Guidelines

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Towards a Rational and Efficient Diagnostic Approach in Children Referred for Tall Stature and/or Accelerated Growth to the General Paediatrician

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Abstract
Tall stature and/or accelerated growth (TS/AG) in a child can be the result of a primary or secondary growth disorder, but more frequently no cause can be found (idiopathic TS). The conditions with the most important therapeutic implications are Klinefelter syndrome, Marfan syndrome and secondary growth disorders such as precocious puberty, hyperthyroidism and growth hormone excess. We propose a diagnostic flow chart offering a systematic approach to evaluate children referred for TS/AG to the general paediatrician. Based on the incidence, prevalence and clinical features of medical conditions associated with TS/AG, we identified relevant clues for primary and secondary growth disorders that may be obtained from the medical history, physical evaluation, growth analysis and additional laboratory and genetic testing. In addition to obtaining a diagnosis, a further goal is to predict adult height based on growth pattern, pubertal development and skeletal maturation. We speculate that an improved diagnostic approach in addition to expanding use of genetic testing may increase the diagnostic yield and lower the age at diagnosis of children with a pathologic cause of TS/AG.

Introduction

The primary goal of the systematic diagnostic approach of children with tall stature and/or accelerated growth (TS/AG) is to diagnose or exclude secondary growth disorders as well as primary (syndromic) growth disorders, most notably Klinefelter syndrome (KS) and Marfan syndrome (MFS). Another goal is to adequately predict adult height based on the growth pattern, pubertal development and skeletal age, and if indicated discuss possibilities regarding eventual adult height reduction therapy.

There is little information about the frequency of pathologic causes of TS/AG detected in a paediatric clin-

Jan M. Wit and Wilma Oostdijk contributed equally to this work. Other members of the Dutch Working Group on Triage and Diagnosis of Growth Disorders in Children are listed in the Appendix.

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ic; in the three available retrospective studies, the frequency varied from 1.5 to 12% [1–3]. We assume that the frequency not only depends on the type of clinic (secondary vs. tertiary care) but also on the quality of the clinical assessment, different diagnostic strategies and limitations regarding genetic testing. In this context, it is noteworthy that at least two clinically important diagnoses associated with TS (KS and MFS) are rarely diagnosed before puberty [4, 5]. We speculate that with increased attention to diagnostic clues as well as easier accessible tools for genetic testing (such as array analysis and specific growth-related whole exome sequencing (WES)-based gene panels), the diagnostic yield will increase.

In contrast to prior reviews on TS/AG [2, 6–9], which mainly discussed the differential diagnosis of TS/AG, we aim at offering a problem-oriented guide to the evaluation of TS/AG by focusing on the question "what is the most rational and efficient diagnostic approach for children referred for TS/AG?," further subdivided into three sub-questions: (1) What are important diagnostic clues in medical history and physical examination? (2) What is the role of the shape of the growth curve as a diagnostic clue? (3) What is the role of additional laboratory and genetic testing? As a result of an extensive literature search, we propose a new systematic approach to evaluate children referred for TS/AG.

As a starting point, we collected data on incidence, prevalence and clinical features of the medical conditions accompanying TS/AG, based on the list presented in the International Classification of Paediatric Endocrine Diagnoses" (ICPED) [10, 11] (online suppl. Table; for all online suppl. material, see www.karger.com/doi/10.1159/000500810). Most conditions are considered very rare, and for all of these there is only scarce information about incidence, prevalence, distribution of height standard deviation score (SDS) and occurrence of TS without additional clinical features. A timely diagnosis of the most frequent medical condition associated with TS (KS), with an estimated incidence of 1.0–1.5 per 1,000 births [12, 13], is hampered by the fact that height in many patients is within the population range (<+2 SDS), while clinical features are generally mild. This is probably the main reason why only 10% of patients are diagnosed before puberty [4]. The diagnosis of the medical condition with the most severe clinical consequences (MFS) is hampered by its rather low incidence (estimated at 23 per 100,000 births [14]) and variable clinical presentation. Furthermore, because of the dominant inheritance, height of children with MFS is usually within the target height (TH) range, so that the distinction between MFS and the familial subcategory of idiopathic TS (ITS) can be difficult. We believe that one of the key aims of the diagnostic approach of TS/AG should be to diagnose KS and MFS at an earlier age.

The central feature of this mini review is a diagnostic flowchart for TS/AG, supplemented by tables containing the most important diagnostic clues for growth disorders, including relevant issues from the medical history and physical signs (including dysmorphic features) indicative for pathology. We also propose indications for additional laboratory and genetic testing.

This paper is an adaptation of a formal evidence-based guideline for children from 0 to 18 years in the Dutch language, authorised by the Paediatric Association of the Netherlands and other medical societies, intended for use by the general paediatrician [15]. We expect that it will also assist primary care physicians, youth health care physicians, general practitioners, clinical geneticists and paediatric endocrinologists in detecting pathologic causes of TS/AG at an early age.

Definitions

Mirroring the criteria for children with short stature and/or growth deceleration, we propose to define TS/AG in childhood or adolescence if linear growth complies with one or more of the following criteria: (1) tall for the ethnic population; (2) tall in comparison to parental heights; or (3) growth acceleration, defined as a positive change of height SDS (HSDS). Cut-off points for each of these criteria are arbitrary, but the conventional approach is to use statistical limits that label approximately 2–3% of children in the population as "abnormally tall." Tall for the ethnic population is usually defined as an HSDS >+2.0, based on suitable reference charts for height for age, sex and ethnicity. About the second criterion (tall for familial genetic origin), there is more discussion, caused by the use of different equations for calculating TH and by uncertainty whether secular trends should be incorporated. We favour the use of the conditional THSDS, defined as the mid-parental height adjusted for assortative mating and regression bias, using the parent-parent correlation and the parent-offspring correlation [16]. This conditional THSDS is 0.72 times the average of parental HSDS (independent of sex), and a child's HSDS is expected to be situated within ±1.6 SDS of the conditional THSDS [16]. The third criterion (AG) is a longitudinal parameter and stands for a positive change in HSDS over time, away from the THSDS. There are no reliable data of what

should be considered "abnormal AG," and any cut-off limit should be adjusted for the duration of the interval. In analogy to short stature, in which a negative change of >1 SDS over an undetermined time interval was considered abnormal (in the age range of 3–10 years) [17], we suggest to label AG as a positive change of HSDS >1 SDS over an undetermined time interval before the onset of puberty. During puberty, this cut-off is expected to have a low specificity, due to considerable variation in pubertal timing.

