Testicular Effects of Isolated Luteinizing Hormone Deficiency and Reversal by Long-Term Human Chorionic Gonadotropin Treatment

Hernan Valdes-Socin, Roberto Salvi, Albert Thiry, Adrian F. Daly, François P. Pralong, Rolf Gaillard, and Albert Beckers

Departments of Endocrinology (H.V.-S., A.F.D., A.B.) and Pathology (A.T.), Centre Hospitalier Universitaire de Liège, University of Liège, 4000 Liège, Belgium; and Division of Endocrinology, Diabetology, and Metabolism (R.S., F.P.P., R.G.), University Hospital, 1011 Lausanne, Switzerland

Isolated gonadotropin deficiency due to inactivating mutations of β-subunits of LH or FSH are rare. Isolated LH inactivation was identified in 1992, although the patient's clinical characteristics had been reported earlier (1, 2). Males with inactivating LHβ mutations (five adults have been reported) present with clinical features of hypogonadism and oligo/azoospermia (1–5). In 2004, we reported the case of a 30-yr-old man with this clinical presentation (3). The patient gave informed consent for a testicular biopsy (Fig. 1, A and B), which showed arrested spermatogenesis and fetal-type Leydig cells (3). A homozygous missense mutation (G36D) in the LH β-subunit gene was identified that abrogated $\alpha\beta$-subunit dimerization and rendered LH biologically and immunologically inactive (3). We initiated treatment with intramuscular human chorionic gonadotropin (hCG) (1500 IU three times a week for 1 month, then 5000 IU weekly). Tanner staging was 5 after 3 months. After 24 months treatment, FSH decreased to 2.3 mIU/ml (normal range, 1–8 mIU/ml) and testosterone increased to 7 μg/liter (normal range, 2.5–10.0 μg/liter). There was near normalization of testicular structure, which was likely related to Leydig cell maturation and subsequent increases in intratesticular testosterone, leading to a sperm count of 1000 spermatozoids/ml. (Fig. 1, C and D). The patient and his wife conceived a child by intracytoplasmic sperm injection from ejaculated sperm. The male child was heterozygotic for the G36D LHβ mutation and was phenotypically normal with normal LH, FSH, and testosterone levels at the age of 4 wk.

Although rare, isolated LH deficiency due to inactivating mutations of LH β-subunit gene is a useful illustration of the precise role of LH in testicular maturation and function in humans. Furthermore, it also provides a good example of the clinical efficacy of LH receptor stimulation using hCG.

Acknowledgments

Address all correspondence and requests for reprints to: Professor Albert Beckers, Chief, Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium. E-mail: albert.beckers@chu.ulg.ac.be.

Disclosure Statement: The authors have nothing to declare.

References

1. **Weiss J, Axelrod L, Whitcomb RW, Harris PE, Crowley WF, Jameson JL** 1992 Hypogonadism caused by a single amino acid substitution in the β-subunit of luteinizing hormone. N Engl J Med 326:179–183
2. **Axelrod L, Neer RM, Kliman B** 1979 Hypogonadism in a male with immunologically active, biologically inactive luteinizing hormone: an exception to a venerable rule. J Clin Endocrinol Metab 48:279–287
3. **Valdes-Socin H, Salvi R, Daly AF, Gaillard RC, Quatresooz P, Tebeu PM, Pralong FP, Beckers A** 2004 Hypogonadism in a patient with a mutation in the luteinizing β-subunit gene. N Engl J Med 351:2619–2625
4. **Daly AF, Salvi R, Ménagé JJ, Pralong F, Gaillard R, Beckers A** Identification of a family harbouring a novel LH subunit mutation associated with hypogonadism. OR52-5. Program of the 88th Annual Meeting of The Endocrine Society, Boston, MA, 2006
5. **Lofrano-Porto A, Barra GB, Giacomini LA, Nascimento PP, Latronico AC, Casulari LA, da Rocha Neves Fde A** 2007 Luteinizing hormone β mutation and hypogonadism in men and woman. N Engl J Med. 357:897–904

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-1584 Received July 23, 2008. Accepted September 17, 2008.

Abbreviation: hCG, Human chorionic gonadotropin.

