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Evaluating the sensitivity and specificity of the UK and Dutch growth referral criteria in predicting the diagnosis of pathological short stature

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ABSTRACT

Objective The aim of this observational study was to evaluate the UK and Dutch referral criteria for short stature to determine their sensitivity and specificity in predicting pathological short stature. Adherence to the recommended panel of investigations was also assessed.

Study design Retrospective review of medical records to examine the auxological parameters, investigations and diagnosis of subjects referred to two paediatric endocrine clinics at the Royal London Children's Hospital between 2016 and 2021. We analysed: height SD score (HtSDS), height SDS minus target height SDS (Ht-THSDS) and height deflection SDS (HtDefSDS). The UK referral criteria were HtSDS <−2.7, Ht-THSDS >2.0 and HtDefSDS >1.3. The Dutch referral criteria were HtSDS <−2.0, Ht-THSDS >1.6 and HtDefSDS >1.0.

Results Data were available for 143 subjects (72% males) with mean (range) age 8.7 years (0.5–19.9). HtSDS and Ht-THSDS were significantly lower in the pathological stature (n=66) versus the non-pathological stature (n=77) subjects (−2.67±0.82 vs −1.97±0.70; p<0.001 and −2.07±1.02 vs −1.06±0.99; p<0.001, respectively). The sensitivity and specificity to detect pathology was 41% and 83% for the UK criteria (HtSDS <−2.7) compared with 59% and 79% for the Dutch criteria (HtSDS <−2.0), 48% and 83% for UK criteria (Ht-THSDS <−2.0) compared with 74% and 72% for Dutch criteria (Ht-THSDS <−1.6) and 33% and 68% for UK criteria (HtDefSDS >1.3) compared with 44% and 63% for the Dutch criteria (HtDefSDS >1.0). On average, each patient had 88% of the recommended investigations, and 53% had all the recommended testing. New pathology was identified in 36% of subjects.

Conclusions In isolation, the UK auxological referral thresholds have limited sensitivity and specificity for pathological short stature. The combination of HtSDS and Ht-THSDS improved the sensitivity of UK criteria to detect pathology from 41% to 68%. Attention to the child's genetic height potential prior to referral can prevent unnecessary assessments.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Effective growth monitoring can identify pathology in apparently healthy children, but the diagnosis of childhood growth disorders is frequently delayed.
⇒ The recommended UK growth monitoring (GM) of a single height measurement at aged 5 years is significantly less than other European countries.
⇒ Baseline screening tests can facilitate early diagnosis and treatment, but there are no standardised recommendations.

WHAT THIS STUDY ADDS

⇒ UK referral criteria for short stature are inferior to other European counties and have low sensitivity for the identification of growth disorders.
⇒ Optimal management requires accurate, detailed clinical and auxological assessment including review of genetic height potential. Greater awareness of non-pathological causes of short stature is needed.
⇒ An effective investigation protocol can identify a significant proportion of pathological short stature.

INTRODUCTION

Childhood growth is a sensitive marker of health and well-being. Growth retardation is an early sign of underlying pathology in children. The early detection and diagnosis of paediatric growth disorders has major health benefits, enabling early intervention to maximise future growth potential and identification of comorbidities that may occur as a result of the underlying pathology.[1]

Serial height measurements in paediatric populations will detect treatable disorders in apparently healthy children.[2] Primary causes of short stature, impacting the growth plate directly, include skeletal dysplasia, dysmorphic syndromes (including chromosomal disorders) and small for gestational age (SGA) with failure of catch-up growth. Secondary growth failure, resulting from a spectrum of disorders adversely affecting growth plate chondrogenesis, include psychosocial problems, endocrine disorders, such as growth hormone (GH) deficiency, chronic conditions such as malnutrition, coeliac disease,

Crohn's disease and renal disease and physical factors such as radiation.