It is generally assumed that in the large majority of children with TS/AG attending the paediatric clinic, no pathologic cause can be found [1–3]. In accordance with the ICPED classification [11], we label children with an HSDS >+2 of unknown origin as ITS, which can be subdivided into familial or non-familial TS (FTS or NFTS), depending on the child's height residing within or above the TH range. It is believed that FTS has a polygenic origin in most children, implying the accumulation of multiple "tall gene variants" in a family [18]. If a child is both tall for the ethnic population and familial genetic origin (NFTS), but also if HSDS is >+1.6 SDS above TH but still within the population range, one would expect an increased a priori likelihood of a pathologic cause, and a higher diagnostic yield of laboratory testing. Growth acceleration (ΔHSDS >+1) can be associated with a height within or above the population range. It has been described in "constitutional advancement of growth" (CAG), the assumed mirror image of constitutional delay of growth and puberty [19], but is also an important sign of a secondary growth disorder.

Stepwise Approach to the Diagnosis of TS

Introduction to the Structure of the Flowchart

Fundamental in the diagnostic approach of TS/AG is the flowchart (Fig. 1). The starting point is the child that is referred under suspicion of a condition associated with TS/AG, or a child visiting the paediatrician for a different reason but with sudden (unexpected) accelerating growth. In our opinion, it is crucial to set this starting point, irrespective of whether the growth pattern is "abnormal" in the statistical sense, since several syndromes associated with TS/AG often present with a height within the population range. To accomplish an effective screening for growth disorders, we formulated diagnostic clues for primary and secondary growth disorders. The most relevant clues are shown in Figure 1, but in fact there are several more, as shown in Tables 1–3. They concern the medical history, family history, physical evaluation and growth pattern. Based on the presence or absence of diagnostic clues for primary or secondary growth disorders, the clinician may decide to perform laboratory investigations or third-line consultations.

General Diagnostic Categories

The three diagnostic categories are: primary growth disorders, secondary growth disorders and ITS. Primary growth disorders are thought to be intrinsic to the epiphyseal growth plate [20], for example most genetic syndromes, such as KS and MFS. Secondary growth disorders are assumed to have a systemic effect on the growth plates, for example central or peripheral precocious puberty, hyperthyroidism and pituitary gigantism. As mentioned earlier, the term ITS just indicates that the aetiology is unknown.

In order to assist the physician to construct a rational differential diagnosis, we extended the list of conditions associated with TS/AG included in the ICPED [11] by adding epidemiological and clinical data (online suppl. Table). The table is subdivided into the three diagnostic categories.

Relevant Issues in the Medical History of a Child Referred for TS/AG (Table 1)

One of the relevant issues to inquire about is foetal growth. A history of excessive foetal growth is strongly suggestive of a primary growth disorder. While information about birthweight can usually be reported by the parents, this is less often the case for birth length. In the absence of numerical information on birth length, the clinician should try to acquire the first length measurement after birth, calculate length SDS (adjusted for gestational age) and use this as a proxy for birth length SDS.

Another diagnostic clue for primary growth disorders is any form of developmental delay, such as slow motor development, cognitive delay (learning problems) or delay in development of speech and language. Also behavioural problems, such as problems in social contacts (autism spectrum disorder) are parts of some genetic syndromes associated with TS/AG, such as KS. Notably, such symptoms are usually not part of the phenotype of MFS. When reviewing the systems, the physician should inquire about cardiac or eye conditions (as clues for MFS). Furthermore, information about the onset and presentation of pubertal signs (as clues for (pseudo)precocious puberty) should be collected, as well as information about symptoms of other secondary growth disorders (Table 1 and 2; Fig. 1). In the family history, infor-

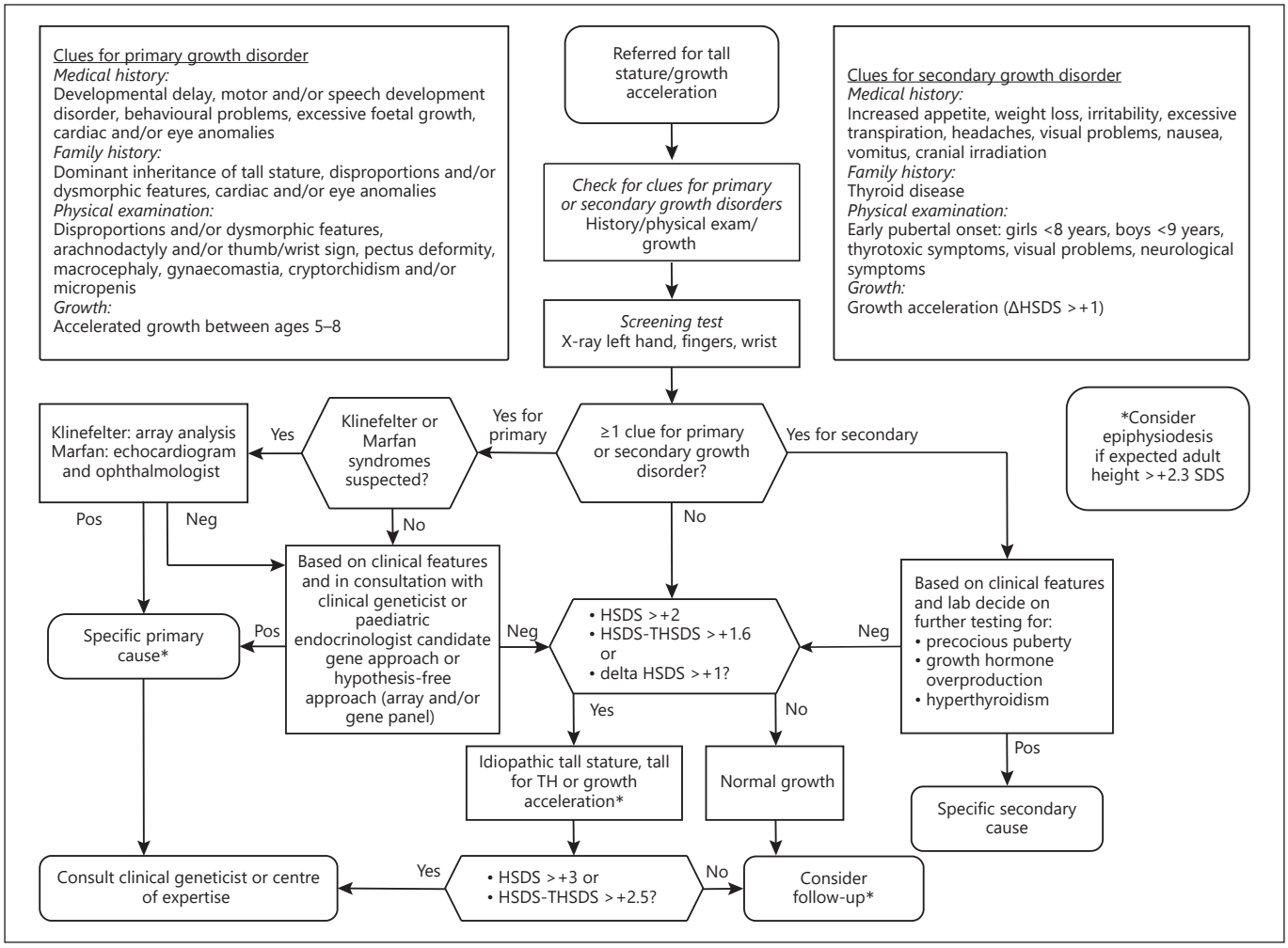

Fig. 1. Flow chart for diagnosis of children referred for tall stature and/or accelerated growth. The starting point is the child that is referred under suspicion of a condition associated with TS/AG but could also very well be a child visiting the paediatrician for a different reason, but with sudden accelerating growth. HSDS, height standard deviation score; TH, target height; Pos, positive; Neg, negative.

mation should be collected about a possible dominant pattern of TS and cardiac or eye conditions, as an indicator of MFS. Pubertal timing of the parents and other relatives may provide clues for a genetic form of early or delayed puberty.

