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Notes

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ABSTRACT

Objective: To establish evidence-based guidelines for growth monitoring on a population basis.

Study design: Several auxological referral criteria were formulated and applied to longitudinal growth data from four different patient groups, as well as three samples from the general population.

Results: Almost 30% of pathology can be detected by height standard deviation score (HSDS) below −3 or at least two observations of HSDS below −2.5 at a low false-positive rate (<1%) in 0–3-year-old infants. For 3–10-year olds, a rule concerning distance to target height of >2 SD in combination with HSDS <−2.0 has the best predictive value. In combination with a rule on severe short stature (<−2.5 SDS) and a minor contribution from a rule on "height deflection", 85.7% of children with Turner syndrome and 76.5% of children who are short because of various disorders are detected at a false-positive rate of 1.5–2%.

Conclusions: The proposed guidelines for growth monitoring show high sensitivity at an acceptably low false-positive rate in 3–10-year-old children. Distance to target height is the most important criterion. Below the age of 3 years, the sensitivity is considerably lower. The resulting algorithm appears to be suitable for industrialised countries, but requires further testing in other populations.

Growth monitoring in infancy and childhood has been part of preventive child health programmes for more than a century, and short stature or growth retardation is regarded as a relatively early sign of poor health. Despite this longstanding and wide acceptance of growth monitoring, there is little evidence for its effectiveness and efficiency.[1] In developing countries, growth monitoring is primarily aimed at detecting malnutrition. In industrialised countries, the major purpose of growth monitoring is early detection of growth disorders, such as Turner syndrome (TS), growth hormone deficiency and coeliac disease (CD).

For early identification of children with abnormal growth, one requires good growth-monitoring systems as part of preventive child health programmes, well-defined and accurate referral criteria, and good diagnostic work-up after referral. Although most industrialised countries have a child health programme that includes regular growth monitoring, there is a wide diversity in protocols used for growth monitoring and diagnostic work-up of growth disorders, and a virtual absence of experimental studies on the efficacy of these screening and diagnostic procedures.[2] Few guidelines have been published on referral criteria and

diagnostic work-up for children with impaired growth, and these are based on consensus meetings rather than experimental evidence.[3 4] In the few experimental studies on growth monitoring, various referral criteria have been used.[5–7]

In The Netherlands, a consensus meeting was held in the mid-1990s to establish auxological referral criteria.[3] Three auxological parameters were chosen: height standard deviation score (HSDS), change in HSDS (HSDS deflection), and distance between height and target height SDS. Additional criteria included clinical signs (disproportion or dysmorphism), specific symptoms (such as those associated with emotional deprivation), or previous history of low birth weight and/or length (small for gestational age, SGA). Thereafter, however, it was shown that application of these auxological criteria would lead to far too many unnecessary referrals.[8]

Consequently we started a project aimed at producing evidence-based guidelines for growth monitoring, with a high positive predictive value at an acceptable false-positive rate. We previously studied the predictive value of various auxological criteria for the detection of TS,[9] and evaluated the auxological parameters of patients with various causes of growth failure referred to paediatric clinics (unpublished). In this report, we describe the performance of the best screening rules in terms of sensitivity and specificity in four groups of patients with growth disorders and in three reference samples, and propose that these can be used in growth-monitoring protocols.

METHODS

Materials

Longitudinal height and weight data from four different patient groups and three reference populations were used. Each group was analysed separately. For the patient groups, only measurements before or at age of diagnosis or start of diet (CD cohort) were taken into account.

The first group of patients consisted of 777 girls with TS, collected from three sources and previously described by van Buuren et al.[9] The second group contained new patients referred for short stature to the outpatient clinics of the general paediatric departments of two hospitals (Erasmus MC - Sophia Children's Hospital, Rotterdam and Spaarne Hospital, Haarlem) in 1998–2002. Of 542 children referred to the clinic, 27 were found to have a pathology (mainly growth hormone deficiency (n = 7), CD (n = 7) and TS (n = 3)). Only these 27 children were included in the analyses. The third group consisted of patients with cystic

Table 1 Number of children and mean number of measurements per child (shown in parentheses) in each group

