Diagnostic Approach in Children with Short Stature

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Introduction

Growth monitoring in infancy and childhood has been part of preventive child health programs for more than a century, and short stature or growth retardation are regarded as relatively early signs of poor health. Growth failure occurs all over the world, and there are no indications that pathological causes of primary or secondary growth failure have a different prevalence in different countries, except for growth failure caused by malnutrition which is obviously strongly dependent on socio-economic circumstances. Despite the similarity of the clinical presentation of growth failure in different parts of the world, there is a substantial variation in the national guidelines for the diagnostic approach to short stature \cite{1}. Although at a consensus meeting on idiopathic short stature (ISS) \cite{2, 3} a list was proposed, there was little scientific basis for it.

In the diagnostic approach two questions are important. (1) Which criteria should be used to refer children with impaired growth and to start diagnostic procedures? (2) What kind of diagnostic approach should be followed in the referred group of children? In this review the literature on this issue will be discussed, and practical guidelines for growth monitoring and diagnostic proce-

Key Words
Growth · Short stature · Growth disorders

Abstract
For early detection of pathological causes of growth failure proper referral criteria are needed, as well as a thorough clinical, radiological and laboratory assessment. In this mini-review we first discuss the two consensus-based and one evidence-based guidelines for referral that have been published. The evidence-based guidelines result in a sensitivity of approximately 80\% at a false-positive rate of 2\%. Then, relevant clues from the medical history and physical examination are reviewed, and specific investigations based on clinical suspicion listed. In the absence of abnormal clinical findings, an X-ray of the hand/wrist and a laboratory screen are usually performed. Scientific evidence for the various components of laboratory screening is scarce, but accumulated experience and theoretical considerations have led to a list of investigations that may be considered until more evidence is available.
Referral Criteria for Children with Short Stature

In the evaluation of growth [supine length or standing height (stature)] there are basically three parameters that can be assessed. First, height can be compared with age references, and expressed as standard deviation score (SDS) or centile position. Height SDS (HSDS) is a measure of the deviation of the individual height from the mean, and is expressed as the number of standard deviations below or above the mean height of the population for the same age and sex. Second, HSDS can be compared with the sex-corrected midparental height (target height) SDS. There are several methods to calculate target height, which we recently summarized [2]. The formula proposed by Hermanussen and Cole [4] may be most firmly based on theoretical arguments, but its value has not been confirmed. If there is a substantial secular trend, the target height formula should be corrected for that (in The Netherlands a correction factor of 4.5 cm/30 years is used). Third, a longitudinal analysis of growth can be used, either expressed as height velocity (cm/year or SDS) in comparison to age references, or as an HSDS deflection (deviation) from the original SDS position (delta HSDS, which is the difference in HSDS between two measurements, preferably approximately 1 year apart).

Guidelines for growth monitoring should ideally have a high sensitivity (true positive rate), so that they detect a high percentage of pathological causes of impaired growth, as well as a high specificity (true negative rate), so that the health system is not overburdened with referrals with a low yield of pathology. As far as we know only four guidelines have been published on referral criteria and diagnostic workup for children with impaired growth. The first was the Finnish guideline, based on a longitudinal dataset of normal infants and children [5–7]. This guideline is still in use in Finland, and is based on cutoff limits for HSDS minus target height SDS (±2.3) and on a range of cutoff limits for delta HSDS (depending on age and the length of the age interval). There are no data on its sensitivity and specificity.

Two growth monitoring guidelines were based on consensus meetings [8, 9]. The United Kingdom guideline (‘Coventry Consensus’) concentrates on the referral of children with short stature after a single height measurement at school entrance [a height <0.4th centile (−2.66 SDS) at 5 years of age] [8]. Recently a discussion about this criterion was started after the publication of a systematic review by Fayter et al. [10] about height screening during the primary school years. In an editorial, Fry [11] pleaded for measuring parents and at least three or four height measurements to be put back on the UK agenda. Hall et al. [12] agreed that the issue of adjusting the school entry height measurement for parental height deserved to be revisited, but also mentioned the low coverage and inaccurate measurements in the UK and pleaded for a better implementation of the ‘Coventry Consensus’.