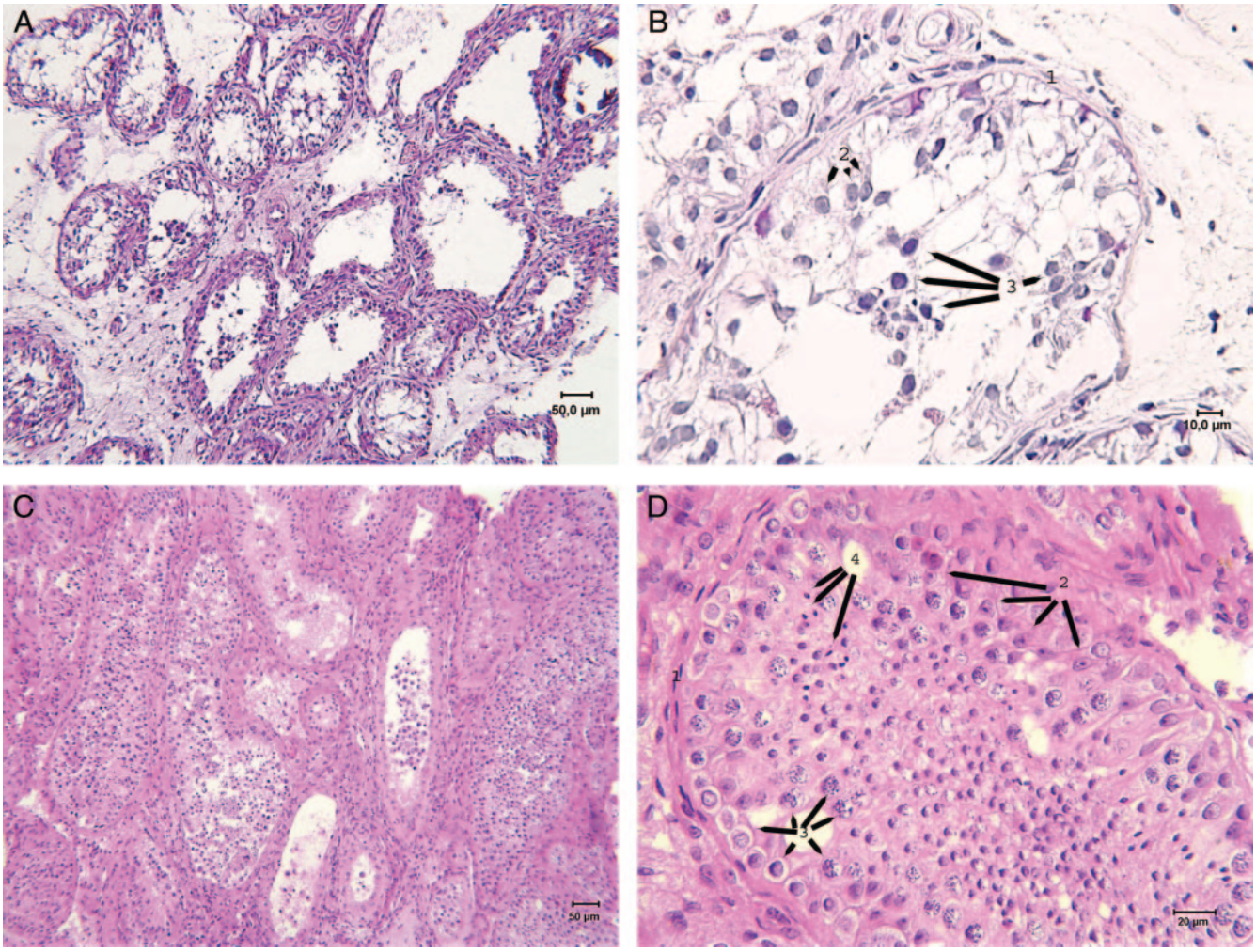

FIG. 1. Testicular biopsy from a patient with isolated LH deficiency due to an inactivating G36D mutation in the LH β-subunit gene before hCG administration. A and B, Before treatment. The testicular volume was 8 ml. Hypocellular tubules with greatly decreased spermatozoid numbers, arrested spermatogenesis, and absent mature forms were seen. B, 1, Tunica propria; 2, normal Sertoli cells; 3, and primary immature spermatocytes. A, Hematoxylin and eosin stain; magnification, ×100; B, hematoxylin and eosin stain; magnification, ×400. C and D, After treatment with 5000 IU hCG im once weekly for 24 months. The volume of the testis increased to 14 ml. Large hypercellular tubules with increased spermatogenesis and complete maturation forms are seen. D, 1, Tunica propria; 2, normal Sertoli cells; 3, primary immature spermatocytes; 4, with the addition of spermatids. C, Hematoxylin and eosin stain; magnification, ×100; D, hematoxylin and eosin stain; magnification, ×400.