Age group	Number of measurements	Limburg (n = 970)	ZHN (n = 400)	SMOCC (n = 2151)	TS (n = 777*)	SSP (n = 27)	CF (n = 216)	CD (n = 120)
0–3	≥1 and at least 1 weight measurement before 0.1 years	931 (11)	341 (11)	1942 (8)	353 (4)	23 (6)	89 (5)	86 (7)
	≥2 with 0.5–1 year interval and at least 1 weight measurement before 0.1 years	810 (12)	321 (14)	1835 (9)	158 (8)	15 (9)	32 (10)	66 (12)
3–10	≥1	958 (3)	361 (4)	0	524 (5)	17 (3)	25 (2)	22 (4)
	≥2	893 (4)	339 (4)	0	472 (6)	13 (3)	14 (3)	16 (5)

*492 children had measurements under the age of 3 years.
CD, coeliac disease; CF, cystic fibrosis; Limburg, all children born in the years 1989 and 1990 in Landgraaf and Kerkrade; SMOCC, Social Medical Survey of Children Attending Child Health Clinics; SSP, short stature due to pathology; TS, Turner syndrome; ZHN, children born in 1985–1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn.

fibrosis (CF) collected from three major CF clinics in The Netherlands: Erasmus MC - Sophia Children's Hospital in Rotterdam (n = 166), University Hospital Maastricht (n = 30) and Juliana Children's Hospital in The Hague (n = 20). The last group contained patients with CD consisting of two separate subgroups: (1) a retrospective study described by Damen *et al*,[10] in which they studied catch up growth in patients with coeliac disease; (2) a prospective study on catch up growth by Boersma *et al*.[11]

The first reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2151 children born in The Netherlands in 1988–1989, consisting of length and weight data for children up to the age of 2.5 years.[12] The second reference population was a cohort of all children born in the years 1989 and 1990 in Landgraaf and Kerkrade, located in the southern part of The Netherlands ("Limburg", n = 970).[8] The third population was a sample of children born in 1985–1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn, The Netherlands ("ZHN", n = 400).[12a]

Screening rules

By combining evidence found in previous studies, three auxological referral criteria were formulated. Only criteria of practical value for child health programmes were considered.

The first rule takes genetic height potential into account by comparing the HSDS of the child with its target height in combination with a HSDS below a certain cut-off. In our earlier study on TS,[9] as well as in a study on a mixed population of short children (unpublished work), we found that this combination offers the best predictive value. We calculated the test characteristics for a distance between HSDS and target height of more than 2 SDS, with cut-off points for height SDS of −2, −1.5 or −1.0 SDS. This rule was labelled "short for target height".

The second rule concerns HSDS. HSDS is generally considered one of the most important referral criteria, especially when parental height is not available.[2][4] To keep the percentage of false-positives low, we chose, for historical and pragmatic reasons, a cut-off of −2.5 (~0.6th centile), as it is the lowest line on various growth charts. This rule was labelled "very short".

The third rule applies to a deviation from the expected growth channels, expressed as either height velocity (cm/year or SDS for age) or a change in HSDS. The change in HSDS is thought to be more suitable, because it better reflects the deviation from canalisation of the growth curve, and because height velocity depends not only on age but also on HSDS position. Although the usefulness of low growth velocity for

growth screening appears limited,[7][13] it has long been considered the most important growth parameter, and many clinicians can show examples of cases where deflection of the growth curve is the only indication of a growth disorder—for example, an acquired growth hormone deficiency caused by a brain tumour, or primary hypothyroidism caused by Hashimoto disease. Van Buuren *et al*[8] found that a "height deflection" of more than 0.25 SDS per year would lead to a large number of false-positives. The predictive value of a deflection can be improved if one demands a continuous deflection over 3 years (eg, 0.25 SDS/year over at least 3 years),[9][13] a larger deflection over an undefined time interval (eg, a deflection of >1.0 SDS), or in combination with an absolute HSDS <−2. In the present analysis, we combined various expressions of "height deflection" (per year or cumulative) with various cut-off points for HSDS (<−2.0, <−1.5 or <−1.0). This decision rule was labelled ""height deflection"". We decided that deflection with a cut-off of 1.0 SDS over an undetermined time interval would be most practical, as this should detect both a slow and fast bend in the growth curve, and several growth reference diagrams include lines with a distance of 1 SDS.[14] In countries where a distance of 0.66 SD is used, a deflection of 1 SD can be easily assessed by multiplying the 0.66 SD interval by 1.5.

