Short communication

Inv(10) in a patient with hypogonadotropic hypogonadism

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Abstract. Hypogonadotropic hypogonadism (HH) was diagnosed in a 22-year-old patient with 46,XY,inv(10) karyotype. It may be associated with some gene mutations of chromosome X, (KAL-I: Kallman syndrome; and DAX-I: congenital adrenal hypoplasia), as well as of certain autosomes, including chromosome 10. This study aimed to: (1) elucidate the aetopathogenesis of the disease in the studied case; (2) diagnose chromosome aberrations as accurately as possible; and (3) determine if the observed clinical picture can be referred to the diagnosed chromosomal aberration or it is a mere coincidence. The FISH technique, with the use of non-commercial DNA probes, was applied for a precise description of chromosome breaking points. The application of FISH enabled karyotype description: 46,XY, inv(10)(p15.2q11.22).ish inv(10)(p15.2q21.3)(p15×3)(q21×3)(p15conq21×2). The SSCP method revealed no mutation within the DAX-I gene and no deletion in the KAL-I gene.

Key words: FISH, hypogonadotropic hypogonadism, inv (10), SSCP.

The genetic and molecular basis of most cases of hypogonadotropic hypogonadism (HH) remains unrecognised. However, in about 5-10 % of patients, single mutations have been identified for certain hypothalamic and pituitary genes, including mutations in KAL (Xp23.3) and DAX (Xp21) genes. In cases of Kallman syndrome (KS) and congenital adrenal hypoplasia (CAH), a possible existence of several autosomal loci is suggested, both with recessive and dominant inheritance. The mutations, occurring in genes encoding gonadotropin-releasing hormone GnRH (8p21-8p11.2), GnRH receptor (4q21.2), leptin (7q31.3), and leptin receptor (1p31), induce the autosomal recessive HH syn-
drome. An isolated deficiency of FSH and LH gonadotropins may be a result of mutations in subunit β genes (11p13 and 19q13.2, respectively) and PROP1(5q), as well as in homeobox HESX1 (3p21.1-21.2) (cause: septo-optic dysplasia) (LAYMAN 1999).

It appears from literature data that aberrations of chromosome 10 may also be involved in this process. Patients with abnormal sexual development have been described, presenting with interstitial and terminal 10q deletion. It is assumed that the terminal deletion of 10q may, first of all, be associated with abnormal development of male genital organs (WILKIE et al. 1993). A particular cytogenetic instability is observed in the regions that are proximal to the centromere. Pericentric inversions – inv (10) – are also observed in patients with disorders of sexual development (COLLINSON et al. 1997).

The presented case describes a 20-year-old man, TN110880, with inv (10) (p15.1q21.3), in whom HH was diagnosed. At the age of 13-15 years, the patient did not observe any breaking of voice and, in history, he reported lack of ejaculation, despite maintained erection ability. The patient has been treatment for the latest three year with testosteron with prolonged effect, resulting in clear masculinization of genital features.

In clinical examination (in 20-year of age), the patient’s height was 165 cm and body weight was 64.5 kg. Gynoidal type of body structure, lack of ancillary hair, with scarce facial and pubic hair. Normal build of the chest, mammary glands increased but painless. A small scrotum with little, soft testes. In sonographic imaging, the volume of the left testis was estimated at 0.79 cm³ and that of the right testis, at 0.75 cm³. Bone age was assessed on the basis of wrist x-ray as 14-15 years.

In neurological examination, decreased muscle power was found in the left lower limb (paresis in 4/5). No other abnormalities were observed. EEG revealed pathological changes in bilateral temporal-occiputal leads, presenting as paroxysmal series of theta and sharp waves. No pathologies were found in otolaryngological examination, together with normal sense of smell.

While no features of pituitary enlargement were demonstrated in MRI scanning, a focal change, about 5 mm in size, was found within the right pituitary lobe; the change was resistive to contrast amplification. This MRI image may reflect microadenoma of the pituitary gland. Structures of the sella turcica region had no visible changes.