Diagnostic delays of primary and secondary growth disorders are frequent. Commonly missed diagnoses include Turner syndrome (TS),[3–5] coeliac disease,[6] inflammatory bowel disease[7 8] and growth hormone deficiency (GHD).[9] In the UK, the majority of girls with TS are diagnosed after the age of 5 years (20% between the ages of 12 and 18 years) with short stature triggering the evaluation in most children and adolescents.[4] Large Danish and US TS cohorts showed similar delays with median/average ages at diagnosis of 15.1 and 9.0 years, respectively.[3 5] This delay exposes undiagnosed girls to the protracted risk of cardiovascular complications, ovarian dysfunction and autoimmune disease. In the UK, ~90% children/adolescents with TS present with short stature and early treatment with GH can translate into excellent growth responses.[4 10] Early diagnosis of GHD allows the identification of other associated pituitary deficiencies.[9] Additionally, the age of starting GH treatment in childhood GHD negatively correlates with long-term height gain.[11] Diagnostic delays are recognised in young patients with Crohn's disease resulting in more pronounced growth failure.[7 8] Delayed diagnosis in coeliac disease negatively impacts catch-up growth.[6]

A child suffering a prolonged suboptimal growth rate deviates away from normal centiles and genetic target height. The age of diagnosis and therapeutic initiation is critical in terms of both childhood growth and adult height. Historically, routine growth monitoring practices have varied across the UK with differences in policy, equipment and growth charts.[12] Outside the UK, similar variations across different countries have been reported.[13] Optimal growth monitoring should have adequate sensitivity and specificity to detect pathology while minimising the referral of healthy children.[14 15]

The UK National Child Measurement Programme (NCMP), introduced in 2005 to address the obesity epidemic, records single height and weight measurements of children in state-maintained education at reception (aged 4–5 years) and year 6 (aged 10–11 years).[16] UK guidance recommends referral of children with height below the 0.4th centile (<−2.67 standard deviations (SDs) from the mean) at 4–5 years.[17 18] This consensus cut-off has been estimated to identify 80% and 50% of children with undiagnosed GHD and TS, respectively.[19] Therefore, a significant number of children with the most common causes of pathological short stature will not be identified under the current programme.

The UK-WHO 2–18 years growth charts state three screening rules to define abnormal linear growth that should prompt referral to secondary care: a single height measurement below the 0.4th centile (equivalent to −2.67 SDS), a height centile more than three centile spaces (>2.0 SDS) below the midparental height centile and a drop in height (height deflection) of more than two centile spaces (>1.3 SDS).[18] When applied to children referred to growth clinics in the Netherlands, these UK guidelines performed poorly compared with the Dutch cut-off values in terms of diagnosis.[20]

Following referral, an effective diagnostic protocol should reliably identify primary and secondary growth disorders. Existing investigation protocols vary widely, and there are health economic controversies where there is low diagnostic yield in apparently healthy short children.[21] In 2008, a consensus statement on the management of idiopathic short stature recommended a comprehensive scheme of laboratory screening investigations,[22] subsequently endorsed by other expert groups.[1 15]

We present data from a cohort of children referred with short stature to a tertiary paediatric endocrinology centre in the UK. We assessed the diagnostic yield when applying the UK and Dutch growth referral criteria to determine the optimal use of growth monitoring strategies to identify pathological causes of short stature. Adherence to the recommended panel of investigations was also assessed.

METHODS

Participants

We retrospectively reviewed the medical records of a consecutive series of new patient referrals of children and adolescents with short stature referred to two tertiary paediatric endocrinology clinics at the Royal London Children's Hospital between 2016 and 2021 inclusive. Individuals were excluded if their medical records were incomplete, or the cause of short stature was known at the time of referral.

Auxology

Measurements were taken by a trained auxologist using a wall mounted Harpenden stadiometer, calibrated before each clinic. At the first presentation, the child and their attending parent(s) were measured once. If only one parent was present at the initial visit, the other parent was measured at a subsequent appointment. The child was remeasured 6–12 months later to assess the change in growth over time. These measurements were used to determine the following auxological parameters:

1. HtSDS: height SD score, that is, the height of the child at presentation compared with the average UK national standards (1990) for age and sex.
2. Ht-THSDS: the distance of the child's height SDS from the target height SDS. TH is the expected height of a child given the heights of the parents (mother's height (MH); father's height (FH)) and was calculated by Tanner's method: TH (boys)=(FH+MH+13)/2+4.5 and TH (girls)=(FH+MH−13)/2+4.5, where 13 is the mean height difference (in cm) between male and female adults and 4.5 is an estimate (in cm) for the secular trend.[23] Where FH was unknown, the TH was calculated using these formulae: TH boys (cm)=99.9+0.492 MH (cm) and TH girls (cm)=96.3+0.436 MH (cm) in which we assume a mother–offspring correlation of 0.45.[23]

3. HtDefSDS: change in the child's height SDS over time (height deflection). Individuals who were discharged after their first visit or had fused epiphysial plates on their initial bone age X-ray were not included in HtDefSDS calculations.