Relevant Issues in the Physical Examination of a Child Referred for TS/AG (Table 2)

Besides height, weight and head circumference, also body proportions should be assessed. We recommend to measure sitting height and calculate the sitting height/height ratio, and convert this to an SDS based on reference data from a country with a similar average height compared with the ethnicity of the patient. Reference data are available for the UK [21], the Netherlands [22], China [23], Spain [24] and Turkey [25].

Furthermore, arm span can be measured and compared with height (as a difference: arm span minus height [26], or as a ratio: arm span divided by height [27]). An arm span/height ratio above 1.05 is considered indicative for MFS [27], although its value as a diagnostic clue in children is dubious [28]. It is furthermore noteworthy that skeletal manifestations of MFS such as a positive arm span/height ratio or scoliosis are less common in Asian MFS patients [29, 30]. Also adult KS patients typically show a positive arm span/height ratio, with arm span exceeding height with at least 2 cm [31], but there is no evidence regarding this in childhood. Arm span furthermore

Table 1. Relevant issues in the medical history of a child referred for TS/AG

Ask for	Interpretation
Chief complaint	
Previous data about growth (growth pattern)	A complete growth curve provides information that influences the *a priori* likelihood of pathogenic causes of growth disorders
Patient's and parents' perspective and coping	Worries about expected adult height influence the decision concerning possible treatment (epiphysiodesis)
Past medical history	
Length, weight and head circumference at birth	Excessive foetal growth is associated with Sotos, Malan, Simpson-Golabi-Behmel, Weaver and Beckwith-Wiedemann syndromes
Neonatal hypoglycaemia	Seen in Beckwith-Wiedemann syndrome
Global developmental delay/intellectual disability	Associated with KS, Sotos, Fragile X, Malan, Lujan-Fryns, Shprintzen-Goldberg syndromes, homocystinuria, 47,XYY and 47,XXX syndromes
Behavioural problems (aggressiveness, passivity, non-self-reliance, anxiety, autism spectrum disorder)	Associated with KS, Sotos, Fragile X, and Malan syndrome, and homocystinuria
Myopia >3 dpt, ectopia lentis, scoliosis, pneumothorax, umbilical/inguinal hernia, joint hypermobility, joint luxation, and/or club feet	Suggestive for MFS and Marfan-like[a] syndromes
Cranial irradiation	Precocious puberty due to cranial irradiation
Review of systems	
Age at first physical signs of puberty (low and high cut-off points for girls: breast development 8 and 13 years; for boys: pubic hair and testicular enlargement 9 and 14 years, respectively)	Precocious, normal or late puberty
Symptoms suggestive for heart or eye conditions	Heart murmurs, visual problems including myopia and astigmatism may be suggestive for MFS
Endocrine: irritability, weight loss, heat intolerance, diarrhoea	Laboratory test for hyperthyroidism
Excessive transpiration	Increased sweating indicates hyperthyroidism and growth hormone excess
CNS: headaches, visual problems, nausea, vomiting	Screening for GH excess and pituitary adenoma
Family history	
Ethnicity, country of origin	Determines the choice of growth diagram
Stature of parents (preferably measured)	To calculate target height. If height of one parent >+2 SDS, consider an autosomal dominant condition
Consanguinity	Increases the probability of an autosomal recessive disorder
Timing and tempo of puberty of parents	Indicates the probability of a familial pattern of early or late puberty
Occurrence of Marfan syndrome, cardiac conditions, sudden cardiac death, eye conditions, endocrine conditions, MEN syndrome, thyroid disease	Indicates the probability of a genetic cause

[a] Marfan-like syndromes: homocystinuria; Ehlers-Danlos syndrome, kyphoscoliotic type; Lujan-Fryns syndrome; congenital contractural arachnodactyly; Loeys-Dietz syndrome; Shprintzen-Goldberg syndrome; multiple endocrine neoplasia type IIB.

Table 2. Relevant issues in the physical examination of a child referred for TS/AG

Examinations	Interpretation
Growth	
Height	Calculate HSDS, TH SDS and ΔHSDS over time
Body mass index or body weight mass in relation to body height	Low BMI of the features of MFS and Marfan-like[a] syndromes Obesity is a feature of CAG and Beckwith-Wiedemann syndrome
Head circumference	A large head circumference is suggestive for Fragile X, Sotos, Malan, and Weaver syndromes
Sitting height/height ratio	A ratio of <–2 SDS is seen in MFS, KS, and triple copy *SHOX* gene syndrome
Arm span/height ratio	Arm span/height ratio >1.05 can be seen in MFS
Physical evaluation	
General impression	Search for dysmorphic features (see Table 3) Asymmetrical growth is suggestive for Beckwith-Wiedemann syndrome Eunuchoid habitus indicates Klinefelter, oestrogen receptor dysfunction or deficiency A feminine appearance in boys can be found in KS
Asymmetry	Suggestive for BWS
Eyes and vision	Ectopia lentis and myopia may occur in MFS and homocystinuria A pituitary adenoma can result in visual disturbances, e.g. affected visual fields
Neck	Goitre can be a sign of hyperthyroidism
Cardiovascular system	Cardiac murmur can be due to mitral valve insufficiency in MFS or an atrial septal defect in Fragile X syndrome Hypertension and tachycardia indicate hyperthyroidism
Genitals	Precocious, normal or delayed puberty Cryptorchidism, small testes and micropenis are associated with KS; cryptorchidism is also seen in Simpson-Golabi-Behmel syndrome Macro-orchidism is seen in Fragile X syndrome
Muscle tone	Hypotonia can be seen in KS, MFS, Shprintzen-Goldberg and Sotos syndromes
Skin	Hyperpigmentation of the skin is associated with familial glucocorticoid deficiency Lipomas and supernumerary nipples can be seen in Simpson-Golabi-Behmel syndrome Striae, abnormal scarring, hematomas, hyperlaxity and varices are associated with MFS and Marfan-like[a] syndromes
Joint mobility	Joint hypermobility can be seen in MFS, Marfan-like[a] and Fragile X syndromes A reduced elbow extension can be found in MFS
Signs	The thumb and wrist sign[b] may point to joint hypermobility and/or arachnodactyly are seen in MFS, Marfan-like[a] and Fragile X syndromes Flexion contractures are indicative of congenital contractural arachnodactyly

[a] Marfan-like syndromes: homocystinuria; Ehlers-Danlos syndrome, kyphoscoliotic type; Lujan-Fryns syndrome; congenital contractural arachnodactyly; Loeys-Dietz syndrome; Shprintzen-Goldberg syndrome; multiple endocrine neoplasia type IIB.