Analytical procedures

Length, height, weight, target height, body mass index and weight for length or height were expressed as SDS, using recent Dutch, Turkish and Moroccan reference data.[15–18] All criteria were first analysed for all age groups. As growth curves in the first 3 years can cross SDS lines when birth length SDS is far from target height SDS, and length measurements are less accurate, specificity of the various rules is expected to be lower than in later years, leading to too many referrals.[8] We therefore performed separate analyses in two age groups (0–3 and 3–10 years), and calculated test characteristics for different cut-off values (HSDS −3.0, −2.5, −2.0, −1.5 and −1.0) and other additive parameters.

Data on parental height were often (4–58%) missing from the various datasets. We imputed these data under the assumption that data were missing at random using multivariate imputation by chained equations (MICE).[19][20] The imputation model consisted of the last known HSDS (except for the CF population, where we chose the HSDS closest to the age of 5 years instead because in most children catch-up growth has resulted in a normal height at this age[21]), HSDS, weight SDS, weight for height SDS, body mass index SDS, gender (except for the TS group as these were all girls), HSDS of the father and/or HSDS of the mother (if available), ethnicity (except for the TS and Limburg cohort) and, for the CF and CD cohorts, age at

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Table 2 Referral criteria with the best test characteristics

Rule	Criteria	Rule No
0–3 years		
Repeatedly very short: at least twice a length SDS <-2.5	HSDS_1 <-2.5 and HSDS_2 <-2.5 AND 0.5$\leqslant$Age_2-Age_1$<$1 year AND (birth weight $\geqslant$2500 g or, if no birth weight available, then first measurement within 0.1 year (5 weeks) with weight SDS$\geqslant-2$, and gestational age $\geqslant$37 weeks (or not available))	1
Extremely short: at least once a length SDS <-3	HSDS <-3 AND (birth weight $\geqslant$2500 g or if no birth weight available, then first measurement within 0.1 year (5 weeks) with weight SDS $\geqslant-2$, and gestational age $\geqslant$37 weeks (or not available))	2
Combination of rules 1 and 2		3
3–10 years		
Short for target height	HSDS-THSDS <-2 AND HSDS <-2	1
Very short: length SDS <-2.5	HSDS <-2.5	2
Height deflection	ΔHSDS <-1 AND HSDS <-2	3
Combination of rules 1, 2 and 3		4

diagnosis or start of diet. The number of iterations was set to 15. Predictive mean matching was used to create parental height imputations.

Target height (TH) was calculated by Tanner's method with an additional correction for secular trend:

TH(boys) = ((FH+MH+13)/2)+4.5

TH(girls) = ((FH + MH−13)/2) +4.5

where FH is father's height, and MH is mother's height. The target height standard deviation score (THSDS) was calculated as THSDS(boys) = (TH(boys)−184)/7.1 and THSDS(girls) = (TH(girls)−170.6)/6.5.

Calculations were based on the assumption that a child is referred if the growth pattern meets the criteria of a given screening rule for the first time. If a child only has one measurement, the child cannot comply with criteria concerning deflection or repetition and is therefore considered as non-referred. All rules were analysed separately as well as in combination with the others. A false-positive rate of <1% for the separate rules and <2% for the combined rules was assumed to be acceptable from the perspective of preventive child healthcare.

RESULTS

Table 1 shows the number of children per age group and the mean number of measurements.