Auxology V.1.0 b 17 (copyright 2003 Pfizer) calculated SD scores (SDS) for height data based on the UK 1990 reference cohort. Bone ages (non-dominant hand/wrist radiographs using the Greulich-Pyle method) were performed on the same day as the height measurements and were considered normal if they were within ±2 SDS of the chronological age.[24]

UK and Dutch referral criteria

Auxological parameters were evaluated using the UK and Dutch referral criteria to determine which thresholds were met and allowed comparison of the sensitivities and specificities of each referral criterion for correctly identifying pathological short stature. The UK and Dutch referral criteria were[14 18 20]:

- HtSDS <−2.7 (UK)<−2.0 (Dutch).
- Ht-THSDS >2.0 (UK)>1.6 (Dutch).
- HtDefSDS >1.3 (UK)>1.0 (Dutch).

Diagnostic classification

We defined normal stature as HtSDS >−2.0 (>2nd centile) and normal distance from target height as Ht-THSDS <1.6, in-line with the Dutch definition of Ht-THSDS adopted by the European Society of Paediatric Endocrinology (ESPE) diagnostic classification of growth disorders.[25 26]

Individuals were categorised into four groups. Group 1: 'Pathological short stature': children diagnosed with primary or secondary growth failure according to the ESPE classification.[26] Group 2: 'Short stature of unknown aetiology': subjects with normal investigations but following a period of surveillance, HtSDS and Ht-THSDS remained abnormal (<−2.0 SDS and >1.6 SDS, respectively). Group 3: 'Non-pathological short stature': comprised familial short stature (FSS) where HtSDS was <−2 SDS but within the expected range for parental height (HtSDS-THSDS <1.6)[22] and constitutional delay of growth and puberty (CDGP) (absence of pubertal onset at age 14 years in males and 13 years in females with bone age delay >1 year).[27] Group 4: 'Normal': comprised subjects with 'normal stature' (HtSDS >−2.0 and Ht-THSDS <1.6) and subjects with 'normal growth trajectory' where HtSDS <−2.0 and Ht-THSDS >1.6 at presentation but in whom the growth parameters normalised (HtSDS >−2.0, Ht-THSDS <1.6) during the surveillance period.

Diagnostic investigations

Selected individuals referred with short stature underwent full clinical assessment including detailed history and examination by a consultant paediatric endocrinologist. No strict schedule of investigations was adhered to, and tests were requested according to the clinician's clinical judgement. Adherence to the recommended panel of investigations (proposed in the 2008 international consensus statement for the diagnosis and management of idiopathic short stature) was assessed (table 1).[2 15 22]

Statistical analysis

Continuous variables are summarised as mean±SD unless otherwise specified. For statistical analysis, the subjects were divided into pathological stature (groups 1 and 2) and non-pathological stature (groups 3 and 4). Descriptive statistics were used to display auxological data and

Table 1 Investigations recommended in children referred to secondary or tertiary care with short stature[2 15 22]

Investigation	To detect or exclude
Biochemical	
Full blood count (FBC)	Anaemia*
Renal function (creatinine and electrolytes)	Renal disorders
Liver function test	Liver disease
Erythrocyte sedimentation rate (ESR)	Infection/inflammatory disorders*
Calcium, phosphate (Ca/PO_4) alkaline phosphatase (ALP)	Renal/Ca/PO_4 disorders
Tissue transglutaminase (TTG)	Coeliac disease
Immunoglobulin A (IgA)	Coeliac disease
Insulin-like growth factor-1 (IGF-1)	Growth hormone deficiency
Free thyroxine (fT4), thyroid stimulating hormone (TSH)	Hypothyroidism
Karyotype (or if not available Follicle Stimulating Hormone (FSH) if <2 or>9 year)†	Turner syndrome
Radiological	
Bone age	Assess growth delay
Skeletal X-rays (if disproportion is present)	Skeletal dysplasias

Panel of investigations proposed in international consensus statements from Oostdijk *et al*[2], Cohen *et al*[22] and Grote *et al*[15].
*To screen for coeliac disease/cystic fibrosis.
†Only in females.