[b] Thumb sign: wrapping the fingers around the thumb in adduction, the entire distal phalanx of the thumb reaches beyond the ulnar edge of the fist with or without assistance to achieve maximal adduction. Wrist sign: the thumb overlaps the entire fingernail of the fifth finger when wrapped around the other wrist.

seems to vary depending on the origin of the supernumerary X-chromosome [32].

During the full physical evaluation, the physician should pay special attention to dysmorphic features that are associated with growth disorders (Table 3). Tanner stage should be determined and comparison with reference data (or its expression as SDS for age and sex) can provide information about a possible disorder of pubertal timing [33–35]. Observations obtained at physical examination can be compared with a list of clinical features of

Table 3. Selected dysmorphic features indicative for a pathological cause of TS/AG

Dysmorphic feature	Suspected growth disorder
Head	
Macrocephaly	Fragile X, Sotos, Weaver, Malan, Simpson-Golabi-Behmel, Beckwith-Wiedemann, PTEN hamartoma tumour
Dolichocephaly	Marfan, Sotos Lujan-Fryns, Fragile X, Shprintzen-Goldberg
Broad forehead	Sotos, Weaver, Fragile X, Simpson-Golabi-Behmel
Prominent forehead	Malan
Long face	Marfan, Lujan-Fryns, Malan, Fragile X, Sotos
Coarse face	Fragile X, Simpson-Golabi-Behmel, 47,XYY, 47,XXX
Hypertelorism	Simpson-Golabi-Behmel, Weaver, Sotos, Loeys-Dietz
Downslanting palpebral fissures	Marfan, Marfan-like[a], Sotos, Malan, Simpson-Golabi-Behmel
Enophthalmos	Marfan, Marfan-like[a]
Large ears	Weaver, Fragile X
Ear pits/creases ear lobe	Beckwith-Wiedemann
Cleft lip	Loeys-Dietz, Simpson-Golabi-Behmel
Bifid uvula	Loeys-Dietz, Simpson-Golabi-Behmel
Cleft palate	Simpson-Golabi-Behmel, Lujan-Fryns, Loeys-Dietz
Gothic palate	Marfan, Marfan-like[a], Sotos
Irregular dentition	Marfan
Macroglossy	Beckwith-Wiedemann, Simpson-Golabi-Behmel
Everted lower lip	Malan
Micrognathy	Marfan, Lujan-Fryns
Retrognathy	Weaver, Marfan, Lujan-Fryns
Prognathy	Sotos
Prominent chin	Fragile X, Sotos, Malan
Thorax	
Gynecomastia	Klinefelter
Accessory nipple	Simpson-Golabi-Behmel
Pectus excavatum/carinatum	Marfan, Marfan-like[a], Fragile X, Malan
Omphalocele	Beckwith-Wiedemann
Kyphosis/scoliosis	Klinefelter, Marfan, Marfan-like[a], Malan, Fragile X, Sotos
Extremities	
Arachnodactyly	Marfan, Marfan-like[a]
Polydactyly	Simpson-Golabi-Behmel
Camptodactyly	Weaver
Contractures	Congenital contractural arachnodactyly, Shprintzen-Goldberg
Dolichostenomelia	Marfan, Marfan-like[a]
Pes planus/planovalgus	Fragile X, Marfan, Marfan-like[a], Sotos

[a] Marfan-like syndromes: homocystinuria; Ehlers-Danlos syndrome, kyphoscoliotic type; Lujan-Fryns syndrome; congenital contractural arachnodactyly; Loeys-Dietz syndrome; Shprintzen-Goldberg syndrome; multiple endocrine neoplasia type IIB.

KS (Table 4) [4] and MFS (see Revised Ghent criteria [27] and for the systemic score see Table 5). Although a systemic score ≥7 points indicates systemic involvement in adults, cardiac sonography and/or genetic testing for MFS should be considered with a lower threshold (e.g. when the systemic score is ≥3–4 points) in children [36].

Expert consensus and/or overview articles are available for many other syndromes associated with TS, including Sotos syndrome (including a clinical score, Table 6) [37, 38], Fragile X syndrome [39], Beckwith-Wiedemann syndrome [40], Simpson-Golabi-Behmel [41], Ehlers-Danlos syndrome, kyphoscoliotic type [42], Loeys-Dietz syndrome [43], homocystinuria [44], Lujan-Fryns syndrome [45], congenital contractural arachnodactyly [46], MEN type IIB [47], Weaver syndrome [48], PTEN hamartoma tumour syndrome [49], Malan syndrome [50] and Shprintzen-Goldberg syndrome [51].

Table 4. Clinical features of Klinefelter syndrome

Age of manifestation	Clinical features
Childhood	Motor and/or speech development disorders Learning difficulties Behavioural problems and/or autism spectrum disorder Increased growth 5 to 8 years Scoliosis Kyphosis Micropenis Cryptorchidism
Puberty	Gynaecomastia Eunuchoid habitus Small testicles Late or stagnant puberty Hypergonadotrophic hypogonadism
Adulthood	Sexual dysfunction Azoospermia/severe oligospermia Osteoporosis Metabolic syndrome Increased risk of breast cancer

Adapted from Aksglaede et al. [4].

Table 5. Marfan syndrome systemic score according to the Revised Ghent criteria

Systemic score	
Feature	Points
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Three or more facial features: dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia	1
Skin striae	1
Myopia >3 dpt	1
Mitral valve prolapse (all types)	1

From Loeys et al. [27]. ≥7 points indicates systemic involvement. Cardiac sonography and/or genetic testing for MFS should be considered with a lower threshold (e.g. when the systemic score is ≥3–4 points [36]) in children.

Interpretation of Growth Curve

Analysis of the linear growth curve essentially includes three elements: (1) HSDS at presentation; (2) the difference between HSDS and THSDS [52]; and (3) the shape of the linear growth curve against the background of population reference chart, objectified by longitudinal data on height, its SDS and the change over time. Besides linear growth, also data on weight or (preferably) body mass index (BMI) over time have to be analysed, as well as head circumference.

In Figure 2, growth curves of boys with KS are shown [53]. While in most boys HSDS stays within the population range, growth accelerates from 3 years onward, which is particularly clear between 5 and 8 years, predominantly due to an increase in leg length growth [4, 12, 53, 54]. Before the onset of puberty, height usually remains stable. Reports about the pubertal growth spurt vary from normal [12] to diminished [32, 53, 54]. Most boys have an HSDS in the upper half of the reference range [55]. Average adult height is approximately 4–10 cm above the mean for the population [12, 55, 56].

