BSPED recommendations for the initial clinical assessment, investigation and genetic testing of children with growth failure and/or short stature

The BSPED Growth Disorders Special Interest Group (SIG) has produced these clinical standards for the initial clinical assessment, investigation and genetic testing of children with short stature. These recommendations are aimed at all clinicians referred children with short stature and provide an overview of the investigation pathway from primary to secondary / tertiary care.

Aim: To optimise and standardise the initial diagnostic approach to children with short stature:

- Improve the recognition and early diagnosis of growth disorders in children
- Standardise the current investigations for short stature including judicious use of genetic investigations
- Position genetic testing earlier in the investigative pathway
- Avoid unnecessary investigations

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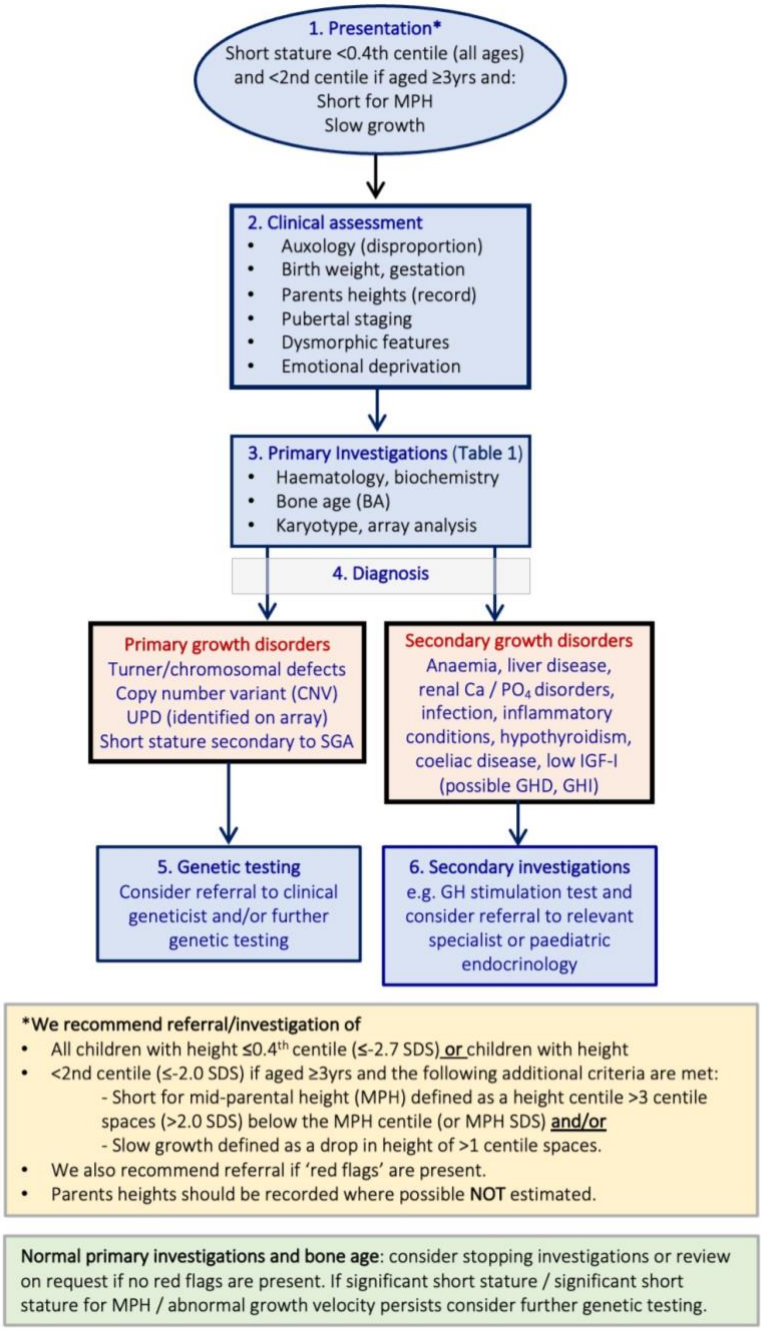
CLINICAL ASSESSMENT, INVESTIGATION AND GENETIC TESTING OF CHILDREN WITH GROWTH FAILURE AND/OR SHORT STATURE

Figure 1. Clinical diagnostic approach to short stature



MPH, mid-parental height; SDS, standard deviations below the mean; UPD, uniparental disomy; SGA, small for gestational age (defined as birth weight and/or length <-2 SDS); GH, growth hormone; GHD, growth hormone deficiency; GHI, growth hormone insensitivity.

1. Presentation of short stature: See the *BSPED-SIG Clinical standards for the growth assessment and referral criteria for children with a suspected growth disorder*[1].

- *Short stature* Short stature may be a normal variant. However, we recommend referral/investigation of all children with height ≤0.4th centile (≤-2.7 SDS) or <2nd centile (≤-2.0 SDS) if aged ≥3yrs and the additional criteria are met (see below).

We also recommend referral/investigation if the following additional criteria are met:

- *Short for mid-parental height (MPH)* defined as a height centile more than 3 centile spaces (>2.0 SDS) below the MPH centile (or MPH SDS) and/or
- *Slow growth* defined as a drop in height of >1 centile spaces and/or
- Presence of 'red flags' see below.