The Dutch consensus guideline focused on the three auxological referral criteria mentioned above: HSDS, change in HSDS (HSDS deflection) and distance between HSDS and target height SDS [9]. Besides these three growth criteria, it was emphasized that it specifically assesses the presence of body disproportion, defined as an abnormal sitting height/height ratio, in view of the high likelihood of a primary growth disorder in short children with abnormal body proportions. Other criteria included the presence or absence of dysmorphic features, specific symptoms (such as those associated with emotional deprivation), or a history of low birth weight and/or length (small for gestational age). The sensitivity of this guideline was reasonable [13], but it was shown that application of these auxological criteria would lead to far too many unnecessary referrals (approximately 25%), and thus to an unacceptably low specificity of 75% [14].

For this reason an evidence-based guideline for the referral of children with short stature was developed (fig. 1) [15]. A large difference in the efficacy and efficiency of referral criteria between infants and toddlers (0- to 3-year-olds) and children between 3 and 10 years old was found. Between 0 and 3 years of age the decision rules involving target height and length deflection had a low predictive value, and the only useful referral rule for this age group was based on an extremely low or repeatedly low HSDS. With such criteria, only 15–26% of the growth disorders studied was detected, at a specificity of approximately 98%. In subsequent studies comparing growth of 0- to 3-year-old children with celiac disease (CD) or cystic fibrosis (CF) we showed that body mass index is a better auxological tool than length [16–18].

In our analysis the best decision rule for detecting children of 3–10 years with pathology was the ‘short for target height’ rule (HSDS minus target height SDS <2 and HSDS <2), detecting 77% of the girls with Turner syndrome and 59% of the children with short stature due to mixed pathology as detected after referral. The combination of the HSDS rule (an HSDS <−2.5), the target
height rule and the height deflection rule (an HSDS decrease >1.0 SD) detected 86% of girls with the Turner syndrome and 77% of children who were short because of various disorders. The estimated specificity of this approach was 98%. Insufficient data were available to give evidence-based guidelines for children >10 years. One might consider referral and diagnostic procedures in this age group if HSDS >–2.5.

If one compares the UK consensus guideline and the recent evidence-based Dutch guideline, it is clear that the sensitivity of the latter must be higher, and that pathology will be detected at a younger age. For example, based upon the Dutch evidence-based guidelines a diagnosis would be made before the age of 3 years in 30% of the children with pathology. In contrast, according to the UK consensus these children would not have been diagnosed at that point, as this consensus recommends a single measurement at the age of 5 years [13]. On the other hand, the specificity of the UK guideline is considerably higher (99.5 vs. 98%). Validation of these and other guidelines in prospective studies are needed, possibly in combination with a cost-benefit analysis, before a definite conclusion can be drawn.

**Diagnostic Procedures**

**Classification of Growth Disorders**

When a child is referred to a pediatrician, the diagnostic process is aimed at detecting the cause of his/her
shortness. In most diagnostic classifications, including the ESPE Classification of Paediatric Endocrine Diagnoses, three main groups of growth disorders are distinguished: primary growth disorders (conditions thought to be intrinsic to the growth plate), secondary growth disorders (conditions that change the milieu of the growth plates), and a remaining group in which no recognizable cause is found (table 1) [19]. This last group is currently known as ISS. In two recent reviews [2, 20] and a consensus statement, diagnosis and management of ISS were extensively described [3]. ISS is subdivided into familial and nonfamilial short stature, and both can be further subcategorized into children with delayed and normal puberty. The last category is roughly equivalent with the clinical entity ‘constitutional delay of growth and puberty’. For a good differential diagnosis the patient’s history, physical examination and growth data should be collected to determine signs and symptoms that may indicate a specific disease. The diagnostic approach to the short infant or child can be divided into three consecutive steps.