Figures 3a and 3b show the growth curves of Korean male and female MFS patients [30], compared with their Korean contemporaries. The mean HSDS in this cohort is consistently above +2 SDS from age 2 onwards. It is noteworthy that not all patients are tall compared with the reference charts.

Figure 4 shows an example of accelerating growth in a prepubertal girl due to growth hormone excess caused by a pituitary adenoma [57]. It shows accelerating growth over time, with the HSDS increase eventually surpassing +2.5 SDS. At 7 years and 8 months, the adenoma was surgically removed followed by decelerated growth. At the age of 13, puberty was medically induced and growth hormone was started.

Bone Age and Predicted Adult Height

In line with common practice, we advise to assess bone age in each child referred for TS/AG. The purpose is threefold. First, it serves as a diagnostic tool, influencing the likelihood of several causes. For example, advanced bone age is part of the presentation of certain primary growth disorders (e.g. Sotos syndrome, Weaver syndrome), but also of (pseudo)precocious puberty, hyperthyroidism and CAG [19, 58, 59]. Second, the radiograph can suggest certain diagnoses, such as long slender phalanges in MFS. Third, bone age serves as the basis of adult height prediction in children above approximately 10 years. In fact, adult height prediction is a frequent reason for referring a tall child.

Table 6. Clinical score for Sotos syndrome

Feature		Points
Facial features[a]	5 or 6 present	5
	2, 3 or 4 present	3
	0 or 1 present	0
Height in comparison with the target height (HSDS – THSDS)	>+2 SDS (at all previous height measurements)	2
	≤+2 SDS, in >2 of previous height measurements >+2 SDS	2
	≤+2 SDS (at all previous height measurements)	0
Skeletal age	>p90	2
	p = 90 or too old to determine skeletal age	1
	<p90	0
Head circumference	≥+2 SDS	1
	<+2 SDS	0
IQ and development	IQ <90 or global developmental delay	1
	IQ ≥90	0

From de Boer et al. [38]. One to 4 points: atypical Sotos syndrome, 5–8 points: dubious Sotos syndrome, 9–11 points: typical Sotos syndrome. [a] Facial features: frontal bossing, receding hairline, prominent jaw, high palate, dolichocephalism, downslanting palpebral fissures.

Bone age is usually assessed using the Greulich and Pyle method [60], and predicted adult height (PAH) is usually calculated with the Bayley and Pinneau (B&P) method [61]. Obviously, the reliability of PAH increases with age and bone age, and one should realise that for boys there is an average overprediction of 2.5 cm (with an SD of 4.3 cm), while in girls PAH is on average similar to the attained adult height (with an SD of 4.6 cm) [62]. At the present time, a computerised system is available which assesses bone age and PAH (BoneXpert) [63], with a mean difference of 0.2–0.3 years below G&P. The resulting PAH is based on the B&P method and validated in several populations [64–66], but not specifically for tall children. There is an underprediction of 0.8 cm with an SD of 3.1 cm in girls and 2.8 cm in boys [66].

If PAH is >+2.3 SDS (>200 cm for boys, >185 cm for girls in The Netherlands), we advise to repeat a bone age and PAH estimation when height has reached 185 cm in boys or 170 cm in girls. If puberty starts late or shows a slow progression, one should be aware of the possibility that attained height may be substantially higher than predicted, so that more frequent bone age assessments may be indicated.

Estimation of the Likelihood of a Primary or Secondary Cause

After a careful medical history, physical examination, growth analysis and bone age determination, the clinician makes an estimate of the likelihood of a pathogenic growth disorder (primary or secondary), based on the collected diagnostic clues (Fig. 1). This will indicate the direction of further diagnostic steps. If there are clues for both categories, both routes can be taken.

Approach in Case of Clues for Primary Growth Disorders

In case of at least one clue for a primary growth disorder, the clinician should decide if there are sufficient indications to test for KS, MFS or other syndromes, given the important therapeutic implications of early diagnosis and management.

Diagnosis of Klinefelter Syndrome

Early detection of KS allows for timely recognition of psychosocial problems enabling syndrome-specific guidance. It can also lead to adequate management of gynaecomastia and hypogonadism (for a list of other clinical features of KS, see Table 4). If pubertal development is delayed or slow, androgen treatment can be administered, and timely discussions can be started about testicular sperm extraction [12].

It is difficult to diagnose KS in childhood and adolescence. Most individuals are diagnosed antenatally or in adulthood, for example in men who are investigated for

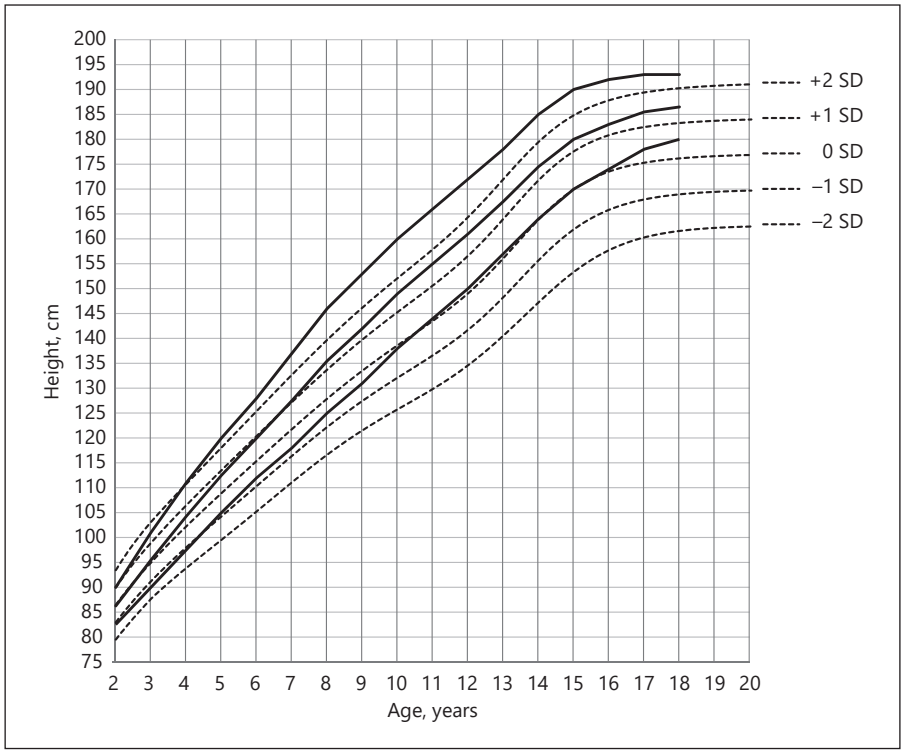

Fig. 2. Range of growth curves of boys with Klinefelter syndrome against population references. The middle continuous line is the mean of the cohort, and the upper and lower continuous lines show the upper and lower ranges of the cohort, respectively. While in most boys HSDS stays within the population range, mean height of the cohort accelerates from 3 years onward, which is particularly clear between 5 and 8 years. The population references (dotted lines) are based on the 2000 CDC (Centers for Disease Control and Prevention) stature-for-age charts for males aged 2–20 years [90]. Redrawn from Ratcliffe [12].

azoospermia. The most important clinical features include a characteristic growth pattern (as detailed in a previous paragraph), small testicular volume, elevated luteinising hormone and follicle-stimulating hormone levels in contrast with normal serum testosterone levels, and various psychosocial issues [55, 67]. For example, in a Danish cohort all patients had a smaller testicular volume in adulthood, gynaecomastia in 44%; cryptorchidism was reported in 14%, and 36% required speech therapy or educational support [55]. The abnormal biochemical parameters became evident after onset of puberty and correlated with histological findings of a gradual deterioration of seminiferous tubules and massive Leydig cell hyperplasia in adults [55].

