Unexplained infertility in Charles Darwin’s family: genetic aspect

Sir,

The recent paper of Siristatidis and Bhattacharya (2007) argues that the term unexplained infertility (UI) appears sustainable from a clinical and practical perspective, in spite of some fuzziness. I agree with this conclusion having in mind complicated multi-step processes of gametogenesis, meiosis and fertilization. The UI term leaves a door open for diverse unexpected scenarios of reproductive errors. For instance, UI was observed in a two century examination of records of one Scottish family with paternally derived twinning (StClair and Golubovsky, 2002). Authors suggested an action of a certain dominant factor which being active in male gametes during fertilization promotes an increased incidence of dispermy with subsequent triploidy, partial and complete moles, chimeras and pregnancy failure (Golubovsky, 2003). The paradox consist here in the UI origin due to an ‘super-active’ male gametes but not due to an oligospermy or immotile sperm.

The other important rationale is that the term UI keeps a door open for a retrospective reproduction analysis of infertility occurred in some famous historical figures and genealogies. Thus, George Washington, the founder of the USA, suffered from infertility and harbored great personal sadness. Basing on contemporary knowledge, Amory (2004) presented careful retrospective differential diagnosis for Washington’s UI, eliminating here at first a female origin of UI and elucidating possible role of some major categories of male infertility like Kleinfelter’s syndrome, endocrine and sexual dysfunction, anatomic defects like cryptorchism and toxic exposures. Genitourinary infection as a sequel of pulmonary tuberculosis seems more plausible according to biographic details. Certainly, the discussion of Washington’s UI cannot diminish his great historical status.

The other striking case of UI demonstrates the Charles Darwin pedigree which I first regard here in genetic terms. Starting from the grand-father Erasmus Darwin, this family endowed the human civilization with two cousin genius—Francis Galton and Charles Darwin. Ironically, Galton the founder of eugenic movement was childless. And three children of Charles Darwin suffered from UI. The Emma Nora Barlow, the daughter of Charles Darwin’s son Horace, lived 104 years (1885–1989) and first published in 1958 family tree with relevant reproduction data (Barlow, 1958).

Charles Darwin was 30 when he married his 31-year-old cousin Emma Wedgwood. Charles and Emma were cousins and had common Wedgwood grandparents from the maternal part. Their first son William was born 11 months after marriage and eight more children were born in a period of next 11.5 years. Then, after 5 year lag-period Emma at age 48 delivered her last 10th child, Charles Waring, who died 2 years lately. Two daughters and five sons lived to adulthood. Elisabeth never married. From six siblings with long-term marriage history William, Henrietta and Leonard manifested UI. The male infertility of Leonard is accentuated by his two childless marriages (the duration of the first one was 16 years).

There is serious reason to suggest that dramatic three children infertility in Darwin progeny is due to cousin marriage and segregation of a certain recessive meiotic mutation. All three infertile children William, Henrietta and Leonard expressed normal vitality, living 75, 86 and 93 years, correspondingly. William was an active banker. Leonard became prominent war engineer and economist. Since 1911–1928 he was a chairman of British Eugenic Society. Curiously, other three fertile Darwin’s sons—George, Francis and Horace—made remarkable academic carrier and each was elected the Fellow of the Royal Society.

What kind of recessive mutation in Darwin’s consanguineous marriage might lead in his progeny both to male and female infertility? A possible candidate is an inherited a gona
dotrophic hormone lesion. Similar family reproduction pattern was presented in recent description of a consanguineous family in which three siblings, two men and one woman,
expressed infertility (Lofano-Porto et al., 2007). All infertile siblings were homozygous on luteinizing hormone deficiency due to mutation in the LH beta-subunit gene (LHB). In spite of noticeable external similarity with the Darwin pedigree, there is a deep difference. Described LHB defect in male homozygous carriers is accompanied by hypogonadism, enucleoid habitus, a juvenile voice and absence of facial hair. All these features are absolutely incompatible with the William and Leonard obvious male phenotype. The both sexes infertility in Darwin’s progeny and maternal cousin lineage exclude an occurrence of UI due to transfer of some Y-chromosome microdeletion.

Another genetic rationale for UI in Darwin’s family might be a meiotic mutation leading to leisure of both male and female gametes. As early as in the middle of 1970s, the involvement of a 100 loci in the genetic control of meiosis became clear. A series of autosomal recessive mei-mutations was isolated then in heterozygotes from natural populations of classic Drosophila model (Baker et al., 1976). Since that time a lot of ortholog conservative mei-genes were found in all animals, including humans. Conducted under the guidance of M. Fellous, first systematic molecular studies of mei-mutations in human populations showed heterozygous polymorphism and homozygosity on meiotic defects of such genes as MSH and DMCI in some cases of male and female UI (Mandon-Pepin et al., 2002). In distinct consanguineous pedigrees were discovered first evidences of segregating autosomal recessive mei-mutations arresting meiosis on stage MI and connected with idiopathic infertility (Cantu et al., 1981; Schmiady and Neitzel, 2002). Accordingly, I propose that the most likely cause of the UI in the Darwin–Emma might be the segregation of a certain recessive autosomal mei-mutation. This mutation was transmitted both to Charles Darwin and Emma Wedgwood from their maternal grandparents (Josiah Wedgwood I and Sarah Wedgwood). It might be detected in future in the Wedgwood genealogical lineages.

References
Amory JK. George Washington’s infertility: why was the father of our country never a father?. *Fertil Steril* 2004;**81**:495–499.

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