Letter to the Editor

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Reforming the male Tanner genital scale

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Dear Editor,

The Tanner scale, used to assess pubertal stage in children, was first described by J.M. Tanner and R.H. Whitehouse in 1955 [1]. For boys, it consisted of genital (G) and pubic hair (P) stages 1 to 5. Description of the genital development stage (G) included growth and changes of the penis, scrotum and testes. In a longitudinal study on pubertal development of 228 boys living in a children's home (the Harpenden Growth Study), the age of arrival at these different genital and pubic hair stages were accurately assessed and described [2]. In a later study, reanalysing data from the British 1965 growth study [3], Tanner reshaped the genital stages into penis stages (excluding testes) and showed at which ages a testis volume of 4 mL and 12 mL was attained [4]. The testicular volumes were measured with the Prader orchidometer, which was introduced in 1966 [5]. In this study, the 50th centile of both penis stage 2 and a testis volume of 4 mL was at 12 years. Accordingly, in most cases, a testis volume of 4 mL corresponds to a certain degree of pituitary-gonadal axis activation, producing enough androgens to yield genital stage 2. Hence, genital stage 2 (G2) is generally considered the first physical sign of central pituitary gonadal activation and thereby initiation of puberty. In the current male Tanner scale used by most physicians, testicular size is incorporated in Tanner stage G and an explicit subdivision of

genital development stages into penis/scrotum stages and testicular size is not in practice anymore [6].

It is, however, important to realise that changes to both the testes and penis/scrotum are a result of pituitary-gonadal activation (normally), but develop by different pathways. Under the influence of androgens, there is a gradual change in the penis/scrotum and eventually testicular growth. However, testicular growth initially occurs because of follicle-stimulating hormone (FSH)-driven Sertoli cell and seminiferous tubule growth.

Because of the incorporation of testicular growth in the genital Tanner stages, pubertal assessment is prone to misclassification. A careful evaluation (and classification) of the testes and penis/scrotum separately guards the physician for diagnostic pitfalls. The following three cases illustrate why genital development stages (better: penis/scrotum stages) should be reserved for evaluating androgen production, and that the assessment of testicular size has a different purpose in physical examination.

- A. An 8-year-old boy was referred to our clinic because of premature pubarche and growth acceleration. The main diagnostic considerations were central precocious puberty, premature adrenarche and late-onset congenital adrenal hyperplasia (CAH). His Tanner stage was assessed as G3P3. The testicular volume was 2 mL. Small testes indicated an inactive pituitary-gonadal axis which ruled out central precocious puberty. Additional investigations were performed for non-central causes of precocious puberty and led to the diagnosis of late-onset CAH.
- B. A 14-year-old boy with short stature supposedly due to constitutional delay of growth and puberty was investigated by the paediatric endocrinologist. He had a Tanner stage of G3P3 and the testicular volume was 20 mL. Such testicular development was an unexpected finding, as virilisation had just recently begun. Additional blood investigation showed relatively low gonadotropin and testosterone levels. Thyroid function tests indicated central hypothyroidism, and genetic testing led to the diagnosis of IGSF1 deficiency syndrome. This explained the discrepancy between

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pubertal development and testicular volume as macroorchidism is a key feature of this syndrome [7].

- C. A 15-year-old boy was assessed for pubertal development and had a Tanner stage of G5P5. The testes were 6 mL and were soft upon palpation. He had a history of medulloblastoma for which he had received treatment with craniospinal irradiation and chemotherapy (cisplatin) at the age of 11 years. His plasma testosterone level was in the normal adult range. The incongruence between Tanner stage and testis volume was explained by the gonadotoxic effects of chemotherapy mainly affecting Sertoli cells (which determine testicular volume) and not Leydig cell function.

These three cases illustrate that separate classification of penile/scrotal change and testicular volume provides a more accurate description of pubertal development, especially in pathological conditions where G2 is not accompanied by a testicular volume of 4 mL and vice versa. Penile and scrotal change is a result of increasing androgen production, whereas testicular growth is a result of central activation of the pubertal axis or pathogenic *IGSF1* variants. Testicular growth may be impeded by chemotherapy or primary endocrine testicular failure (with adrenal androgens promoting penile and scrotal change) such as Klinefelter syndrome (partial/stagnating virilisation and small firm testes).

The penis/scrotum and testes were still considered separately by Tanner in a 1985 longitudinal study on height and development of North American children [8]. They are nowadays joined in the genital Tanner stages. We think it is better to view these two features as distinct components of genital and pubertal development and propose to divide the current Tanner genital development stages for boys into a genital stage (penis/scrotum stage, abbreviated G) and a separately reported testis volume measurement.

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