions. One study also found a high prevalence of pathologic kyphosis. All studies, however, likely represent a selected, perhaps more severe, population of patients followed by academic medical centers. Thus to find prevalence in the general population of individuals with skeletal dysplasias, it will be necessary to evaluate scoliosis and kyphosis in a group of unselected individuals with skeletal dysplasias.

Hearing Loss

Of the six studies that reported on hearing loss in children with skeletal dysplasia, only three performed objective hearing testing. All papers that reported actual hearing testing in young osteogenesis imperfecta patients reported a sizable proportion with hearing loss, although the prevalences varied due to selection and cohort size differences. Subjective reports of hearing problems in achondroplasia patients were common. One study did not show a high level of self-report of hearing in patients with a mix of skeletal dysplasias, including achondroplasia. The available literature supports that children with at least some skeletal dysplasias, specifically achondroplasia and osteogenesis imperfecta, are at risk for hearing problems. Further studies with a larger, unselected population of children with skeletal dysplasia are needed to better define the extent, severity and type of hearing loss.

Sleep Apnea and Respiratory Dysfunction

Of the four papers evaluating sleep and respiratory dysfunction in children with achondroplasia, all found a high incidence of abnormality, including central hypopnea, central apnea, and obstructive apnea. All four papers, however, reported on small numbers of children. Two of the groups contained patients referred for their respiratory or neurologic symptoms, and therefore may not represent the general achondroplasia population. Further studies that look at larger groups of non-selected achondroplasia patients are needed to define the prevalence of apnea in this population.

Little information on pulmonary function in children with skeletal dysplasia was found. One group found abnormal pulmonary function in a small group of children with achondroplasia, and one found no significant abnormality in a smaller group of children with osteogenesis imperfecta. More data are required before meaningful conclusions can be drawn.

Psychology

Only one paper was found that adequately studied the association of short stature due to skeletal dysplasia with psychological outcomes. The study found no evidence for increased rates of depression or anxiety in children with skeletal dysplasia. Further studies that evaluate psychological problems such as depression and anxiety are needed to validate these results.

Question 3. What is the evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of an underlying Disease? Is such a process likely to be disabling?

We reviewed 53 articles that evaluated whether a sustained decrease in linear growth velocity can be used as a marker of the severity of 12 medical conditions and whether such a process is likely to be disabling. Nineteen were prospective longitudinal studies, 19 were retrospective longitudinal studies, 10 were prospective cross-sectional studies, and five were retrospective cross-sectional studies. Four were of good quality, 29 were of fair quality, and 20 were of poor quality. The evidence from four conditions (congenital heart disease, juvenile rheumatoid arthritis, Crohn's disease and (human immunodeficiency virus infection (HIV)) appear to indicate that a sustained decrease in linear growth velocity can be used as a marker of the severity of these underlying conditions. Evidence is less clear for asthma, atopic dermatitis, diabetes, ß-thalassemia, and chronic kidney failure. There was only one study for sickle cell disease, congenital adrenal hyperplasia and cerebral palsy so it is difficult to draw conclusions for these conditions. None of the studies addressed the question of whether the process of having a decreasing linear growth velocity was likely to be disabling.

Asthma

Eleven studies evaluated the relationship between the severity of asthma and growth retardation. Overall, the studies did not find a consistent result. Six of the studies found no association between severity of asthma and growth retardation. No study found an association between mild asthma and growth retardation.

Studies were limited by poorly defined samples, limited data and analysis, missing data and, frequently, by the fact that severity of disease was measured by steroid treatment. These studies do not clearly provide evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of asthma or whether a decrease in growth velocity is likely to be disabling. Future well-designed studies are needed.

Congenital Heart Disease

There were six studies that evaluated the relationship between congenital heart disease and growth retardation. Many studies were limited by incomplete data and statistical analysis and some studies were limited because they excluded children with the most severe congenital cardiac defects. Given the limitations, the results do suggest that height and height velocity retardation is seen in children with severe congenital heart defects and may be a marker for more severe disease. Whether the decrease in height or height velocity in itself is disabling is not answered.