Table 3 Sensitivity of several auxological rules for four different patient groups (true-positives)

Rule	TS (%)	SSP (%)	CF (%)	CD (%)
0–3 years				
Repeatedly very short*	7.1	14.8	0.0	1.2
Extremely short	13.0	26.1	6.7	4.7
Combination	14.7	26.1	6.7	4.7
3–10 years				
Short for target height	76.9	58.8	8.0	27.3
Very short	74.0	58.8	4.0	18.2
Height deflection†	13.4	17.6	0.0	18.2
Combination	85.7	76.5	8.0	27.3

If a child has only 1 measurement, the child cannot be referred according to the repeatedly "very short" rule and the absolute "height deflection" rule.
*In the subgroup with $\geqslant$2 measurements, sensitivity would be 15.8% for TS, 26.7% for mixed pathology, and 1.5% for CD.
†In the subgroup with $\geqslant$2 measurements, sensitivity would be 14.8% for TS, 23.1% for mixed pathology, and 25.0% for CD.
CD, coeliac disease; CF, cystic fibrosis; SSP, short stature due to pathology; TS, Turner syndrome

Applying the three auxological criteria separately to all age groups resulted in a high number of referrals in the general population (presumably false-positives) (data not shown). This was primarily due to referrals in the 0–3 year group, the "height deflection" and "short for target height" rules producing a high false-positive rate. Extra criteria were added and the cut-off points were varied for children under the age of 3 years. The performance of the different rules was then tested in the two age groups. Table 2 shows scenarios with the best test performance, and tables 3 and 4 show the yield of these best scenarios in terms of sensitivity (true-positives) and 1−specificity (false-positives), respectively.

For children under the age of 3 years, the true-positive rate for pathology is modest, if the false-positive rate has to be kept low. The best rule consists of an HSDS <-2.5 at least twice within 1 year (very short repeated) or an HSDS <-3 (extremely short), confined to infants born at or after 37 weeks of gestational age (or when information on gestational age is not available) and born with a weight $\geqslant$2500 g (if birth weight was not available, the first measurement within 0.1 year (5 weeks) with a weight SDS $\geqslant-2$ was used). With this rule, 14.7% of the children with TS can be detected, at a false-positive rate of <1%. This is probably an underestimation, because the value of 7.1% for a repeated HSDS <-2.5 increased to 15.8% when only the subgroup of children with more than two measurements was assessed. The "short for target height" rule did not result in acceptable test characteristics.

Above the age of 3 years, 85.7% of the children with TS and 76.5% of the children with mixed pathology could be detected by the combination of the "short for target height" rule, the "very short" rule and the "height deflection" rule.

If a stepwise approach is taken for 3–10-year-old children, the "very short" rule would add 42 patients (7.7%) to the 76.9% of girls with TS who complied with the "short for target height" rule. For the group of children with short stature due to mixed pathology, three cases (17.7%) would be added to the 58.8% of children who complied with the "short for target height" rule. The addition of this rule would increase the false-positive rate by 0.3% (one child) in the ZHN cohort and 0.7% (seven children) in the Limburg cohort. Applying the "height deflection" rule after the two other rules would only add a few extra patients (four patients (0.8%) for TS, none for the children with mixed pathology), and the false-positive rate would increase by 0.6% (two children).

Table 4 Estimated percentages of referrals in the three reference populations (false-positives)

Rule	Limburg	ZHN	SMOCC
0–3 years			
Repeatedly very short*	0.2	0.0	0.4
Extremely short	0.2	0.6	0.7
Combination	0.3‡	0.6	0.9‡
3–10 years			
Short for target height	0.7	1.1	NA
Very short	0.9	0.8	NA
Height deflection†	0.1	0.8	NA
Combination	1.5¶	1.9¶	NA

If a child has only 1 measurement, the child cannot be referred according to the repeatedly "very short" rule and the absolute "height deflection" rule.
*Based on subgroup with ⩾2 measurements; specificity is 0.2% for Limburg and 0.4% for SMOCC.
†Based on subgroup with ⩾2 measurements; specificity is 0.1% for Limburg and 0.9% for ZHN.
‡No significant difference between Limburg and SMOCC for the combined rule 0–3 years (χ^2 (1) = 2.79, p = 0.10).
¶No significant difference between Limburg and ZHN for the combined rule 3–10 years (χ^2 (1) = 0.38, p = 0.54).
NA, not available; SMOCC, Social Medical Survey of Children Attending Child Health Clinics; ZHN, children born in 1985–1988, attending school doctors between 1998 and 2000 in Leiden and Alphen aan den Rijn.