First Step
The first step consists of a thorough medical and family history and physical examination. Relevant points in the history include birth characteristics, symptoms suggestive of chronic organic diseases, psychiatric diseases and/or severe emotional disturbances (table 2) [2, 21, 22]. The physical examination should aim at detecting clues for one of the many causes of short stature. First, supine length or height, weight, head circumference, sitting height (or lower body segment) and arm span will be measured. One should also consider measuring forearm length, as a short forearm is an important marker of SHOX haploinsufficiency [23]. Measurements will be compared with the best available references. For height, weight and head circumference the most recent available growth references for the country or specific ethnic population should be used. References for sitting height/height and arm span are scarce and a choice for the most appropriate reference has to be made [24–29]. Abnormal body proportions are strongly suggestive of a form of skeletal dysplasia. A careful examination for facial and body dysmorphic features should also be performed to detect syndromes (table 3).

Second Step
The second step consists of specific investigations, depending on specific clinical clues at the medical history and physical examination, for example the presence of disproportions or dysmorphic features. An international inventory revealed that in only 45% of the responding countries specific guidelines on diagnostic procedures in children with short stature in secondary health care were reported, but most of the mentioned protocols were not nationally implemented [1]. In the literature some protocols have been described summing up the various investigations to consider, but flow diagrams of how to choose a specific investigation are scarce [30–32]. We propose the diagram shown in figure 2 as the second step in the diagnostic approach.

When skeletal dysplasia is suspected based upon disproportions, radiographic analysis is important to get a more precise diagnosis or to narrow down the number of possibilities. Various guidelines for radiographic analysis of disproportionate short stature are available. They had recently been summarized by Kant et al. [33] and based upon this review a recommendation for radiographic analysis was made (table 4). Results of this radiographic analysis can guide targeted molecular DNA analysis and can contribute to an efficient approach to diagnosing growth disorders.

There are many syndromes associated with short stature. When dysmorphic features in a child with short stature are present, diagnostic investigations have to focus on syndromes. If there are signs of Turner syndrome, obviously a karyotype has to be made, and even in the absence of such features it is generally advised to order a karyotype in a short girl. It has also been proposed to perform a karyotype in a short boy with unexplained short stature [34], but in view of the high costs this may be restricted to boys with some sign of genital abnormality [3].

In the last decades more and more genetic causes of syndromes have been unraveled. If such a syndrome is suspected, the pediatrician, in collaboration with the clinical geneticist, may consider targeted DNA analysis. For a systematic diagnostic approach we refer to a review by Kant et al. [33], in which an overview of the different genetic causes of short stature is given, and a flow chart for molecular analyses is proposed. For a recent review on the diagnostic procedures to detect genetic disorders in the growth hormone-insulin-like growth factor I axis we refer to the paper by Walenkamp and Wit [35].

Third Step
As in the majority of cases no specific clues from medical history and physical examination will be present, the third step is a nonspecific radiographic and laboratory screening.

There is wide consensus that as part of the diagnostic workup of the short child a radiograph of the hand and
A Primary growth disorders
A1 Clinically defined syndromes
   Turner syndrome
   Cornelia de Lange syndrome
   DiGeorge syndrome (velocardiofacial syndrome)
   Down syndrome
   Noonan syndrome
   Prader-Willi-Labhart syndrome
   Von Recklinghausen’s disease (neurofibromatosis type 1)
   Silver-Russell syndrome
A2 Small for gestational age with failure of catch-up growth
   IGF-I deficiency, IGF resistance
   Due to known cause, e.g. prenatal infections, drugs, smoking, alcohol
   Idiopathic
A3 Skeletal dysplasias
   Achondroplasia
   Hypochondroplasia
   Dyschondrosteosis (Leri-Weill and other defects in the SHOX gene)
   Osteogenesis imperfecta I–VI
   Mucopolysaccharidosis (type IH, IS, II–VII)
   Mucolipidosis (type II and III)
A4 Dysplasias with defective mineralization