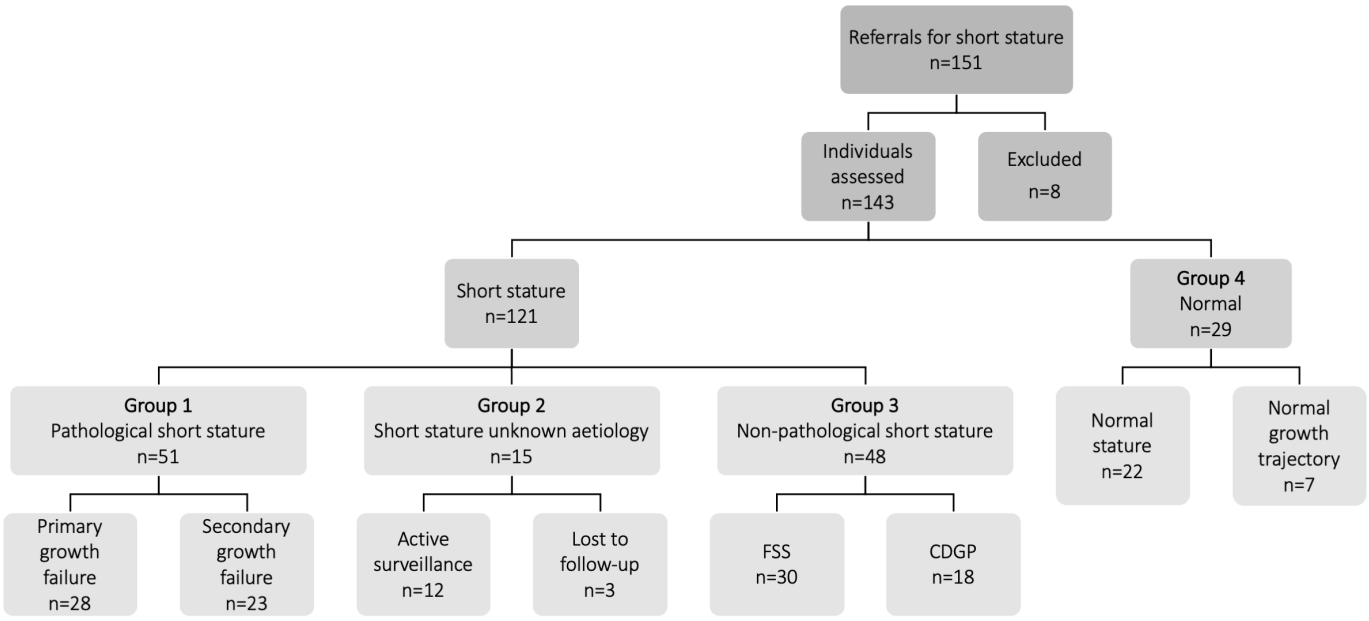

Figure 1 Flow diagram showing the outcomes of 151 consecutive patients referred to two London-based clinics for investigation of short stature. CDGP, constitutional delay of growth and puberty; FSS, familial short stature.

determine the proportions of children meeting the referral thresholds. The binomial test of proportions was used to compare the observed ratio of males to females referred. Unpaired t-tests compared the age and height SDS at referral and the SD scores of auxological measurements between the pathological and non-pathological groups. Specificity, sensitivity and likelihood ratios were calculated for referral thresholds, and the Wilson-Brown method calculated 95% CIs. GraphPad Prism V.9.0 (GraphPad Software, Inc, San Diego, California, USA) was used for statistical analysis. P values of <0.05 were considered statistically significant.

Patient and public involvement

Patients were not involved in the study design or recruitment. However, standardisation of short stature referral and investigation has been identified as a research priority by the Child Growth Foundation (CGF), a key UK patient group for childhood growth disorders. It is expected that data from this publication will be disseminated to patients and the public by the CGF.

RESULTS

Referrals and source of referrals (figure 1)

The medical records of 151 patients referred with short stature were reviewed. A total of 8 patients were excluded as their medical records were incomplete (n=3) or the cause of their short stature was already known at the time of referral (n=5) (Silver-Russell syndrome (11p15LOM): n=1, GH deficiency diagnosed at another centre: n=2, acquired hypothyroidism: n=1, mosaic male TS (46XY/45XO): n=1). Data were available for the remaining 143 individuals in whom mean (range) age was 8.7±4.82 (0.5–19.9) years. HtSDS data were available for all 143 subjects, Ht-THSDS data were available for 136 subjects (133 subjects with measurements for both parents and three with maternal measurements alone), and HtDefSDS data were available for 135 subjects. A significantly high proportion of patients, 103 (72%), were male (p=<0.0001), but there was no difference in the mean age at referral of males versus females (8.7±5.0 years; vs 9.4±4.3) (p=0.51) or the height status (mean HtSDS −2.2 vs −2.5) (p=0.11). Forty-six (32%) referrals originated from primary care, 93 (65%) from secondary care and 4 (3%) from tertiary centres.