DISCUSSION

We have established evidence-based guidelines for growth monitoring on a population basis. In 0–3-year-old infants, after exclusion of babies born preterm and with a low birth weight, we found that a HSDS <-3 or at least two observations of a HSDS <-2.5 within 1 year gives the best performance at a low false-positive rate. However, only 14.7% of the children with TS and 26.1% of the children with other growth disorders could be detected with these rules. For 3–10-year-old children, the "short for target height" rule in combination with the "very short" rule and a minor contribution of the "height deflection" rule detected 85.7% of children with TS and 76.5% of children who were short because of various disorders at a low false-positive rate.

The low efficacy and efficiency of growth monitoring between 0 and 3 years of age, particularly for rules involving target height and length deflection, is probably mainly caused by the low correlation between length and mid-parental height at birth, which rapidly increases during the first 3 years of life.[22] Crossing over SDS lines in this age period is therefore not unusual. This is in line with our observation that referral based on a low length velocity or a large distance to target height would lead to too many referrals in this age group, and confirms our earlier data.[8] For this age group, the only useful referral rule
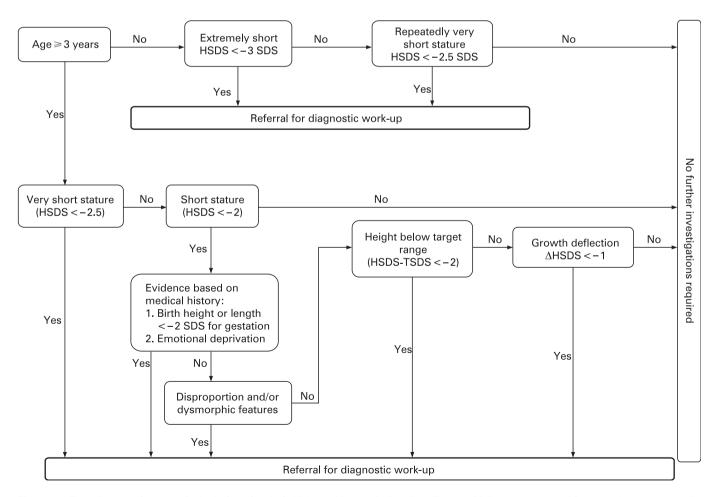

Figure 1 Flow diagram of proposed criteria for referral of children with growth disorders. These guidelines are proposed for screening purposes only. In the case of an unusual growth pattern, certainly if associated with clinical symptoms or signs, even if it did not comply with the rules for referral or the recommendations, doctors should still be free to follow their clinical judgement. HSDS, height standard deviation score; THSDS, target height standard deviation score.

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What is already known on this topic

- ▶ Short stature is regarded as a relatively early sign of poor health.
- ▶ Early identification of children with abnormal growth requires a good growth-monitoring system, well-defined and accurate auxological screening criteria, and a good diagnostic work-up afterwards.

What this study adds

This is the first large evidence-based investigation on various types of auxological criteria for the assessment of children with short stature, with a flow diagram as a result.

was based on an extremely low or repeatedly low HSDS. Only 15–26% of the growth disorders studied were detected, and even fewer infants with CF or CD. This is in concurrence with our previous studies on CF and CD, in which we found that weight is a better auxological tool than length at this young age (unpublished).

In concurrence with our earlier observations on TS,[9] we found that, also in a mixed set of growth disorders diagnosed in a paediatric clinic, the best decision rule for detecting children older than 3 years with pathology is the "short for target height" rule. This result contrasts with earlier speculations that this parameter might be too inaccurate because of the uncertainty of parental height.[4] From the preventive healthcare perspective, the "height deflection" rule is of little use. We propose to keep this rule in the algorithm, as it is important that the rare cases of growth deflection due to acquired growth disorders are detected in good time. To keep the false-positive rate low, we combined HSDS deflection with a HSDS <-2.0, but a severe deflection irrespective of the HSDS reached should be considered as an alarm signal.