B Secondary growth disorders
B1 Insufficient nutrient intake (malnutrition)
   Cardiac disorders
   Pulmonary disorders, e.g. cystic fibrosis
   Liver disorders
   Intestinal disorders, e.g. Crohn’s disease, malabsorption syndromes
   Short bowel syndrome
   Renal disorders, e.g. Fanconi syndrome, renal acidosis
   Chronic anemia
B2 Disorders in organ systems
   Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4, GHRHR, GH)
   Associated with syndromes or cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
   Associated with prenatal infections, e.g. rubella
   Acquired (craniopharyngioma, other pituitary tumors, e.g. germinoma, hamartoma)
   Head trauma
   Central nervous system infections
   Granulomatous diseases, e.g. histiocytosis
B3 Growth hormone deficiency (secondary IGF-1 deficiency)
   Idiopathic
   Associated with syndromes or cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
   Associated with prenatal infections, e.g. rubella
   Acquired (craniopharyngioma, other pituitary tumors, e.g. germinoma, hamartoma)
   Head trauma
   Central nervous system infections
   Granulomatous diseases, e.g. histiocytosis
B4 Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)
   Bioactive growth hormone
   Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome, Laron syndrome)
   Abnormalities of GH signal transduction, e.g. STAT5B defect
   ALS (acid-labile subunit) deficiency
   IGF-I deficiency
   IGF resistance (IGF1R defects, postreceptor defects)
B5 Other endocrine disorders
   Cushing syndrome
   Hypothyroidism
   Leprechaunism
   Diabetes mellitus (poorly controlled)
   Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, exogenous estrogens or androgens
B6 Metabolic disorders
   Disorders of calcium and phosphorus metabolism
   Disorders of carbohydrate metabolism
   Disorders of lipid metabolism
   Disorders of protein metabolism
B7 Psychosocial
   Emotional deprivation
   Anorexia nervosa
   Depression
B8 Iatrogenic
   Systemic glucocorticoid therapy
   Local glucocorticoid therapy (inhalation, intestinal, other)
   Other medication
   Treatment of childhood malignancy
   Total body irradiation
   Chemotherapy
   Other specified iatrogenic causes

C Idiopathic short stature
C1 Familial (idiopathic) short stature
C2 Non-familial (idiopathic) short stature

Classification according to the ESPE classification [19].
Table 2. Special points of interest in medical history and physical examination of short children