Pathological stature subjects (groups 1 and 2)

Fifty-one (36%) of children with mean HtSDS −2.63 (±0.85) had pathological short stature (group 1) with 28/51 (55%) having primary and 23/51 (45%) secondary causes of growth failure (table 2). A further 15 children, with mean HtSDS −2.78 (±0.75), had short stature of unknown aetiology (group 2) following detailed investigation. This group included 12 who had persistent abnormal growth following active surveillance (range 1.8–5.4 years), and three children with abnormal growth who were lost to follow-up.

Non-pathological stature subjects (groups 3 and 4)

Group 3 comprised 48 (34%) referrals with mean HtSDS −2.34 (±0.67) who had non-pathological short stature (30 FSS and 18 CDGP). Of the 29 (20%) 'normal' subjects (group 4) with mean HtSDS −1.45 (±0.52), 22 had normal stature (HtSDS >−2.0, Ht-THSDS <1.6) and were discharged. Following a period of surveillance (range 1.0–2.2 years), a further seven subjects had a normal growth trajectory and were discharged. All subjects in group 4 had normal investigations and bone age.

Table 2 The *range* of diagnoses identified in children found to have pathological causes for their short stature ('pathological short stature' group 1) (n=51)

Diagnosis	Sex M:F	Age or mean age (range)	Clinical details
Primary growth failure (n=28)			
Turner syndrome (n=1)	F	13.9	Mosaic 46, XY (46) and 45, X (4)
Noonan syndrome (n=2)	1:1	7.2 (5.3–9.1)	Het. SOS2 gene mutation (c.1775G>T) (n=1) Het. A2ML1 gene mutation (c.1175G>T) (n=1)
Silver-Russell syndrome (n=1)	M	14.9	Clinical diagnosis with NHCSS score 4/6*
SGA with no catch-up growth (n=21)	15:6	6.2 (1.3–15)	Birth weight SDS <–2.0 and height <–2.0 SDS at 4 years
SHOX (n=1)	M	14.3	Large deletion 47.5 kb 160 kb downstream of SHOX
Other genetic diagnosis (n=2)	2:0	3.0 (2.8–3.2)	Leigh syndrome SURF1 gene mutation (p.Arg264fs) Myhre syndrome SMAD4 gain of function gene mutation
Secondary growth failure (n=23)			
GH deficiency (n=17)	14:3	8.0 (2.0–15.8)	GH peak of <6.7 ng/L
Coeliac disease (n=1)	F	14.0	Anti-TTG IgA >200, confirmed by duodenal biopsy
Hypothyroidism (n=1)	F	19.9	TSH 19.0miU/L, fT4 11.6 pmol/L (NR 0.27–4.2 and 10.5–24.5, respectively)
GH-IGF-I axis disorder (n=4)	3:1	8.5 (2.2–16.5)	Het. GHR gene mutation 42718139T>G, c.810–15T>G) (n=1) Het. missense *IGFI* gene variant (n=1) Large deletion (0.24 mB) at chromosome 15q26.3 (haploinsufficiency *IGF1R* gene) (n=1) Primary IGF-I deficiency - diagnosed by IGFGT (n=1)

*Triangular face, large head, minimal subcutaneous fat, poor feeding and slow weight gain.
GH deficiency, growth hormone deficiency diagnosed on GH provocation test (insulin tolerance or glucagon as per standard protocols) [36] with sex hormone priming for boys >10 years and testicular volumes of 9 years with Tanner breast stage ≤2; IGFGT, IGF-1 generation test (GH 0.033 mg/kg/day over 5 days according to standard 'IGFGT' established protocol) primary IGF-I deficiency defined as IGF-1 increment <15 ng/mL; NR, normal range; SDS, SD scores; SGA, small for gestational age (birth weight and/or length <–2 SDS) with no catch-up growth after 2–3 years; SHOX, short stature homeobox gene.

Comparisons of pathological and non-pathological subjects

HtSDS and Ht-THSDS were significantly lower in the pathological (groups 1 and 2 combined) compared with the non-pathological stature (groups 3 and 4 combined) groups (−2.67±0.82 vs -1.97±0.70; p<0.0001) and (−2.07±1.02 vs −1.06±0.99; p<0.0001), respectively. HtDefSDS during assessment did not differ between the pathological and non-pathological groups (−0.49±2.71 vs −0.16±2.82; p=0.49) (online supplemental table 1).