Not only auxological rules are important, but also a number of clinical symptoms and signs. If medical history reveals that birth weight and/or length was low, and HSDS is <-2.0 from the age of ~3 years, the diagnosis of persistent short stature after SGA can be made. It is known that ~10% of children born SGA do indeed remain short and do not achieve normal adult height.[23] Referral to a growth clinic is needed for further diagnostic tests and for the decision on growth hormone treatment. As catch-up can occur within the first 2 years, but sometimes it occurs between the age of 2 and 3, we set the age limit for catch-up at 3 years. It is important in the medical history to check for symptoms of emotional deprivation (psychosocial short stature) but fortunately this a rare finding.[24–26] Obviously, a thorough physical examination should be carried out, and special attention should be given to body proportions and dysmorphic features. Abnormal body proportions are important signs of skeletal dysplasia, and dysmorphic features can direct attention to various primary growth disorders ("syndromes"). We propose that combining a HSDS <-2.0 with any of these clinical symptoms and signs is sufficient reason for referral. Figure 1 is a graphical representation of the algorithm.

Concern has been raised about the applicability of target height, as the height of the father is often missing. One can either ignore the height of the mother altogether and not correct for parental height, or one can assume that the father's height is the same as the mother's with a correction of 13 cm (the mean difference in adult height between men and women). It is not known which option is better, but we favour the latter. A similar approach can be taken if one of the parents is known to have a pathological growth disorder.

The UK90 standards use an inter-centile bandwidth of 0.67 SDS instead of 0.5 or 1 SDS, so that the two lower centiles are

the 0.4th and 2.3th centiles, equivalent to -2.67 and -2.0 SDS. If the 0.4th centile (-2.67 SDS) was used instead of -2.5 SDS (0.6th centile), specificity would be slightly higher and sensitivity slightly lower than calculated for a height SDS of -2.5. With respect to the "deflection", crossing an interval of 1 SD is equal to 1.5 times the interval between two reference lines on the UK charts (or 50% of the interval between the P50 and P2.3). For a more accurate estimate, the first SDS and the second SDS can be calculated and then subtracted.

In conclusion, the proposed guidelines for growth monitoring show a high sensitivity at an acceptably low false-positive rate in 3–10-year-old children. Distance to target height is the most important criterion. Below the age of 3 years, the guidelines can only detect a small percentage of pathology at an acceptably low false-positive rate, and are therefore of limited use. Besides auxological rules, clinical information taken from the medical history and physical examination can offer important guidance in taking the decision to refer patients for further tests. Finally, no algorithm can fully replace clinical judgement, and, in the case of an unusual growth pattern, even if it does not comply with the rules for referral, doctors should be encouraged to follow their clinical judgement.

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Images in paediatrics

The midline nasal lesion

This 2-year-old boy presented to the otolarynology department with a discharging midline nasal lesion. The lesion, present since birth, had occasionally discharged some pus-like fluid. It was usually treated with oral antibiotics, but, on this occasion, it had failed to respond, and there was some associated local swelling (fig 1). The child was pyrexial but otherwise well.

CT and MRI revealed the lesion to be a nasal dermoid with a meningeal communication. There was associated dural enhancement (fig 2). Pneumococcus was isolated from blood cultures. The acute infection was managed with intravenous antibiotics before being evaluated by the local craniofacial team.

Nasal dermoids arise when there is failed involution of the dural projection which extends through the foramen caecum in the first trimester. Encephaloceles and nasal gliomas may form in the same way.[1] The nasal dermoid may have an associated sinus on the nasal dorsum and discharge hairs or sebaceous material.[1] Around 20% have a persisting dural communication, which may result in the development of intracranial complications.[1 2]

CT and MRI enable accurate evaluation of bony detail and the detection of intracranial disease. Complete surgical

Figure 1 Clinical photograph showing a midline nasal punctum with some widening of the nasal bridge.
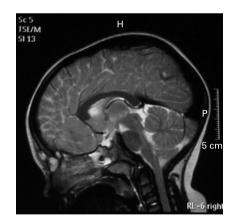

Figure 2 Sagittal T2-weighted magnetic resonance image showing hyperintense nasal dermoid and sinus with meningeal enhancement.

excision is the treatment of choice. This may be performed by a variety of approaches depending on the size and extent of the lesion.[3]

Midline nasal lesions may not always be clinically impressive. However, they should be taken seriously, given the potential complications associated with them, and referred early for surgical evaluation.

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Patient consent: Consent has been obtained for publication of this case and the figures.

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