2. Diagnosis of short stature: It is important to commit to a diagnosis
Classification of short stature[2]**:**

1. **Primary:** Intrinsic to growth plate e.g., skeletal dysplasia, SGA*, chromosomal disorders
2. **Secondary:** Extrinsic to growth plate
    i. Nutritional insufficiency
    ii. Endocrinopathy e.g., GHD
    iii. Excess inflammatory cytokines e.g., Crohn's disease
    iv. Extracellular fluid e.g., acidosis
    v. Physical factors e.g. trauma/radiotherapy

***Short stature related to being born small for gestational age (SGA)** The label SGA is **not a diagnosis** and further investigations may still be required to establish the precise aetiology. It is defined as children born with a birth weight or length <-2 SDS without spontaneous catch-up growth by 2-4 years.

Idiopathic short stature (ISS) The label ISS is **not a diagnosis** and further investigations may still be required to establish the precise aetiology. It is defined as short stature (height <-2 SDS), normal birth size, absence of abnormal physical features, normal general investigations, normal body proportions and absence of major dysmorphic features.

3. Clinical assessment Early assessment of short stature is important to establish a diagnosis, institute health surveillance if required and to enable early access to therapy to improve outcomes. The assessment involves history, examination (careful phenotyping), pubertal staging and accurate auxology. Parents heights should be recorded (not estimated).

History

- Family history of short stature / other disorders
- Consanguinity
- Birth weight and length
- Developmental milestones
- Feeding problems in the first year
- Maternal lifestyle
- Ethnic background
- Systems enquiry
- Recurrent infections

Examination

- Height
- Weight
- Head circumference
- Disproportion (sitting height)
- Asymmetry
- Pubertal staging
- Dysmorphic features
- Muscular hypertrophy

Red flags for a genetic origin of short stature

History

- SGA with no catch-up growth*
- Severe short stature <-3 SDS
- Consanguinity
- A short parent - autosomal dominant defect
- Family history of short stature

Examination

- Dysmorphic features
- Microcephaly
- Relative macrocephaly
- Disproportion
- Features of growth Hormone Insensitivity (GHI) or IGF-1 deficiency - possible GH-IGF-1 axis defect

*Remember Netchine-Harbison clinical scoring system for Silver Russell syndrome[2]

3. Investigation

Table 1. Primary investigations recommended in children referred to secondary or tertiary care with short stature.[3-5]

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-I)†	Growth hormone deficiency
Free thyroxine (fT4), thyroid stimulating hormone (TSH)	Hypothyroidism
Karyotype (or if not available Follicle Stimulating Hormone (FSH) if <2 or >9 yr)**	Turner syndrome
Radiological	
Bone age‡	Assess growth delay
Skeletal X-rays (if disproportion is present)	Skeletal dysplasia

Panel of investigations proposed in international consensus statements from Oostdijk et al, Cohen et al and Grote et al. *To screen for coeliac disease/cystic fibrosis; †undernutrition and chronic illness cause low values and < 3 years of age difficult to interpret as normal range encompasses lower limit of assay, **only in females, ‡less reliable under 2 years of age; anatomical abnormalities may also be detected and suggestive of skeletal dysplasia.

5. Genetic testing

Consider a joint approach with clinical genetics or a research/specialist centre. Accurate phenotyping is essential to guide the approach. A genetic cause may be present in up to 40% of cases. Consider pursuing a genetic diagnosis if red flags (above) are present. A genetic cause for short stature can:

- Guide decisions for GH therapy including potential contraindications
- Provide prognostic information
- Facilitates surveillance of associated co-morbidities that may require treatment
- End diagnostic odyssey for caregivers and end diagnostic uncertainty
- Prompt genetic counselling and diagnosis in other family members

Techniques available:

i. *Candidate gene sequencing* Request specific gene analysis. Useful if typical features of a particular syndrome or strong clinical suspicion of a growth disorder e.g. SHOX deficiency*

ii. *SNP or CGH array* Both techniques can be used for CNV assessment (identification of genomic deletions or duplications which can lead to faltering growth). To assess for uniparental disomy (UPD) use SNP array.

iii. *Methylation analysis* If an imprinting disorder is suspected e.g., SRS or Temple syndrome.

iv. *Gene panels* Targeted sequencing of a panel of genes. Consider for atypical presentation or wide genetic basis e.g. skeletal dysplasia or Noonan syndrome.

v. *Exome or genome sequencing* Sequencing of entire exome (coding regions) or genome (coding and non-coding regions). For potential novel syndrome or atypical presentation.

*SHOX deficiency may present with isolated short stature and may be identified by whole exome/genome sequencing (v)

References:

1. https://www.bsped.org.uk/media/oo1hsxet/clinical-standards-for-growth-assessment-and-referral-criteria-for-children-with-a-suspected-growth-disorder.pdf
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3. Oostdijk W, Grote FK, de Muinck Keizer-Schrama SM, Wit JM. Diagnostic approach in children with short stature. Horm Res. 2009;72(4):206-17.
4. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. The Journal of clinical endocrinology and metabolism. 2008;93(11):4210-7.
5. Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama SM, Verkerk PH, Wit JM, et al. Developing evidence-based guidelines for referral for short stature. Arch Dis Child. 2008;93(3):212-7.