<table>
<thead>
<tr>
<th>Issue</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td>Birth length, weight, head circumference, gestational age</td>
<td>Compare with intrauterine growth standards (SGA or AGA?; proportionate or disproportionate?)</td>
</tr>
<tr>
<td>Special features regarding pregnancy (intrauterine growth retardation, drug intoxications, infections) and birth (breech delivery, asphyxia, jaundice)</td>
<td>Fetal (intrauterine) growth retardation can lead to an SGA birth weight, and 15% of SGA born children do not catch up in height. Intrauterine intoxications and infections can lead to diminished fetal growth. Pituitary dysfunction is associated with breech delivery and prolonged jaundice</td>
</tr>
<tr>
<td>Previous growth data</td>
<td>A complete growth curve is essential for a good assessment of a growth disorder</td>
</tr>
<tr>
<td>Age at start of pubertal signs (girls: breast development, boys pubic hair and testicular enlargement)</td>
<td>Early, normal or delayed pubertal onset</td>
</tr>
<tr>
<td>Previous diseases and operations, medication (e.g. inhalation therapy with corticosteroids)</td>
<td>Organic or iatrogenic causes</td>
</tr>
<tr>
<td>Medical history of the various systems, e.g. symptoms suggestive of heart, pulmonary, intestinal (abdominal pain, distended abdomen, diarrhea, constipation), kidney, endocrine (fatigue) and CNS (headache, visual disturbance nausea, vomiting), fatigue</td>
<td>Organic causes (e.g. celiac disease). CNS symptoms suggestive of brain tumor. Fatigue can be a symptom of anemia, celiac disease, IBD, renal disorder, hypocortisolism</td>
</tr>
<tr>
<td>Hypotonia, snoring</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Feeding history first year/nutrition (if nutrition is poor, weight is usually affected more than height)</td>
<td>In SGA and Prader-Willi syndrome feeding difficulties in first year frequently occur. In case of failure to thrive detailed assessment of feeding pattern. In toddlers: note symptoms of emotional deprivation. In adolescents: note symptoms of anorexia nervosa</td>
</tr>
<tr>
<td>Country of origin, ethnicity</td>
<td>This influences the decision about which reference charts will be used</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>Strongly increases the likelihood of recessive genetic disorders</td>
</tr>
<tr>
<td>Parental height (preferably measured, rather than reported)</td>
<td>Required for calculating target height</td>
</tr>
<tr>
<td>Global impression of the parents</td>
<td>Dysmorphic features (specially facial and hands), body proportions</td>
</tr>
<tr>
<td>Tempo of puberty of the mother (age at menarche)</td>
<td>To assess likelihood of a familial pattern of delayed puberty</td>
</tr>
<tr>
<td>Tempo of puberty of the father (age at start of pubic hair, age at growth spurt, prolonged growth)</td>
<td>To assess likelihood of a familial pattern of delayed puberty</td>
</tr>
<tr>
<td>Family history (autoimmune diseases, thyroid disorders, growth disorders, skeletal disorders, endocrine disorders)</td>
<td>To assess likelihood of a genetic cause</td>
</tr>
<tr>
<td>Milestones delayed, intellectual retardation</td>
<td>Associated with syndromes, chromosomal disorders, metabolic disorders</td>
</tr>
<tr>
<td>Social environment and psychosocial functioning; school performance (grade, social behavior, physical activities); social contacts; personality development (self-reliance); vitality (mood, activities, sleeping, drinking); behavior (mascot, clown, aggressive); unexplained physical complaints; parental attitude</td>
<td>Neglect, emotional deprivation, undernutrition, depression, anorexia nervosa. Impression of parental concern and support</td>
</tr>
</tbody>
</table>
wrist is useful [1]. On this X-ray, bone age is determined, which can also be used for adult height prediction with one of the available atlases [36, 37]. The degree of bone age delay is an aid in distinguishing between various classes of growth disorders. In addition, on a hand/wrist X-ray, abnormalities associated with SHOX haploinsufficiency can be seen, as well as signs of vitamin D deficiency [23].

If there are no signs of any dysmorphic features or disproportion, nor of any chronic disease, most centers perform a screening set of laboratory investigations. However, there is no consensus about which tests should be performed [1, 2], and scientific evidence supporting the various proposed lists is scarce. Ideally, the choice of the laboratory parameters should depend on the prevalence of the disease, the frequency with which the disease presents with only growth retardation, the sensitivity and specificity of the test, and the implications for the patient.

We have collected evidence that only for one test the evidence should be considered sufficient. In a systematic review we found a strong scientific basis to check for CD