Referral criteria (see tables 3 and 4)

The auxological measurements for each child were compared with the UK referral criteria (table 3). Only 28%, 30% and 33% of referrals fulfilled the HtSDS, Ht-THSDS and HtDefSDS criteria, respectively, but 63% of children met the threshold for at least one referral criterion and 45% met the threshold for HtSDS and/or Ht-THSDS. The sensitivity (to detect pathology), specificity (correctly identify 'healthy' children who do not meet the criteria) and likelihood ratios (diagnostic accuracy) for each criterion are presented in table 4. All three individual UK criteria had low sensitivities (33%–48%) with HtSDS and Ht-THSDS giving the highest values. The combination of HtSDS and/or Ht-THSDS improved the sensitivity to 68%. Any positive criteria gave the highest sensitivity (80%) but with reduced specificity (52%). Application of the Dutch referral guidelines improved the sensitivity but reduced the specificity in our cohort (table 4).

Diagnostic investigations (table 5)

Four children (one FSS and three normal stature) had no investigations performed. Of the children who were investigated (n=139), group 2 (unknown aetiology) had the most testing performed (mean 97% of the recommended tests shown in table 1 and group 4 (normal) had the fewest tests (mean 82% of the recommended tests). Fifty-three per cent had the complete panel of laboratory investigations. IGF-I and full blood count were the mostly frequently performed tests (94% and 93%, respectively).

Table 3 The number of children meeting the UK referral criteria

UK referral criterion	Pathological stature (groups 1 and 2) n (%)	Non-pathological stature (groups 3 and 4) n (%)	Total n (%)
Height SDS (HtSDS)			
<–2.7	27 (41)	13 (17)	40 (28)
>–2.7	39 (59)	64 (83)	103 (72)
Ht-THSDS			
>2.0	29 (48)	13 (17)	42 (30)
<2.0	32 (52)	62 (83)	94 (70)
Height deflection SDS (HtDefSDS)			
>1.3	21 (33)	23 (32)	44 (33)
<1.3	43 (67)	48 (68)	91 (67)
Any positive criterion			
1+positive criteria	53 (80)	37 (48)	90 (63)
0 positive criteria	13 (20)	40 (52)	53 (37)
HSDS and/or Ht-THSDS criteria			
1 positive criteria	45 (68)	19 (25)	64 (45)
0 positive criteria	21 (32)	58 (75)	21 (32)

Ht-THSDS, height SDS–target height SDS; SDS, SD scores.

Erythrocyte sedimentation rate and bone age were the least commonly performed tests (78% and 81%, respectively), no children had bone age alone. Of the 40 female patients in our cohort, 28 (70%) had karyotyping for Turner's syndrome (71% and 100% of females in groups 1 and 2, respectively). Those in group 1 who did not have a karyotype, already had a diagnosis (SGA, GHD or hypothyroidism). GH provocation testing was performed in 39 (27%) individuals. GH deficiency (peak GH <6.7 ng/mL) was diagnosed in 17 (40%), and all GHD patients were commenced on recombinant human growth hormone (hGH) therapy. The remaining 22, with normal GH secretion, were subsequently diagnosed with GH-IGF-I axis disorders (n=3), Noonan syndrome (n=1), Silver-Russell syndrome (n=1), SGA (n=1), non-pathological SS (n=7; 4 FSS, 3 CDGP) and nine had unknown aetiology. Fifty-seven children (40%) underwent genetic testing, including microarray, *SHOX, FRAX, STAT5B* gene analysis and Silver-Russell testing, which led to a genetic diagnosis in 11 (19%) patients.

DISCUSSION

Short stature is common, comprising around half of referrals to paediatric endocrinology clinics.[28] In the current study, significantly more males (>70%) were referred but without any sex difference in the age at referral. Other published series report similar striking sex differences with more than twice as many boys as girls referred to specialist care for evaluation of short stature.[29] Research also shows that the degree of short stature in girls who are referred is greater at presentation than in boys and

Table 4 Sensitivities and specificities and likelihood ratios of the UK and Dutch referral criteria

