Growth

Height monitoring as a diagnostic test

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Commentary on the paper by van Buuren *et al*

Measurement of height is an important component of child health care and has been widely incorporated into paediatric practice. Yet little is known about how it performs in terms of sensitivity and specificity for detecting growth disorders. This lack of information impacts on health care in a number of ways. First, it is difficult to inform public health policy via recommendations for height monitoring, which has resulted in a plethora of statements made about referral for height assessment. One consequence of this has been to opt for a minimum standard for practice as exemplified in *Health for all children*.[1] Second, the lack of information on test performance in the early steps of the short stature evaluation decision tree makes it difficult to interpret subsequent tests and ultimately the likelihood of the presence or absence of disease.[2]

The Dutch study reported by van Buuren and colleagues in this issue[3] addresses for the first time these issues of test performance by quantifying the role of height monitoring in the identification of girls with Turner's syndrome (TS). TS is the ideal condition to use to show the methodology as it fulfils several important screening criteria—it is common (1 in 2500 live female births), a confirmatory test is available with high sensitivity and specificity (karyotype), and early intervention can appreciably influence outcome (growth, osteoporosis, and management of ovarian dysfunction). One of the problems with TS is that universal karyotype screening is unfeasibly expensive—a pre-karyotype assessment is required. The clinical manifestations of TS are variable whereas the short stature, particularly with respect to parental height, is not, so height monitoring clearly should play an important role.

The Dutch group treats height monitoring as a diagnostic test using two distinct populations, TS girls (cases) and normal girls (controls), which together provide estimates of sensitivity, specificity, and median referral age for a series of distinct screening rules for referral for height assessment. The three basic rules they consider, which are based on Dutch guidelines, are: (1) height standard deviation score (SDS) below a given cut-off; (2) height SDS below a given cut-off based on target height; and (3) height SDS velocity below a given cut-off. The performance of these rules, both separately and in combination, is assessed for a series of distinct cut-offs and age(s) when they apply, and the best performing rules identified.

What should we look for in a screening rule? It needs a high sensitivity, so it identifies most girls with TS, but more importantly it must have a very low false positive rate (that is, very high specificity). A false positive rate exceeding say 1% (specificity $<99\%$) would have serious implications for the workload of specialist growth clinics. With this in mind the British 1990 height reference chart[4] includes a 0.4th centile curve which predicts a false positive rate of only about 0.4%,[5] corresponding to an absolute height SDS rule with a cut-off of -2.67.

With this in mind the results of the Dutch study are enlightening. The absolute height rule performs relatively poorly, with a specificity of only 98.1% (sensitivity 41%) with a cut-off of -3.5 up to age 3 and 3.0 afterwards. This is appreciably worse than the 99.9% predicted theoretically, and the reason why it performs so poorly is not obvious. It may be because the Dutch height reference does not adjust birth length for gestation.

The parentally adjusted rule has a much higher specificity, up to 99.4% or better, and its sensitivity is also higher, near 70%. The deflection (velocity) rule gives specificities close to 100% but sensitivities below 60%. The authors propose a combined rule involving these two components with specificity 99.4% and sensitivity 79%.

Two strengths of the approach are the ability to compare the performance of different screening rules, and the use of pre-existing data. This means that large prospective studies are not required, and that screening rules can be developed for any growth disorder where suitable data exist. For the purists, one slight disadvantage is that the estimates of sensitivity and specificity are potentially biased. This is because the TS population is itself biased, consisting of girls who have had to draw attention to themselves to be identified. We do not know what proportion of TS patients were missed in assembling the TS cohort. If the factor identifying TS girls was short stature, this might improve test performance. Also, using datasets drawn over a long period of time may tend to incorporate the more severely affected in the earlier years. As a result the sensitivity and specificity results need to be interpreted with caution.

The clinical significance of the findings is intriguing. First, the current UK view is that height velocity does not contribute usefully to growth monitoring,[1 6] yet one of the proposed screening rules includes height velocity. Second, the findings confirm the value of parental height adjustment. So how should these results affect the UK recommendations for height assessment? Measuring height velocity involves two sets of costs: the resource cost of having to collect the longitudinal height data, and the delay cost of potential cases having to wait an extra year or more before being diagnosed, rather that relying on their height at presentation. So does the benefit of including height velocity justify the cost? In our view the answer is no. Adding velocity to the parentally adjusted rule with cut-off -2 increases the sensitivity by just 3% for the same specificity. A better approach would be to focus on the parental height rule, which can in theory be improved using formal regression methods—that is, height adjusted for familial height.[7 8] The authors' methodology could quantify the benefit of this approach.