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**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>A high sitting height/height ratio (or low upper/lower segment ratio) is suggestive of skeletal dysplasia. A low span and short forearm are suggestive of SHOX defect</td>
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<tr>
<td>Intestinal disorders, hypocortisolism, metabolic disorders, SGA</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism, Cushing’s syndrome, GH deficiency, pseudohypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Primary growth disorders (syndromes)</td>
<td></td>
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<tr>
<td>GH deficiency or resistance, IGF-I deficiency</td>
<td></td>
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<tr>
<td>Cushing’s syndrome</td>
<td></td>
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<tr>
<td>Watch for tonsillar hypertrophy</td>
<td></td>
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<tr>
<td>Enlarged (or decreased) in Hashimoto thyroiditis</td>
<td></td>
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<tr>
<td>Hypothyroidism</td>
<td></td>
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<tr>
<td>Kidney disease, Cushing’s syndrome</td>
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<tr>
<td>GH deficiency</td>
<td></td>
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<tr>
<td>Celiac disease</td>
<td></td>
</tr>
<tr>
<td>Hepatic or metabolic disorder</td>
<td></td>
</tr>
<tr>
<td>Early, normal or late puberty</td>
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<tr>
<td>Hypogonadism, hypopituitarism</td>
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<tr>
<td>Hypogonadism</td>
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<tr>
<td>Cushing’s syndrome</td>
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<tr>
<td>Muscular disorder</td>
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<tr>
<td>CNS pathology</td>
<td></td>
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<tr>
<td>Emotional deprivation</td>
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</table>

SGA = Small for gestational age; AGA = appropriate for gestational age.
We showed that in 2–8% of the children with short stature and no gastrointestinal symptoms CD may be the underlying cause, and the risk increases to 19–59% if other causes for short stature are excluded. For a proper interpretation of the results of these tests total IgA remains important, as 7–10% of the CD patients have IgA deficiency [39]. Although anti-tissue transglutamase and anti-endomysium antibodies have a high sensitivity and specificity, the gold standard for the definite diagnosis of CD remains an intestinal biopsy.

In most centers hematological parameters, such as cell indices, leukocyte differentiation, and erythrocyte sedimentation rate, are included in the laboratory screening, to detect or exclude anemia and infections or inflammatory diseases. Our international inquiry showed that these tests were recommended in most countries with guidelines for diagnostic workup [1]. We did not perform a thorough literature search on the prevalence of short stature in combination with anemia, but the available literature shows that there is a strong relationship between thalassemia, sickle cell disease and growth retardation [40–43]. Likewise, Stephensen [44] showed evidence of the association between infectious diseases in general and linear growth. Anemia and inflammation parameters can also be the first signs of other growth-related disorders like inflammatory bowel diseases, CD or CF. The erythrocyte sedimentation rate is also an important parameter in detecting inflammatory bowel diseases. We have shown that the prior probability of CF in infants or children with a low weight or length for age is too low for a reliable result of a sweat test [16]. The same conclusion might be drawn for the infectious parameters, but experimental data are lacking. However, as anemia and infectious parameters are important for the detection of other growth-related disorders, and as they are noninvasive for the patient and relatively cheap, we recommend these parameters to be kept in the routine diagnostic workup of short children.

Another possible category of the routine diagnostic workup contains parameters to exclude liver diseases. Especially ASAT and ALAT were recommended in more than 50% of the countries with an existing guideline for the assessment of short stature [1], but γGT was usually considered optional. Although Sokol and Stall [45] concluded that growth retardation is common in children with chronic liver disease, in more than 30 years of experience we have not encountered any asymptomatic short child in whom liver function tests revealed a liver disorder. Therefore, we believe that it is extremely unlikely that the sole presenting sign of a liver disorder is growth retardation. However, we have not been able to perform an