Criterion	UK			Dutch		
	Sensitivity – pathology (% (95% CI))	Specificity – pathology (% (95% CI))	Positive likelihood ratio	Sensitivity – pathology (% (95% CI))	Specificity – pathology (% (95% CI))	Positive likelihood ratio
HtSDS	41 (30 to 53)	83 (73 to 90)	2.4	59 (47 to 70)	79 (69 to 87)	2.8
Ht-THSDS	48 (36 to 60)	83 (73 to 90)	2.7	74 (62 to 83)	72 (61 to 81)	2.6
HtDefSDS	33 (23 to 45)	68 (56 to 77)	1.0	44 (32 to 56)	63 (52 to 74)	1.2
HtSDS and/or Ht-THSDS criteria	68 (56 to 78)	75 (65 to 84)	2.8	83 (73 to 90)	61 (50 to 71)	2.2
Any +criteria	80 (70 to 88)	52 (41 to 63)	1.7	91 (82 to 96)	39 (29 to 50)	1.5

UK criteria: HtSDS <–2.7, Ht-THSDS >2.0 and HtDefSDS >1.3 SDS. Dutch criteria: HtSDS <–2.0, Ht-THSDS >1.6 and HtDef SDS >1.0[14].
HtDefSDS, height deflection SDS; HtSDS, height SDS; Ht-THSDS, height SDS–target height SDS; SDS, SD scores.

Table 5 Laboratory investigations performed in the subjects

Individuals in each diagnostic category having investigations	Mean % of recommended investigations	% of group who had all the recommended investigations
Pathological (group 1) (n=51)	89	47
Primary growth failure (n=28)	88	39
Secondary growth failure (n=23)	89	57
Unknown aetiology (group 2) (n=15)	97	73
Under active surveillance (n=12)	97	75
Lost to follow-up (n=3)	93	67
Non-pathological (group 3) (n=47)	86	60
FSS (n=29)	83	53
CDGP (n=18)	91	72
Normal (group 4) (n=26)	82	41
Normal stature (n=19)	78	41
Normal growth trajectory (n=7)	94	43
Total (n=139)	87	53

CDGP, constitutional delay of growth and puberty; FSS, familial short stature.

that both physicians and parents can contribute to the gender bias in patterns of referral and treatment.[30] The referral bias may reflect differing attitudes towards short stature between the sexes and social pressures that may impact males more than females. This bias could lead to missed diagnosis of underlying disease in short girls. Indeed, a recent cross-sectional analysis of short stature in England revealed higher prevalence in girls compared with boys (2.09% vs 1.77%).[31] In our cohort, the height status of males and females at referral were comparable. Our data demonstrated similar proportion of underlying pathology (35%) in males and females, refuting the theory that growth disorders are more common in referred males.

The 1998 UK 'Coventry consensus" meeting recommended that single height measurements, with a cut-off point at the 0.4th centile (1990 charts), came closest to satisfying the criteria for growth surveillance.[17] However, the reported sensitivity of the UK recommended cut-off (height <0.4th^{t}centile) is very low (30%) for the diagnosis of pathological growth disorders.[20 32] Our data support this, as only 41% of patients with pathological stature had height <0.4th percentile. Application of the less strict Dutch cut-off of <2.5 SDS improved the sensitivity to 59% but at the expense of the specificity, which fell from 83% to 79%.

Additional guidance of distance from target height of more than three centile spaces (>2.0 SDS) and height deflection of more than two centile spaces (>1.33 SDS) are specified on the current UK-WHO 2–18 years growth charts.[18] When applied to a Dutch cohort, these additional rules give low reported sensitivities of 39% for distance from target height and 4% for height deflection.[20] Our study also reports low sensitivities of 48% and 33%. For any one of the three UK criteria being fulfilled, the reported sensitivity was much lower (57%) than in our study (80%).[20] Particularly low sensitivities are achieved for height deflection, and this may reflect logistical difficulties in obtaining serial measurements and the time needed to demonstrate growth trends. Repeated measurements needed for height deflection assessments also require more expertise than single measurements. Low sensitivities were also noted for height deflection cut-offs used in the Netherlands and Finland (4% and 9%, respectively).[20] The Hackney Growth Initiative study concluded that due to inherent inaccuracies, height deflection was not recommended for screening in the community.[33] The significant improvement in sensitivity of height deflection from 4% to 33% in this study may reflect the accuracy and reliability of our clinic measurements compared with those performed in the community. This suggests that with appropriate training and time, accurate height measurement should be achievable by all healthcare professionals, including those in primary care. Importantly, the sensitivity increases to 68% if a combination of HtSDS and/or Ht-THSDS are applied to our cohort. This sensitivity can be further enhanced to 83% if the less stringent Dutch HtSDS and/or Ht-THSDS cut-offs are adopted, but this reduces specificity from 75% to 61%.