From the epidemiologist's standpoint these results are valuable in showing how to study the performance of growth assessment techniques ''in the field''. The ideal approach would be to compare height measurement performance with a karyotype assessment in all girls born in the UK, but such a study would be very expensive—only 120–150 TS girls are born each year, so the study would need to last several years. However, if one accepts that the sensitivity and specificity may be different in the ''field'', then at least the proposed approach allows for a more precise estimate of the role of height monitoring in the population, and provides a methodology which could be applied to other areas of interest such as growth hormone deficiency. The approach and the information it provides are to be welcomed and should now be used to inform height monitoring practice.

Arch Dis Child 2004;**89**:296–297.
doi: 10.1136/adc.2003.039560

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Infection

MRSA: the problem reaches paediatrics

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Commentary on the paper by Khairulddin *et al*

The pattern of MRSA in UK hospitals nowadays is very different to that seen a decade or so ago. Then, MRSA was confined mainly to a relatively small number of hospitals in the southeast of England and some of the large provincial conurbations.[1] However, new strains of epidemic MRSA, especially EMRSA-15 and EMRSA-16, have since emerged and spread to become established to some extent in virtually every hospital in the country.[1] Between 1992 and 2002 the proportion of blood culture isolates of *Staphylococcus aureus* reported by microbiology laboratories to the Communicable Disease Surveillance Centre that were methicillin resistant increased from 3% to 43%.[2] The pervasiveness of MRSA is underlined by the fact that MRSA now accounts for over 30% of *S aureus* bacteraemias in every health care region in England, Wales, and Northern Ireland.[3]

MRSA are frequently not only resistant to methicillin and other β-lactam antibiotics, but to other classes of antibiotics as well.[1] The glycopeptide antibiotics teicoplanin and vancomycin are currently the mainstay of treatment of infections with MRSA.[1] However, strains of MRSA have emerged that exhibit higher than usual minimum inhibitory concentration values for these antibiotics: glycopeptide-intermediate *S aureus* (GISA), or vancomycin resistant *S aureus* (VISA).[4] Although not fully glycopeptide resistant, infections with these isolates often respond poorly to treatment with these agents. Fortunately only a small number of infections with these bacteria have been reported so far. Nevertheless, they present a considerable threat for the future.

MRSA has been considered to be less of a problem in children, and indeed it is sometimes suggested by non-paediatric microbiologists that children may be less susceptible to colonisation or infection with MRSA. However, this seems unlikely, given the ubiquity of *S aureus* as a childhood pathogen. It is much more likely that the lower incidence of MRSA in children relates to demographic and epidemiological differences. A relatively small proportion of children receive in-patient hospital treatment, which is the most important risk factor for acquisition of MRSA.[1] Paediatric units tend to be relatively independent of adult services, and to have better provision of isolation facilities, so that even in hospitals with a high prevalence of MRSA it is possible for paediatric services to be relatively unaffected.[5]

> ''There is an increasing incidence of healthcare associated infections with MRSA in children with underlying conditions predisposing to infection with *S aureus*''

However, the situation in children may be changing. There was a recent report in this journal of an increasing incidence of MRSA in children in Leeds with cystic fibrosis,[6] and in this issue, Khairulddin and colleagues[7] report that the proportion of bacteraemias with *S aureus* in children in England and Wales that were due to MRSA increased from 0.9% to 13.1% between 1990 and 2000. Also, Arkwright and colleagues[8] have recently reported an age related increase in MRSA prevalence in children in Manchester with atopic dermatitis. Neonatal units are another area of concern, with several reported MRSA outbreaks that have been difficult to control and associated with considerable morbidity.[9 10] What all of these studies point to is an increasing incidence of healthcare associated infections with MRSA in children with underlying conditions predisposing to infection with *S aureus*. At the same time, recent data from the USA indicate that MRSA accounts for up to 60% of community acquired infections with *S aureus* presenting to hospitals.[11–15] Many of these cases occurred in children with few or no risk factors for acquisition of MRSA, suggesting that MRSA is circulating among children in those communities.[11 12 14 15]

The emergence and spread of MRSA in children is of considerable concern, because *S aureus* is a major paediatric pathogen, both in hospitals and in the community. In hospitals, aside from the fact that infections with MRSA are expensive and inconvenient to treat, MRSA tends to occur as an additional pathogen, rather than replacing methicillin sensitive *S aureus* (MSSA).[1] Thus when MRSA becomes established in a hospital, the overall burden of health care associated infections tends to increase. The occurrence of MRSA among children in the community could mean that common childhood cutaneous infections such as impetigo would begin to present a real therapeutic challenge, with few, if any, options for oral or topical therapy.[16]

> ''There should still be an opportunity to halt, and even reverse, the current increase in MRSA in children''

Recent data on MRSA in children suggest that paediatrics may be where adult practice was in the mid 1990s. If that is so, then there should still be an opportunity to halt, and even reverse, the current increase in MRSA in children. First, we need more information on the current extent of the problem.