The studied material included peripheral blood lymphocytes from the patient and his parents, and skin fibroblasts from the patient. The FISH technique was applied for a cytogenetic examination. DNA was isolated for this study by MILLER et al. (1998) method. The analysis of mutation in the DAX-1 gene was performed by the SSCP method (NAKAЕ et al. 1996), evaluating the sequences involving both of exons of the DAX-1 gene.

By using classical cytogenetic techniques, the following karyotype was determined: 46,XY inv (10)(p15.2?q 11.2?). The application of the painting probe (WCP10)(Vysis) in FISH did not demonstrate translocation of either chromosome
10 itself or of any of its fragments by another chromosome (Figure 1A). With the use of the LSI KAL Spectrum Orange/CEP X Spectrum Green Control Probe (Vysis), no deletions in the KAL-1 gene were found (Figure 1B). The following karyotype was determined: 46,XY, inv(10).ish inv(10)(wcp10×2, KAL×1. At that stage of the study, no search was attempted towards possible finding of mutations in the gene in question. Mutations in KAL-X gene were detected in 52% of patients with IHH and in 5% of sporadic cases of hypogonadism (SEMINARA et al. 1998).

The suggested breaking points were verified by FISH with unique 10p15 and 10q21 probes (Resgen)(Figures 1C and 1D), which enabled obtaining the final description of the karyotype: 46,XY, inv(10)(p15.2q21.3)(p15×3),(q21×3)(p15conq21×2).
HH is also associated with mutations within the \textit{DAX-I} gene. Admittedly, no features of the CAH syndrome were noted in the examined case, but some researchers suggest that the mutations in the \textit{DAX1} gene may be the cause of either adrenal insufficiency or of the HH syndrome (MERKE et al. 1999). With the use of the SSCP method, no mutations were found within the \textit{DAX1} gene in the examined patient.

The karyotype of the patient’s father was normal – 46,XY – but in the phenotypically normal mother, an inversion of chromosome 10 was detected, the inversion being similar to that observed in the son.

The hypogonadism in our patient can be defined as isolated hypogonadotropic hypogonadism (IHH), which was confirmed in hormonal tests. The observed lack of increased LH and FSH concentrations, following the administration of LH-RH, may indicate primary impairment of the gonadotropic function of the pituitary gland.

The occurrence of the HH syndrome can be either familial or sporadic. Families have been reported with a complete picture of KS (hypogonadism + anosmia or hyposmia), i.e., an idiopathic HH without smell disturbances and with isolated anosmia. In the examined case, no smell disorders were observed. Numerous chromosomal rearrangements in patients with HH suggest an existence of also autosomal gene loci, responsible for GnRH deficiency in IHH (SCHINZEL et al. 1995, BEST et al. 1990, CASAMASSIMA et al. 1993). An inversion of chromosome 10, similar to the one observed in our patient, was also described in a female with IHH. The same inversion was diagnosed in the female’s mother, otherwise presenting with a normal phenotype. IHH, associated with autosomal genes, is familial in the majority of cases (SEMINARA 1998).

Pericentric inversions, which are balanced aberrations, do not – in general – induce phenotypic changes in carriers, thus they can be asymptptomatically inherited for many generations. They can, however, affect the process of reproduction, causing spontaneous abortions or infertility in men. The risk of bearing abnormal offspring by carriers of such an inversion is close to that in the general population (BALICEK 2001).

The bone age delay, occurring in our patient, is to be associated with HH, although neither functional insufficiency of the hypothalamus-pituitary system, following cranial trauma at the age of 11, nor the \textit{COL13A} gene, encoding the chain of a-collagen type XIII, were localised in the 10q21.2q22.1 region (PAJUNEN et al. 1989).

It is also interesting that the gene locus responsible for hypogonadism in rat, occurs on chromosome 10 (SUZUKI et al. 1999). Moreover, a large part of 10q in man is homologous with chromosome 6,7 10, 14, and 19 in mouse and rat (HAIG 1999).

At the stage of our study, we were not able to determine the molecular basis of HH in the examined patient. Still, the fact of chromosome 10 involvement
in the aetiopathogenesis of hypogonadism may turn out not incidental, the evidence for which may be the presented references to literature.

REFERENCES