EBioMedicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Long-term Healthcare of People with Disorders of Sex Development: Predictors of Pubertal Outcomes of Partial Androgen Insensitivity Syndrome – Authors' Reply

Ngee Lek [a,b,c], Rieko Tadokoro-Cuccaro [a], Ieuan Hughes [a,*]

[a] University of Cambridge, Department of Paediatrics, Cambridge, United Kingdom
[b] KK Women's and Children's Hospital, Department of Paediatrics, Singapore
[c] Duke-NUS Medical School, National University of Singapore, Singapore

We thank Dr. Fukami for his Commentary [1] which nicely summarises the essentials of our study [2] and is well placed in the context of the challenges facing clinicians in the management of PAIS patients raised male. We would wish to take issue, however, with the emphasis placed on testicular dysfunction and somatic mosaicism of the AR as possible contributors to the phenotypic variation observed in PAIS.

The study of [3] is quoted with respect to evidence of testicular dysfunction in some cases of PAIS. We did not design our study specifically to assess the characteristics of pituitary-gonadal function which are well known in AIS, particularly the CAIS form. An undescended testis which is often longstanding in AIS does not impair Leydig cell testosterone production in general, in contrast to Sertoli and germ cell function. Indeed, adult women with CAIS who have not been gonadectomised have testosterone concentrations well within or above the normal adult male range. An elevated random T:LH ratio may be a biochemical indicator of androgen resistance and indeed was tried, unsuccessfully, in the past as a screen for mild androgen insensitivity syndrome (MAIS) associated with idiopathic male factor infertility (unpublished). However, in view of the lack of precision and specificity in such measurements, we do not see how blood hormone levels could be used as biomarkers for pubertal outcome in PAIS. The other point made by Dr. Fukami in relation to somatic mosaicism has already been covered in the Discussion where it was emphasised that this was highly unlikely in our cohort in view of the number of familial cases and most having had investigations undertaken on DNA extracted from both blood and genital skin fibroblasts. While we do agree that the possibility of somatic mosaicism should not be ignored, its low prevalence is unlikely to be a significant contributor to the common phenotypic variability seen in PAIS. The use of an androgen dependent marker such as APOD as a potential predictor is certainly worth exploring further following the preliminary studies of [4] in both CAIS and PAIS cases, as well as in patients with a PAIS phenotype but no AR mutation.

In his Commentary, Dr. Fukami goes beyond the scope of the subject of our study by emphasising the importance of assessing the psychological aspects of the continuum of DSD, of which PAIS is only one of numerous examples. He raises the problem of identifying predictors of gender as opposed to somatic development in PAIS, a challenge which at present appears insurmountable. We strongly echo his call for prospective, multicentre-based international studies to capitalise on resources such as the I-DSD registry and the DSD Translational Research Network in the United States to garner robust outcome data that leads to improved care for patients with PAIS across the lifespan.

References

[1] Fukami M. Long-Term Healthcare of people with Disorders of sex Development: Predictors of Pubertal Outcomes of Partial Androgen Insensitivity Syndrome. EBioMedicine 2018 https://www.ebiomedicine.com/article/S2352-3964(18)30438-9/fulltext.
[2] Lek N, Tadokoro-Cuccaro R, Whitchurch JB, Mazumder B, Miles H, Prentice P, et al. Predicting puberty in partial androgen insensitivity syndrome: use of clinical and functional androgen receptor indices. EBioMedicine 2018 https://www.ebiomedicine.com/article/S2352-3964(18)30406-7/fulltext.
[3] Lucas-Herald A, Bertelloni S, Juul A, et al. The Long-Term Outcome of Boys with Partial Androgen Insensitivity Syndrome and a Mutation in the Androgen Receptor Gene. J Clin Endocrinol Metab 2016;101:3959–67.
[4] Hornig NC, Ukat M, Schweikert HU, et al. Identification of an AR Mutation-Negative Class of Androgen Insensitivity by Determining Endogenous AR Activity. J Clin Endocrinol Metab 2016;101:4468–77.

DOIs of original article: https://doi.org/10.1016/j.ebiom.2018.09.047, https://doi.org/10.1016/j.ebiom.2018.10.026.

* Corresponding author at: Department of Paediatrics, University of Cambridge, Level 8, Box 116, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom.
E-mail address: iah1000@cam.ac.uk (I. Hughes).

https://doi.org/10.1016/j.ebiom.2018.10.035