Growth monitoring must distinguish pathological from normal variant short stature, as the latter results eventually in normal adult height.[34] Fifteen per cent of referrals to our clinics had completely normal stature (>2nd centile and normal for midparental height). A similar proportion of these were referred from primary and secondary care (22% vs 21% referrals, respectively) but none from tertiary care. An additional 34% referrals had non-pathological short stature. A significant proportion (21% of total children referred) had FSS. These children should be identified by accurate

assessment of parent's height(s) prior to referral. Consideration of the child's genetic target height can prevent unnecessary referral, investigation and health service resource wastage. This highlights the need for enhanced training across the medical community (both primary and secondary care) of accurate height and parental height assessment. Constitutional delay of growth is a common reason for referral to paediatric endocrinology. Lack of pubertal signs in females aged 13 years and males aged 14 years with delayed bone age suggest this diagnosis.[27] It affects 2% of children of pubertal age and was identified in 13% of our referrals. It has a strong familial basis; therefore, identifying a family history of delayed puberty is important. Seven (5%) patients presented with abnormal growth parameters but within a relatively short surveillance period (1–2years) their growth trajectory normalised. Of these, three had height SDS <2, two had subnormal height deflection for age and one was short for target height. This suggests that watchful waiting is appropriate for a small number of children, particularly where only one growth parameter lies outside the normal limits.

A high proportion of children (36%) had 'true' pathology accounting for their short stature. Although this is higher than population-based studies, a similar percentage of organic causes was reported in the UK Oxford growth clinic.[35] The mean age of our referrals was 8.7 years with many children (72%) referred later than school entry (5 years). The most common pathological diagnoses were SGA with no catch-up growth (41%) and GH deficiency (34%). Early initiation of licenced treatments, for example, GH therapy for these and other licenced indications can ensure optimal height gain. Four subjects with genetic/chromosomal disorders (Turner, Noonan, SHOX deficiency and Silver-Russell) were diagnosed very late (9.1–14.9years), and 57% SGA patients were over 5 years of age. Early diagnosis of secondary growth disorders is also associated with enhanced height gain. In the current study, the mean age of GHD diagnosis was 8 years, and the subjects with coeliac disease and hypothyroidism were diagnosed close to or following completion of linear growth.

Sisley *et al*[21] challenge the practice of blanket testing of asymptomatic children with short stature. However, we found that a focused testing panel alongside detailed clinical assessment can confirm or exclude important pathological causes of short stature and could facilitate early diagnosis. As expected, most testing in our cohort was performed in the most challenging group 2 patients (unknown aetiology). Although the patients with normal stature had fewer investigations, many underwent unnecessary testing. This suggests there may be an over-reliance by clinicians on investigations that could equate to increased health service costs. Just over half of our referrals had the complete panel of tests. This is considerably more than in Sisley *et al*[21], where only 2.1% of patients had all the recommended testing. All the girls with short stature of unknown aetiology had karyotyping.

This retrospective study is a relatively small and represents selected cohort, drawn from an ethnically diverse urban population and not representative of all UK communities. However, many of the findings are consistent with existing evidence from other cohorts.

CONCLUSION

The UK NCMP has high national uptake (95%) but the 0.4th centile cut-off has low sensitivity for the detection of pathological growth disorders. Referrals for short stature are rarely initiated by national screening (NCMP) and are primarily driven by parental concern. Current referral patterns lead to overlooked cases, referral gender biases and delayed diagnoses. The present study demonstrates a sizeable minority of referrals were healthy children with normal height or non-pathological short stature. Combining the subject's height and its deviation from target height is more valuable than any isolated criterion in discriminating between normal variant and pathological short stature. This combined approach will lead to improved detection of pathology and reduce inappropriate referrals, enabling more children with genuine short stature to be identified and access rapid baseline investigations earlier to confirm or exclude pathology. Adoption of less stringent Dutch cut-offs may enhance detection of true positives but at the cost of increased healthy referrals.

Contributors HLS conceived and designed the study; GW, SC, AA, LM and RW were involved in acquisition of data; GW and SC analysed and interpreted the data overseen by HLS. HLS, GW and SC drafted the work, and MOS and HLS revised it critically for important intellectual content. All authors approved the final version. HLS is the guarantor for this work.

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Patient consent for publication Not applicable.

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