Case Report

Journal of Global Medical Education and Research
Volume 1 Number 1, January - June 2018

Normosmic-Hypogonadotrophic-Hypogonadism in Women with Primary Infertility

Mathur Neha Satyaprakash[1], Pratibha Singh[2], Suyasha Vyas[3]

Abstract

Introduction: Hypogonadotrophic-hypogonadism is caused by defective GnRH release and results in abnormal gonadotrophin levels thus impaired pubertal development and primary infertility. Hypogonadotrophic-hypogonadism appears with varied syndrome complexes both phenotypically and genotypically

Case Report: A 20 yrs old married female came with complaints of primary amenorrhea and infertility. No history of cyclic abdominal pain, trauma at birth, chronic illness in past and eating disorders. On physical examination, her height was 155cms, weight 46kgs. Her breast was developed to tanner stageI/II, pubic and axillary hair to tanner stage II/III. She had average intellectual ability and normal sense of smell. On local examination, her vulva and vagina appeared normal, and uterus was of small size. USG showed infantile uterus and small ovaries, FSH – 0.23mIU/ml, LH- 0.27mIU/ml, Estradiol – 33 mIU/ml, TSH and Prolactin levels were within normal limits. MRI showed hypoplasia in the anterior pituitary. Karyotype was 46XX. No significant positive history on pedigree charting.

Discussion: With the breakthrough in molecular genetics, identification of genetic abnormality has become possible for the diagnosis the pattern of familial inheritance. Thus management of cases of hypogonadotrophic hypogonadism should not be restricted to individual patient but proper pedigree charting and genetic diagnosis must always be added to optimize the management. These cases need hormonal treatment to develop their secondary sexual characters as well as for fertility.

Conclusion: A through workup of young females presenting with primary amenorrhoea is often rewarding for the patient and the physician. Appropriately timed hormonal treatment can help in proper development of secondary sexual characters as well as fertility.

Keywords: Hypogonadotrophic-Hypogonadism; Primary Amenorrhoea.

Introduction

Hypogonadotrophic hypogonadisim results from impaired secretion of GnRH thereby characterized by a complete or partial lack of pubertal development. The incidence of congenital HH is 1-10:100,000 live births out of which 1/3rd cases are normosmic HH (1). The underlying neuroendocrine abnormalities are classically divided into two main groups: molecular defects of the gonadotrope cascade leading to isolated normosmic congenital hypogonadotropic hypogonadism and developmental abnormalities affecting the hypothalamic location of GnRH neurons, but also olfactory bulbs and tracts morphogenesis and responsible for Kallman's syndrome. Identification of genetic abnormalities related to CHH/KS has provided major insights into the pathways critical for the development, maturation and function of the gonadotropeaxis

[1] Senior Resident [2]Professor, Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.

Correspondence and Reprint Requests: Pratibha Singh, Professor, Department of Obstetrics & Gynecology, AIIMS, Jodhpur, Rajasthan- 342005.
E-mail: drpratibha69@hotmail.com

[2]. HH thus is a heterogenous condition caused by various genetic defect.

Case Report

A 20 yrs old female patient came with chief complaints of primary amenorrhea and primary infertility. She did not have any past history of cyclic abdominal pain, trauma, chronic illness or h/o intake of any drugs for prolonged period. She did not have any history of prior hospitalization or any eating disorders. Her mother had attained menarche at 14 years of age. She is the eldest of 5 siblings, 3 brothers and 2 sisters, none of whom have attained puberty. She did not have any coital difficulty after marriage. Her mother did not have any siblings.

On examination, her height was 155cms, weight was 46kgs. Her secondary sexual characters were not completely developed; breast to tanner stage I/II, pubic and axillary hair to tanner stage II/III. She had average intellectual ability and normal sense of smell. On local examination, vulva and vagina appeared normal and uterus was of smaller size.

Investigations were done. Ultrasound of pelvis showed infantile uterus and small ovaries. FSH -0.23mIU/ml, LH- 0.27mIU/ml, Estradiol– 33 mIU/ml, TSH and Prolactin levels were within normal limits. MRI showed hypoplasia in the anterior pituitary, no other abnormality was found. Karyotype was 46XX. Further genetic analysis was suggested to the patient, and was planned for hormonal treatment.

She received Inj FSH 75 units intramuscularly to stimulate ovulation and that will also increase serum levels of estrogens to take care of other hormonal needs of body; and she is still in follow up. Further genetic testing to know the mutation could not be done.