Diabetes Mellitus

Eleven studies evaluated the relationship between growth retardation and control or severity of insulin dependent diabetes mellitus. Overall, the studies showed mixed results with five studies demonstrating a positive relationship between poor diabetes control or increased severity of disease and decreased growth velocity. Several studies associated growth deceleration with

peripubertal onset of illness. Some studies were limited because they did not use a well-defined, objective measure, such as glycohemoglobin (Hgb A_{1c}), to assess severity or control. Some studies were limited by unclear statistical analysis, lack of specific data included or summary results. These studies did not find clear evidence that a sustained decrease in linear growth velocity can be used as a marker of severity of diabetes or whether a decrease in linear growth velocity is in itself disabling. Further prospective, longitudinal studies of the linear growth of children with diabetes mellitus, using objective measure of control like Hgb A_{1c}, are needed to clarify whether a decrease in linear growth velocity may be a marker for severity of disease.

β-Thalassemia

There were three studies that evaluated the relationship between growth retardation and severity of anemia in ß-thalassemia. One study showed a relationship between increased severity of anemia and reduced height and one study showed a trend toward increased severity of disease and decreased growth. The studies were limited by incomplete data reporting and by inconsistent definitions of severity. These studies do not show clear evidence that a sustained decrease in linear growth velocity can be used as a marker of the severity of the disease. Prospective longitudinal cohort studies with clear definitions of severity (i.e. hemoglobin levels) and measurements of height velocity may answer the question.

Inflammatory Bowel Disease

There were three studies evaluating the relationship between growth retardation and the severity of inflammatory bowel disease. Two studies included only children with Crohn's disease. The other two studies included children with both Crohn's disease and ulcerative colitis. Disease severity was associated with height velocity among children with both Crohn's disease and ulcerative colitis; however, height was not significantly associated with disease severity in any study. There are no data presented to suggest that the process of growth failure is likely to be disabling. Further prospective longitudinal studies that include both larger numbers of patients with ulcerative colitis patients and Crohn's disease and that compare both to population standards and to each other may clarify whether growth retardation is a marker associated with severity of all inflammatory bowel diseases, or is related to one in particular.

Juvenile Rheumatoid Arthritis

Three studies evaluated the relationship between growth retardation and the subtypes or severity of juvenile rheumatoid arthritis. All studies indicated an association between decreased growth velocity and increased severity of the disease. One study noted that height velocity normalized after the first year of treatment. The studies were limited in two cases by excluding children with the most severe disease, by incomplete statistical analyses in one, and by poorly defined outcomes in another. With these caveats, the studies suggest that a decrease in linear growth velocity is associated with more severe disease and may serve as a marker of severity of the underlying disease. There are no data reported addressing the question of whether decreased growth velocity is in itself disabling. Future well-designed studies with broad inclusion criteria are needed to clarify the issue.

Chronic Kidney Disease

Ten studies evaluated the relationship between growth retardation and severity of chronic kidney disease. Eight of the studies found a positive relationship between increased severity of kidney failure and decreased height or height velocity. Single studies of sub-populations of children with autosomal recessive polycystic kidney disease (ARPKD) and very young children with chronic kidney disease found no association of disease severity with height velocity. There was conflicting evidence about the role of steroid use in causing growth retardation. Some studies were limited by using a severity marker other than glomerular filtration rate, by small sample sizes, or by incomplete data reporting. Overall, the studies suggest that a decrease in linear growth velocity is associated with the severity of the underlying disease but this finding was not universal. No data were available to assess if a decreased height velocity is in itself disabling. Additional prospective, longitudinal studies that evaluate whether a decrease in linear growth velocity can be used as a marker of severity of underlying kidney disease are needed.

Human Immunodeficiency Virus Infection

There were two studies evaluating the relationship between growth retardation and progression to disease in HIV positive children. Both studies found that linear growth retardation is a marker for progression to active disease in HIV positive children and linear growth deceleration may precede the onset of symptoms of active disease. These studies were limited by incomplete data reporting and poorly defined methods, predictors and outcomes. Despite the limitations, the studies do indicate that a sustained decrease in linear growth velocity is a marker for progression from seropositive status to active disease. No data were included that assess whether a decreased linear growth velocity is in itself likely to be disabling. Larger, prospective, longitudinal studies of the relationship between decreasing linear growth velocity and progression of disease could confirm the usefulness of decreased linear growth velocity as a marker for increasing severity of disease.