The psychosocial issues vary with age [68]. Between 0–4 years, motor development is slow, and boys can present clumsy. Approximately 50% have speech delay. Between 4 and 11 years, boys still encounter problems with speech and language, and 75% have reading problems (dyslexia) [69, 70]. Diminished short-term memory has also been described. Boys with KS can show withdrawn behaviour and may find it difficult to attain social contacts. In adolescence, low self-esteem and learning problems can occur [71].

The growth data show that if testing for KS would be performed in all boys with TS, the diagnostic yield would be very low. Instead, the combination of AG (with a height in childhood above the TH) with developmental problems (particularly regarding speech and language development) should lead the clinician to perform genetic testing for KS.

With respect to the method of genetic testing, the conventional approach has been to perform a karyotype. We believe that an array analysis (SNP array or CGH array) is currently a more efficient technique, since it also allows for detection of copy number variants (microdeletions and microduplications), and if SNP array is used most forms of uniparental disomy (UPD) [72]. An example of a syndrome associated with TS caused by a microduplication is triple SHOX gene copy syndrome (caused by *SHOX* duplications), associated with relatively long legs [73]. An example of a TS syndrome caused by UPD is Beckwith-Wiedemann syndrome [74]. If the array analysis is positive for KS (or negative in a child with high clinical suspicion of KS), we advise to refer the patient to a centre of expertise. A false negative result of the array analysis or karyotyping can occur in low-grade mosaicism (<10–20%) [75]. When mosaicism is suspected, fluorescence in situ hybridization on ≥200 cells may be used, and additional samples (e.g. epithelial cells from buccal mucosa) can be studied as analysis of cells derived from different germ layers may improve the detection rate [76].

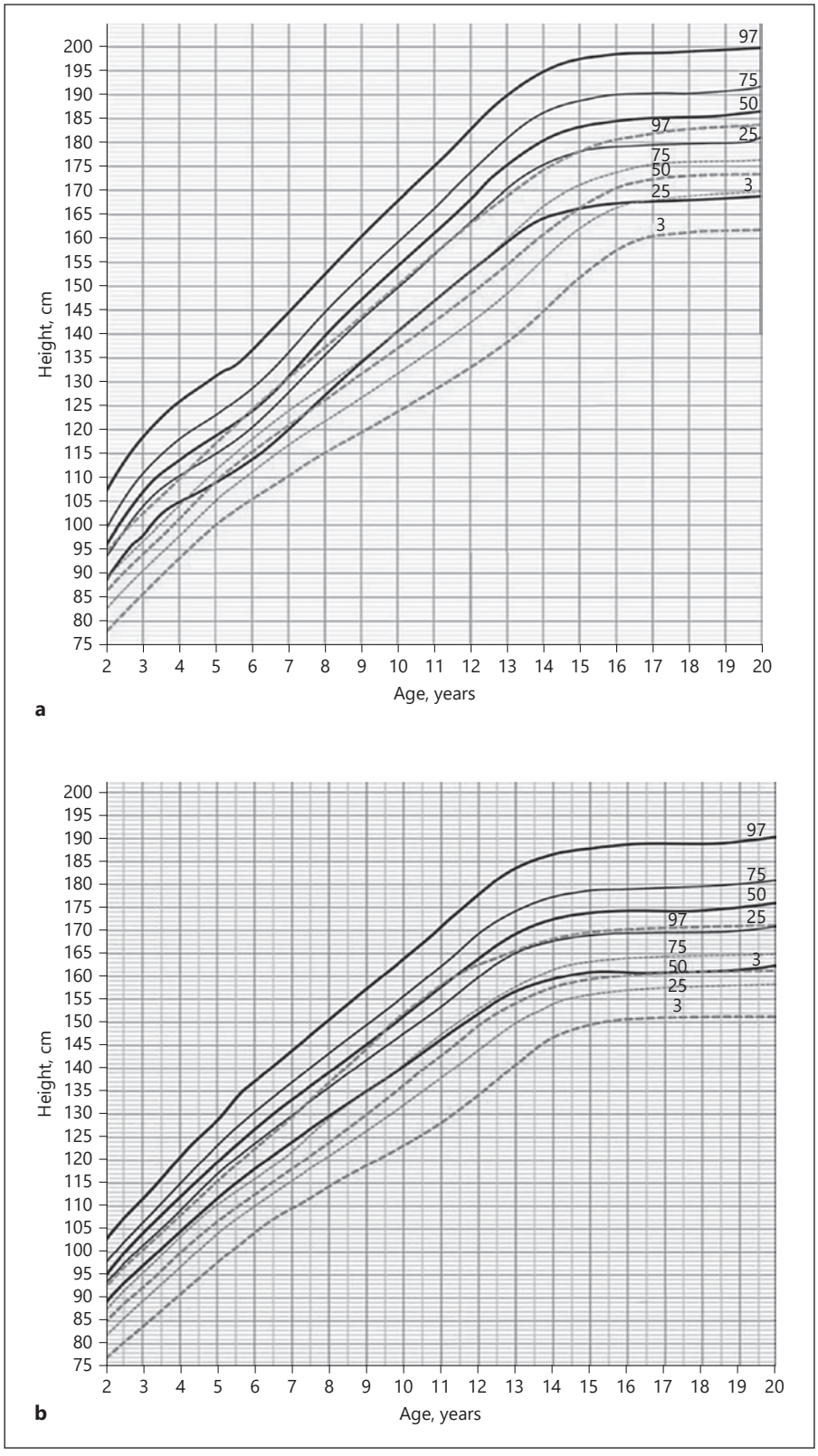

Fig. 3. a, **b** Range of growth curves of Korean boys and girls with Marfan syndrome against population references. The mean HSDS in this cohort is consistently above +2 SDS from age 2 onwards. The population references (dotted lines) are for Korean boys and girls, respectively. The ranges are given in percentiles. It is noteworthy that not all patients are tall compared with the reference charts. Redrawn from Kwun et al. [30]. Reproduced by permission of the Korean Academy of Medical Sciences.