Discussion

Segregation analysis in familial cases has demonstrated diverse inheritance pattern, suggesting the existence of several genes regulating GnRH secretion. GnRH deficiency may be inherited via autosomal dominant, autosomal recessive and X-linked modes of inheritance. While these mutations account for only a small fraction of cases, genetic studies not only provide promise for future treatment, but also insights into the complexity of the GnRH neuronal system [3]. The treatasment of GnRH deficiency is highly successful whether designed for steroid hormone replacement or for fertility. The importance in the treatment of these abnormalities is in the early and accurate diagnosis and the use of replacement therapies that are as close to physiologic as possible. Another challenge is localising the type of inheritance and phenotypic penetrance of these patients. Thus isolated case treatment of infertility or amenorrhea without pedigree charting and molecular analysis would lead to missing of potential cases of delayed puberty.

Another aspect which has come to focus in the past two decades is the reversibility of the disease. Hypogonadotropic hypogonadism was considered an irreversible disease, to treat with a long-life hormonal exposure. A small proportion of patients have shown to undergo reversal of hypogonadism after steroid hormone therapy [4]. These studies are limited to male patient being treated with androgen. Patients affected by KS or normosmic HH with mutations in fibroblast growth factor receptor 1 (FGFR1), KAL1, GNRHR, and CHD7 genes or with still unknown genetic defects are reported to present a reversible phenotype, after therapy withdrawal [5-9].

In these patients a spontaneous recovery of LH pulsatile secretion occurred together with normalization of the testosterone level after therapy suspension [8]. Although the precise mechanism of reversal of hypogonadotropic hypogonadism is unclear, plasticity of the GnRH-producing neurons in adulthood could be involved [8]. The ability of the nervous system to adapt in response to environment is a striking feature of the vertebrate brain. Although, neurogenesis in humans occurs primarily during embryonic and early postnatal stages, multipotential progenitor cells in the subcortical white matter of the adult human brain have been identified as having the potential to replace neuronal lineages [10].

Treatment usually is directed to the cause and in our patient since for her infertility was of concern, she was given Inj FSH and was monitored with transvaginalsonography to see the size of developing follicle as well as the endometrial thickness.

However, the cost of treatment may become a limiting factor to many poor families, as was the case in our patient. She is still in follow up.

Conclusion

Thus the important factor, which comes to highlight is cases of Hypogonadotrophic-Hypogonadism is the diverse genetic etiology and the ever increasing spectrum of genes being identified in the pool. Clinicians if not vigilant in tracing the genetic data would miss the opportunity of probable case of reversal in the index case and identification of other prepubertal case in the family.

References

1. Renato Fraietta, I Daniel Suslik Zylberstejn, I and Sandro C Esteves I. Hypogonadotropic Hypogonadism Revisited. Clinics (Sao Paulo). 2013 Feb;68(Suppl 1): 81–88. doi: 10.6061/clinics/2013(Sup01)09.
2. Ghervan C, Young J. Congenital hypogonadotropic hypogonadism and Kallmann syndrome in males. Presse Med. 2014 Feb;43(2):152-61. doi: 10.1016/j.lpm.2013.12.008. Epub 2014 Jan 20.
3. Kottler ML, Hamel A, Malville E, Richard N. GnRH deficiency: new insights from genetics. J Soc Biol. 2004;198(1):80-7.
4. M. Laitinen, J. Tommiska, T. Sane, K. Vaaralahti, J. Toppari, and T. Raivio. Reversible congenital hypogonadotropic hypogonadism in patients with CHD7, FGFR1 or GNRHR mutations. PLoS ONE, 2012;7(6). Article ID e39450.
5. B. Kulshreshtha, R. Khadgawat, N. Gupta, et al. Progression of puberty after initiation of androgen therapy in patients with idiopathic hypogonadotropic hypogonadism. Indian Journal of Endocrinology and Metabolism, 2013;17(5):851–54.
6. N. Pitteloud, J. S. Acierno Jr., A. U. Meysing, A. A. Dwyer, F. J. Hayes, and W. F. Crowley Jr.Reversible kallmann syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the fibroblast growth factor receptor 1 gene. The Journal of Clinical Endocrinology and Metabolism, 2005;90(3):1317–22.
7. N. Pitteloud, P.A. Boepple, S. Decruz, S.B. Valkenburgh, W.F. Crowley Jr., and F.J. Hayes, The fertile eunuch variant of idiopathic hypogonadotropic hypogonadism: spontaneous reversal associated with a homozygous mutation in the gonadotropin-releasing hormone receptor. Journal of Clinical Endocrinology and Metabolism, 2001;86(6):2470–75.
8. T. Raivio, J. Falardeau, A. Dwyer et al., "Reversal of idiopathic hypogonadotropic hypogonadism," The New England Journal of Medicine, 2007;357(9) 863–73.
9. R. S. Ribeiro, T. C. Vieira, and J. Abucham. Reversible Kallmann syndrome: report of the first case with a KAL1 mutation and literature review. European Journal of Endocrinology, 2003;156(3):285–90.
10. M.C. Nunes, N.S. Roy, H.M. Keyoung et al. Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. Nature Medicine, 2003;9(4):439–47.