Atopic Dermatitis

Two studies evaluated the relationship between growth retardation and severity of atopic dermatitis. The studies reported conflicting results with one study reporting a positive association between increased severity and decreased height and the other study showing no association between increased severity and decreased height or height velocity. In the first study the more severely affected group had higher steroid use and some used systemic steroids. In the second study, those using systemic glucocorticoids were excluded from analysis. This study was also limited by a failure to report complete results and a failure to report statistical analyses. These studies do not clearly provide evidence that a sustained decrease in linear growth velocity is a marker for the severity of the underlying disease. No data were provided that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies are needed to clarify whether growth velocity is affected by the severity of atopic dermatitis, or whether the apparent effect is related to steroid treatment.

Cerebral Palsy

There was only one study with 81 subjects that looked at the relationship between growth retardation and cerebral palsy. The study did not find a significant association between the type of cerebral palsy and decreased growth velocity but cognitive impairment and non-ambulatory status were associated with decreased growth velocity. This suggests that those more severely affected by both motor and non-motor neurological deficits have decreased growth velocity. This study was limited by the exclusion criteria, which likely excluded the most severely affected children. No data were presented to answer the question about whether the process of having a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of children with varying severity of cerebral palsy are needed to confirm whether a decreasing linear growth velocity is a marker for the severity of the underlying disorder.

Sickle Cell Disease

There was only one study with 24 subjects that evaluated the association of growth retardation with the severity of sickle cell disease. That study found a positive association between severe sickle cell disease (measured by need for transfusions and the number of crises) and decreased height percentile compared to controls. The study was small and did not explicitly compare less severe sickle cell disease to more severe disease. The study also did not look at height velocity as a predictor of more severe disease. Further prospective longitudinal studies that compare larger numbers of patients with mild, moderate and severe sickle cell disease are needed to determine if a decreasing linear growth velocity can serve as a marker for the severity of the underlying disease.

Congenital Adrenal Hyperplasia

There was only one study with 9 subjects that looked at the relationship between growth retardation and congenital adrenal hyperplasia. It did not find an association between number of escapes (more severe disease) and decreased growth velocity. The study was limited by its small size and by its reporting of results in graphic form only. There is not clear evidence that a decreasing linear growth velocity can be used as a marker for the underlying severity of congenital adrenal hyperplasia. No data were presented that look at whether the process of a decreasing linear growth velocity is in itself disabling. Further prospective longitudinal studies of larger numbers of patients with congenital adrenal hyperplasia are needed to answer the question of whether decreasing linear growth velocity can be used as a marker for severity of the underlying disease.

Limitations

There were several limitations encountered in evaluating Questions 1 and 2. Very few studies looked specifically at disability as defined by SSA. Most studies in fact were looking at functional ability such as IQ or academic achievement. Such areas are focused on in the published literature because they allow for acquisition of data that can be compared to published norms. Results from such studies have to be extrapolated to determine if the children evaluated meet the SSA definition of disability. For example, one SSA criterion of disability includes

acquiring and using information. A significantly reduced IQ in a child may lead to such limitations, but there is not a clear relationship between IQ and difficulties in acquiring and using information. Even those studies that evaluated functional impairment, such as those that evaluated inability or limitation of walking, do not necessarily correlate directly with SSA's definitions of disability. A further limitation to evaluation of intellectual function for Questions 1 and 2 is that many relevant articles excluded children with limited IQ. Similar biases due to eligibility criteria and sample choices limit the generalizability of many of the studies.

One limitation to evaluating Question 3 relates to difficulties in trying to correlate the severity of disease with decreasing growth velocity. Frequently a report that details height in a specific disorder does not directly correlate this with severity of disease. Also the way in which severity of disease was reported may vary between reports discussing the same disease. The same problem was seen with the reporting of growth data, which is given in a variety of different formats (e.g., one-time height, growth velocity, and standard deviation from the mean). This makes it more difficult to determine the overall validity of the results.