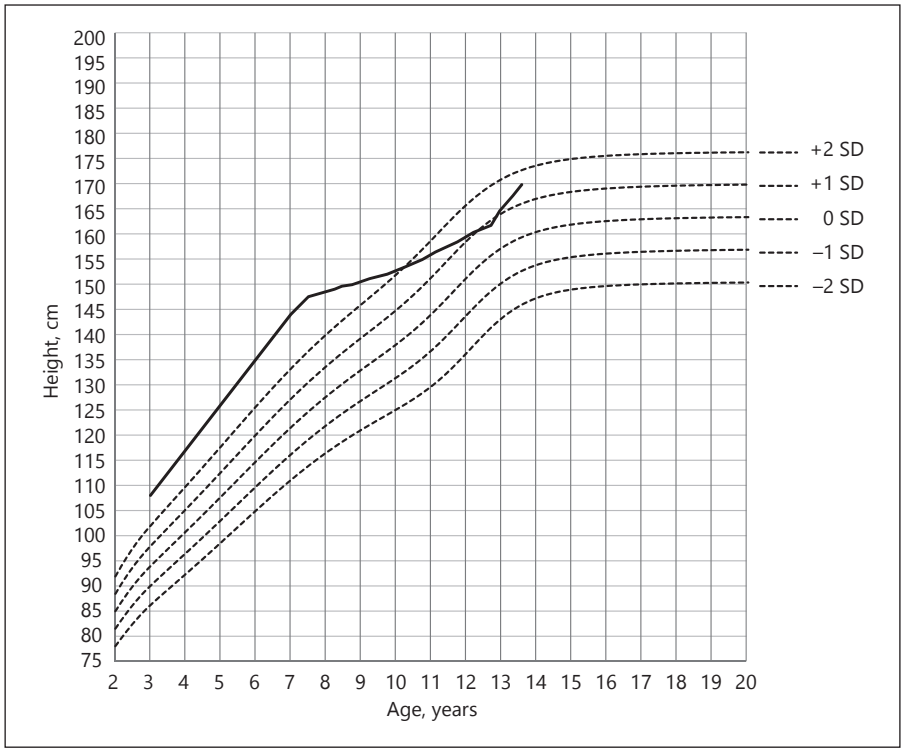

Fig. 4. Growth curve of a girl with pituitary gigantism caused by an *AIP* mutation. The patient's growth curve (continuous line) is shown against the background (dotted lines) of 2000 CDC (Centers for Disease Control and Prevention) stature-for-age charts for females aged 2–20 [90]. The *AIP* mutation caused a pituitary adenoma producing growth hormone. At 7 years and 8 months, the adenoma was surgically removed followed by decelerated growth. At the age of 13, puberty was medically induced, and she was treated with growth hormone. Redrawn from Lebl et al. [57].

Marfan Syndrome

Early detection of MFS enables follow-up of cardiovascular, ocular and other health problems and may also detect MFS in family members upon screening. An early diagnosis is particularly important to prevent life-threatening aortic dissection seen in MFS; prophylactic aortic surgery is usually performed in early adulthood but can also be necessary in childhood [5]. Unfortunately, MFS is often diagnosed at an adult age (especially in case of a de novo mutation). In a Danish cohort, the diagnosis only became apparent because of a major cardiac event in 12.9% of patients [5]. A late diagnosis hampers adequate cardiovascular monitoring, medical intervention to reduce stress on the aortic wall and eventual surgery [77].

The most important systemic features of MFS (Table 5) [27] are included in Tables 1–3. In childhood, height can either be within or above the population range. As approximately 75% of patients with MFS have inherited the *FBN1* mutation from one of their parents, their TS may be falsely interpreted as familial ITS. Therefore, a detailed family history and close inspection of MFS signs in the parents is important in any child referred for TS/AG.

In case of suspicion of MFS, we advise to refer the patient to a (paediatric) cardiologist and clinical geneticist, and especially in children aged ≤5 years also to an ophthalmologist. The cardiologist will perform an ultrasound of the heart, paying special attention to mitral valve insufficiency and the *Z* score of the aortic root diameter. The ophthalmologist will pay special attention to the clinical assessment of ectopia lentis (which most often arises in early childhood, but infrequently also thereafter [78]) and myopia. A clinical geneticist (preferably affiliated to a Marfan expert clinic) may differentiate between MFS and several Marfan-like syndromes (online suppl. Table) and may perform genetic testing of *FBN1* and/or a panel of genes including *FBN1*. In case of a diagnosis, genetic counselling will be offered to the patient and family. Please note that referral to a clinical geneticist is also justified in case of multiple MFS features (systemic score ≥3–4) without aortic root dilatation, ectopia lentis and/or myopia, as these features may not or not yet be present in a child with MFS [36]. If MFS is diagnosed, follow-up should ideally be offered by a multidisciplinary Marfan expert clinic.

The terms "neonatal MFS" or "severe early onset MFS" should be preserved for children with a de novo variant in exon 24–32 in *FBN1* which results in a strong dominant-negative effect. These children have a severe form of MFS and usually die within childhood due to cardiopulmonary insufficiency [79].

Table 7. Additional biochemical and genetic testing in children suspected for specific pathological causes of TS/AG

Suspected growth disorder	Workup
Primary causes	
Klinefelter syndrome	Serum testosterone, LH and FSH. Array analysis (SNP array or CGH array)
Suspicion for Klinefelter syndrome but normal array or karyotype	Referral to clinical geneticist (FISH analysis on blood lymphocytes and/or other samples such as buccal epithelium cells)
Marfan syndrome	Check Revised Ghent criteria including systemic score (Table 5) Referral to clinical geneticist (DNA sequencing of *FBN1* or gene panel for connective tissue disorders including *FBN1*) Referral to (paediatric) cardiologist Referral to ophthalmologist
Marfan-like[a] syndromes	Referral to clinical geneticist (gene panel for connective tissue disorders including *FBN1,* plasma homocysteine level)
47,XYY and 47,XXX syndromes	Array analysis (SNP array or CGH array)
Fragile X syndrome	Referral to clinical geneticist (*FMR1* CGG repeat length)
Sotos syndrome	Referral to clinical geneticist (*NSD1*)
Malan syndrome	Referral to clinical geneticist (*NFIX*)
Weaver syndrome	Referral to clinical geneticist (*EZH2*)
Simpson-Golabi-Behmel syndrome	Referral to clinical geneticist (*GPC3*)
Beckwith-Wiedemann syndrome	Referral to clinical geneticist (epigenetic changes chromosome 11p15)
Secondary causes	
Central precocious puberty	LH, FSH, testosterone, oestradiol, GnRH test
Peripheral (pseudo)precocious puberty	17-OH-progesterone, androstenedione, testosterone, DHEA, DHEAS, urinary steroid profile
Growth hormone excess	GH, IGF-I, OGTT with measurement of GH and glucose
Hyperthyroidism	FT4, TSH
Familial glucocorticoid deficiency	ACTH, cortisol
Gonadotropin deficiency	LH, FSH, testosterone, oestradiol, GnRH test
Idiopathic tall stature	
Constitutional advancement of growth	Radiograph of left hand/wrist: advanced bone age

[a] Marfan-like syndromes: homocystinuria; Ehlers-Danlos syndrome, kyphoscoliotic type; Lujan-Fryns syndrome; congenital contractural arachnodactyly; Loeys-Dietz syndrome; Shprintzen-Goldberg syndrome; multiple endocrine neoplasia type IIB.

