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INVITED COMMENTARY

Male Endocrinology

Comment on reversal of hypogonadotropic hypogonadism in a Chinese cohort

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The reversal of congenital hypogonadotropic hypogonadism (CHH) is a relatively recent phenomenon that has gained increasing attention over the past 10 years. Yet to date, only one prospective study has been conducted estimating that 10% (95% confidence interval [CI]: 2%–18%) of cases undergo reversal.[1] Other retrospective studies have reported rates in the range of 5%–8%[2,3] and a recent study showed 44/308 (14%, 95% CI: 11%–19%) CHH patients underwent reversal.[4] Moreover, a time-to-event analysis in this large cohort revealed a lifetime reversal incidence of 22%. The article by Mao and colleagues presented in this issue is a meaningful contribution to our understanding of reversal as it examines the largest retrospective cohort to date.[5] Interestingly, they report the rate of reversal as 5% (95% CI: 3%–8%) in this Chinese cohort. It is difficult to reconcile the discrepancies in rates of reversibility and direct comparisons are hampered by the variable definitions employed. Using a novel definition for reversal (i.e, either endogenous testosterone (T) >270 ng dl^{-1}, serum T gradually increasing above 150 ng dl^{-1} with increased testicular volume, or normal spontaneous sperm production/normal erectile function/ejaculation), Mao and colleagues posit that testicular size and triptorelin-stimulated LH levels are reliable predictive factors for reversal. However, these cannot be considered as hard and fast rules for predicting reversal as the groups intersect - akin to the overlap observed between CHH patients and those with delayed puberty. Indeed, the fact that approximately half (44%, 95% CI: 25%–66%) of the reversal patients in the study by Mao *et al.*[5] were diagnosed between 17 and 19 years of age, underscores the challenge in differentiating CHH from extreme normal variants of puberty.

This study further lends credence the recently reported observations that reversals may relapse.[4,6] The notion that reversal may not be lasting highlights the vulnerability of the reproductive axis among CHH patients. While the mechanism(s) for relapse are unclear, it seems plausible that environmental, metabolic or psychiatric stressors could contribute. The factors that Mao and colleagues identify as significantly different in cases of reversal, were not informative for identifying those cases that relapsed back to a hypogonadal state. Notably, reversal has been reported in probands harboring mutations in genes underlying CHH.[1,3,4,6] Unfortunately, comprehensive genetic screening on the Chinese cohort is not available.

The reversal phenomenon is fascinating for its glimpse into the plasticity of the neuroendocrine control of reproduction. Future directions will almost certainly include investigation of specific genetic signatures and novel biomarkers for predicting reversal (and relapse). Yet CHH is a rare condition and to fully elucidate the biology of reversible CHH, it will be important to harmonize definitions of what constitutes a reversal, carefully phenotype patients and chart the natural history of their CHH. In this way, this unique human disease model may offer further insights into the control of human reproduction and provide opportunities to translate discoveries into enhanced approaches to improve the care and quality of life for these patients.

COMPETING INTERESTS

The authors declare no competing interests.

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