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The ABCD of target height

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Title: “The ABCD of Target Height”

Dear Editor,

Thanks for valuable comments.

I have entered "midparental height" on the line 15 of the page 3 and subsequently used MPH abbreviation, as requested.

I am more than happy if you can consider this work as an Editorial.

Please let me know – since it was not clear – if this re-submission is fine, or I should re-submit the paper as an Editorial from the beginning.

Best regards,

Dr. Gianluca Tornese

Title: The ABCD of target height

Running title: The ABCD of target height

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ABSTRACT

Short stature is a common referral in paediatric endocrinology, and the role of the target height (TH) is fundamental in its diagnostic management. When considering TH, it is necessary to remember four key features, easily memorized with the ABCD's rule: A for Amplitude: if one of the parents is unusually tall or short, the TH will be a poor predictor of attained height; B for Betrayal: the rate of the paternal discrepancy is not negligible (3.7%) therefore TH may not take into account the actual paternal genetic contribution to child's stature; C for Cheating: when parents report their heights, there is often a substantial error, so they should always be measured too, to have usable data; D for Descendant: a child is part of an entire family; therefore, information on heights (especially an unusually tall or short stature) of other relatives should always be collected to identify an autosomal-dominant pattern or maybe a *de novo* mutation causing short stature. This simple rule can help clinicians to use TH correctly in clinical practice.

Key words: short stature, target height, familial short stature, midparental height, family

TEXT

Short stature is the most common referral in paediatric endocrinology (1). Since approximately 80 percent of height is determined by genetic factors (2), the potential size a child will reach as an adult height can be estimated by calculating the target height (TH), a standard procedure for every paediatrician over the last 50 years. The 90% of children's height is known to be within 1.5 SDS (approximately 2 centile lines) of mid-parental height (MPH) (3), and if the estimated final height is outside this range, a variant growth pattern or a pathologic cause should be considered. While Galton introduced the MPH in 1886, which was simply the average of parents' heights (4), it was Tanner in 1970 who defined an adjustment concerning gender on the MPH in girls, the father's height minus 13 cm is averaged with the mother's height; in boys, the mother's height plus 13 cm is averaged with the father's height (5).

In recent years, several corrections to TH have been proposed: a correction that considers the secular trend (the increase in height over decades) (6), a calculation based directly on the average of the height SDS of parents (7), a revision that takes into account assortative mating and the parent–offspring correlation (8).

However, when considering TH – especially during short stature evaluation - it is necessary to remember four key features, easily memorable with the ABCD's rule.

A is for Amplitude

TH is based on the assumption of an equal magnitude of polygenic factors derived from both parents. However, if one of the parents is unusually tall or short, the TH will be a poor predictor of attained height since genetics is not just a matter of average (8): the child

will inherit traits relating to stature more from one parent than the other. This matter is essential when examining familial short stature (FSS) as it should be considered when at least one parent has height of ≤-2 SDS, even if their TH was not ≤-2 SDS; otherwise, an inherited monogenic condition in an autosomal-dominant pattern cannot be classified as FSS (9). On the other hand, in cases of autosomal-recessive genetic abnormalities, while heterozygous parents may have near-normal height, homozygous child may result in severe short stature (10).

B is for Betrayal

A common Latin phrase said: "Mater semper certa est, pater numquam" (i.e., the mother is always certain, the father is never). It should always be kept in mind that the rate of "paternal discrepancy" (i.e., when children are identified as being biologically different from the man whom they believed to be the father) is not negligible: according to various study, it is estimated from 0.8% in Switzerland to 30% in southern England, with a median of 3.7% (11). These percentages indicate that, even if calculated correctly, the TH may not consider the father's real genetic contribution to the child's stature. However, If the father's height is unknown, a correction could be applied using only the maternal height (12). In addition to this, the possibility of heterologous fertilization must be investigated when taking medical history.

C is for Cheating

Generally, when parents report height, an incorrect measurement is communicated, even higher than 8 cm. In particular, adults with short stature or parents of a children referred for short stature tend to overestimate their height, making the TH unreliable (13,14). This overestimation has its clinical effects as the use of reported rather than measured parental

heights could lead to a high rate of inappropriate GH testing (e.g., when considering a child's height <-1.5 SDS compared to TH) (14) and can also interfere in the evaluation or treatment of several other conditions (e.g., FSS and children born SGA without catch-up growth). Therefore, parents should always be directly measured for usable data.

D is for Descendant

We must not forget that a child is part of a whole family, other than parents; therefore, information on heights (especially an unusually tall or short stature) of siblings, grandparents, uncles, and aunts should always be collected (15). Sometimes an autosomal-dominant pattern can be evident over several generations; rarely, a *de novo* mutation causing short stature can be identified in a parent and his/her child if the grandparent are of average/tall stature.

Conclusion

This simple rule can help doctors to use TH properly in clinical practice. Although we cannot easily identify "paternal discrepancy", all paediatricians should measure the parents' heights (when possible), ask about the other family members' stature, and remember not to consider TH tout court when one parent is unusually tall or short.

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NOTES

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