Other Syndromes

Suggestions for additional biochemical and genetic testing are given in Table 7. When there are no signs for KS or MFS, or if these syndromes have been ruled out, the physician should consider discussing the further diagnostic workup with a clinical geneticist or paediatric endocrinologist. At that level, the clinical features (online suppl. Table) may be sufficiently clear and specific to warrant a candidate gene approach. For example, a large head circumference and specific dysmorphic features could lead to targeted testing of genes associated with Fragile X syndrome, Sotos syndrome, Malan syndrome, Weaver syndrome or PTEN hamartoma tumour syndrome [80] (genetic testing for *FMR1* repeat length, *NSD1*, *NFIX, EZH2* and *PTEN*, respectively). For Sotos syndrome, clinical scores have been developed to guide the physician in deciding whether genetic testing is indicated (Table 6) [37, 38]. Beckwith-Wiedemann syndrome was recently redefined as a spectrum and the provided scoring system has a low threshold for genetic testing [40].

In case of global developmental delay/intellectual disability and TS/AG without any other specific clues that may lead to a diagnosis, we suggest that local clinical guidelines should be followed, which may typically include metabolic screening, *FMR1* repeat lengths study, array analysis, a trio WES-based panel (WES in patient and parents) for genes associated with intellectual disability, and untargeted trio WES or, if already available, whole genome sequencing (WGS).

In case no diagnostic clues are present, a hypothesis-free approach can be chosen, such as an array analysis and a WES/WGS approach, first using a gene panel for TS/AG.

Approach in Case of Clues for Secondary Growth Disorders

If one or more diagnostic clues are indicative of a secondary growth disorder, further diagnostic procedures depend on the specific clinical features (online suppl. Table, Tables 1–3, Fig. 1). Our suggestions for additional laboratory testing are presented in Table 7. The four principal secondary growth disorders are (pseudo)precocious puberty, hyperthyroidism, GH overproduction and obesity. Obese children display an AG and an advanced bone age [81], which sometimes presents as HSDS >+2. However, pubertal and skeletal development are usually advanced, and consequently adult height is within the normal range [82]. The remainder of secondary growth disorders are extremely rare and when these diagnoses are expected, or when height is extreme (>+3 SDS, or >+2.5 SDS taller than TH), we suggest to refer the patient to a paediatric endocrinologist, clinical geneticist or centre of expertise.

Approach if No Clues for Primary or Secondary Growth Disorders Are Present, or if the Evaluation of Primary and Secondary Growth Disorders Renders Negative Results

In the absence of clues indicative of a primary or secondary growth disorder, or after excluding any suspected primary or secondary growth disorders, the next step is to decide if the growth pattern can be considered statistically normal, abnormal or very abnormal. If HSDS >+2, the diagnostic label can be ITS, which can further be subdivided into familial and non-familial. If HSDS <+2, but 1.6 SD taller than TH, the child is unusually tall for his/her parental height. If height accelerates more than expected (ΔHSDS >+1) without signs of puberty, one can consider the diagnosis CAG. If this seems unlikely, further follow-up may be a watchful approach.

If height is extremely tall for the population, we recommend referring the child to a paediatric endocrinologist, clinical geneticist or centre of expertise. We acknowledge that there is no scientific evidence for any cut-off points for these growth measures; we arbitrarily chose >+3 SDS for the population or >2.5 SDS taller than TH. In such patients, further genetic tests, for example a specific WES-based gene panel or a "trio WES" can be considered.

Reduction of Adult Height

Most children referred for TS/AG end up with the "non-diagnosis" ITS. Some of these (and some patients with primary TS syndromes as well) may wish to limit their adult height. Our present approach is that if the PAH is above +2.3 SDS, the therapeutic options (percutaneous epiphysiodesis or no treatment) are discussed with the patient and parents, taking their perspectives and coping abilities into consideration. Although in the Netherlands epiphysiodesis is only carried out if PAH is >205 cm for males and >185 cm for females, a slightly lower cut-off point for discussing this topic was chosen because of the inaccuracy of PAH (in the order of magnitude of ±5 cm). In this discussion, the physician explains the current status of percutaneous epiphysiodesis of the growth plates around the knee in terms of efficacy and safety [83]. Percutaneous epiphysiodesis can result in a diminution of one-third of the expected residual growth and is associated with few adverse effects [83–85]. The previously used treatment with supraphysiologic sex hormone treatment in adolescence is currently regarded as obsolete, because of the potential risk of decreased fertility in women and the low benefit to risk ratio in men [86–89].

Conclusion

In comparison to previous reviews on the diagnostic approach in children with TS/AG [2, 6–9], our approach starts with the child that is referred because of suspicion of TS/AG, instead of starting with the tall child. The main potential advantage of our approach is that this may lead

to a higher percentage of boys with KS already diagnosed before puberty, because prepubertal boys with KS usually have a height within the normal range but are crossing SDS lines between 5 and 8 years. Primary child health professionals should be aware of the spectrum of clinical (e.g. speech problems) and growth characteristics of KS and refer boys suspected for KS to the paediatrician. Similarly, the clinical features of MFS should be well known to primary and secondary child health care professionals, so that the mean age of diagnosing MFS may be decreased.

Our approach is also different because it offers a stepwise approach based on diagnostic clues from medical history, physical examination and growth assessment (Fig. 1). Other novel elements are the advice to use array analysis instead of karyotyping to diagnose or rule out KS, which may also lead to other diagnoses (copy number variants and uniparental isodisomy). We emphasise that most diagnoses associated with TS/AG are rare and usually associated with specific clinical features. This implies that a thorough medical history, physical examination and growth analysis are crucial in the diagnostic process.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

J.M.W. is member of advisory boards of OPKO, Merck, Ammonett, Aeterna Zentaris, Agios and Biomarin and received speaker's fees from Pfizer, Versartis, Sandoz, Lilly, Novo Nordisk, JCR, Merck and Ipsen. The other authors have no conflicts of interest to declare.

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Author Contributions

P.L. took the lead in writing the manuscript. J.M.W., W.O. and G.A.K. were involved in planning and supervised subsequent versions of the manuscript, and L.A.M. provided critical feedback of the draft guideline and revised subsequent drafts of this manuscript. All authors consented to the submitted version. Other members of the Working Group (B.B., S.G.K., R.J.O. and J.A.d.W.) approved the submitted version.

Appendix

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