<table>
<thead>
<tr>
<th>Dysmorphic feature</th>
<th>Associated syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short nose with anteverted nostrils</td>
<td>Smith-Lemli-Opitz</td>
</tr>
<tr>
<td>Continuous eyebrows</td>
<td>Cornelia de Lange</td>
</tr>
<tr>
<td>Absence of adipose tissue</td>
<td>Leprechaunism</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Progeria</td>
</tr>
<tr>
<td>Ambiguous genitalia/abnormal genitalia</td>
<td>Mixed gonadal dysgenesis/46,XY/45X chromosomal mosaicism/Smith-Lemli-Opitz/Aarskog</td>
</tr>
<tr>
<td>Asymmetry of the face/arms/legs</td>
<td>Russell-Silver</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>Turner</td>
</tr>
<tr>
<td>Bird-headed face</td>
<td>Rubinstein-Taybi</td>
</tr>
<tr>
<td>Broad thumbs and toes</td>
<td>Hallermann-Streiff</td>
</tr>
<tr>
<td>Cataract (congenital)</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Cleft lip and/or palate</td>
<td>Russell-Silver</td>
</tr>
<tr>
<td>Clinodactyly</td>
<td>Noonan, Prader-Willi</td>
</tr>
<tr>
<td>Coarctatio aortae</td>
<td>Rubinstein-Taybi</td>
</tr>
<tr>
<td>Cryptorchism</td>
<td>Turner</td>
</tr>
<tr>
<td>Cubiti valgi</td>
<td>Coffin-Siris</td>
</tr>
<tr>
<td>Digital V missing/no nails</td>
<td>Skeletal dysplasias</td>
</tr>
<tr>
<td>Disproportion</td>
<td>Down</td>
</tr>
<tr>
<td>Elfin face</td>
<td>22q11 deletion syndrome/SHOX</td>
</tr>
<tr>
<td>Epicanthus</td>
<td>Coffin-Siris, Cornelia de Lange</td>
</tr>
<tr>
<td>High arched palate</td>
<td>Robinow, Smith-Lemli-Opitz</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Turner</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Turner</td>
</tr>
<tr>
<td>Hypoplastic nipples</td>
<td>Turner</td>
</tr>
<tr>
<td>Hypospadia</td>
<td>46,XY/45X chromosomal mosaicism</td>
</tr>
<tr>
<td>Inverted nipples</td>
<td>Turner</td>
</tr>
<tr>
<td>Lymphedema (congenital)</td>
<td>Turner</td>
</tr>
<tr>
<td>Madelung deformity</td>
<td>Leri-Weill, SHOX abnormalities</td>
</tr>
<tr>
<td>Microopenis</td>
<td>Prader-Willi, growth hormone deficiency</td>
</tr>
<tr>
<td>Muscular hypotonia</td>
<td>Down, Prader-Willi</td>
</tr>
<tr>
<td>Nail convexity/dysplasia</td>
<td>Turner</td>
</tr>
<tr>
<td>Nevi (multiple)</td>
<td>Prader-Willi, Aarskog, Dubowitz, Noonan, Turner</td>
</tr>
<tr>
<td>P toes</td>
<td>Noonan, Turner</td>
</tr>
<tr>
<td>Pulmonary valvular stenosis</td>
<td>Aarskog</td>
</tr>
<tr>
<td>Shawl scrotum</td>
<td>Aarskog</td>
</tr>
<tr>
<td>Short 4th and 5th metacarpals</td>
<td>Pseudohypoparathyroidial</td>
</tr>
<tr>
<td>Single central incisor</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Small hands/feet</td>
<td>Prader-Willi</td>
</tr>
<tr>
<td>Telangiectasia in face</td>
<td>Bloom</td>
</tr>
<tr>
<td>Triangular face</td>
<td>Russell-Silver</td>
</tr>
<tr>
<td>Webbed neck</td>
<td>Noonan, Turner</td>
</tr>
</tbody>
</table>

Diagnostic Approach in Children with Short Stature

extensive literature search on the prevalence of mono-
symptomatic short stature at diagnosis in children with
liver disorders and further research has to be performed
to collect experimental evidence on the issue. At present,
we consider it justified to remove these parameters from
the routine diagnostic workup of short stature.

The next category of serum determinations, in com-
bination with routine screening of a urine sample, is
aimed at detecting renal diseases, calcium/phosphate
disorders and malabsorption. More than 50% of the
countries with guidelines for a diagnostic workup in
children with short stature recommended that electro-
lytes, albumin and creatinine should be evaluated [1].
This agrees with the literature that shows that several
renal diseases are in fact associated with short stature
and that growth retardation is often present at diagnosis
while other clinical symptoms are still absent [46–49].
An acid-base equilibrium measurement, an easy and
cheap test to screen for kidney diseases such as renal
acidosis, was only recommended in 32% of the countries
with guidelines [1] and was seldom done in the hospi-
tals familiar with the Dutch Consensus Guideline [50].
Probably the main reason for skipping this test was
that an extracapillary blood sample is necessary, besides
the routine venous blood sample to rule out other dis-
eases. Preliminary results of a study on the growth of
infants and children with renal tubular acidosis have
confirmed previously published data that several pa-
tients with distal renal tubular acidosis often show fail-
ure to thrive as the first and main symptom [51–55].
However, this diagnosis is rare, and virtually always
made in the first 3 years of life. We, therefore, propose
to limit this investigation into growth failure in that age
group.

There seems to be international consensus on testing
TSH and free T\textsubscript{4} to diagnose or rule out hypothyroidism
in the diagnostic workup in children with short stature
[1]. Although a systematic literature search has not been
performed, clinical experience combined with the preva-
ience of hypothyroidism is in favor of including these
tests in the diagnostic workup [56].

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Fig. 2. Diagnostic approach in children with short stature. TH = Target height; SGA = small for gestational age.
As growth hormone deficiency is one of the most important conditions to be detected by auxological screening and because of its relatively high prevalence (reported prevalence 1:2,500 to 1:6,000) it is obvious that IGF-I should be kept in the diagnostic workup [57, 58]. This opinion is shared by most of the countries with current guidelines [1]. IGFBP-3 adds little to the evaluation of children with short stature, except in children younger than 3 years, where low IGFBP-3 levels are helpful in the diagnosis of growth hormone deficiency [59].

FSH is recommended as a screening tool for Turner syndrome in the diagnostic workup for short stature in 50% of the countries with guidelines [1]. In our retrospective study, FSH was determined in less than a quarter of the girls in the group of children correctly referred to secondary health care [13]. When the age rules recommended by pediatric endocrinologists (to measure plasma FSH only in girls ! 2 years and ! 9 years) were applied, the figures hardly changed. From the literature, as well as from clinical experience, it is known that the diagnosis of Turner syndrome should be considered in any girl with unexplained short stature [60, 61]. Therefore, we believe that irrespective of the FSH result, a chromosomal analysis should be carried out in each girl in whom the initial laboratory screening has not shown an abnormality. Thus, we did not include FSH in the recommended list of laboratory investigations.

There are some reports suggesting that zinc (Zn) deficiency may be a cause of short stature, and that the determination of Zn might be considered as part of the laboratory screening. Reasons to consider Zn deficiency as cause of short stature are that Zn is essential for somatic growth in children and that even in developed countries marginal to moderate Zn deficiency is not unusual [62]. On the other hand, the prevalence of Zn deficiency in western countries is unknown, and may be very low. Furthermore, there are no data on sensitivity and specificity of the various tests, and apparently the available tests are suboptimal [63, 64]. Further research is necessary to find a reliable marker for Zn deficiency, and to collect data on the importance of Zn status for growth in western societies.

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A further possible screening parameter could be a sweat test in an infant with a low length or weight for age. We investigated this in detail and concluded that such screening is not indicated, as the prior probability of CF is less than 1%, and length or height are insensitive predictors [18]. If clinical symptoms or signs suggestive of CF are found in combination with growth faltering, further diagnostic steps are warranted, as the prior probability is then expected to be higher.

Based on the above considerations, we believe that, at present, laboratory screening of short children should include the parameters shown in table 5.

### Conclusion

Although growth monitoring has been performed for more than 100 years, until recently a scientific approach to assessing its efficacy and efficiency has been lacking. The guideline we proposed in 2008 may serve as a starting point for further validation studies and cost-benefit analyses. With respect to laboratory investigations, the scientific evidence base is also narrow, so that the major part is only based on theoretical considerations and clinical experience. Further studies are needed to assess how often short stature is the only clinical feature of the disorders which are candidates for laboratory testing.

#### References


Diagnostic Approach in Children with Short Stature


