Семейный случай нормосмического гипогонадотропного гипогонадизма в сочетании с полидактилией, ассоциированный с дефектом гена *FGFR1*

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Врожденный изолированный гипогонадотропный гипогонадизм — группа преимущественно моногенных заболеваний, связанных с нарушением выработки, секреции и/или действия ГнРГ, приводящих к выраженной задержке или отсутствию пубертата. Для данной группы заболеваний характерна клиническая и генетическая гетерогенность. На сегодняшний день известно порядка 30 генов-кандидатов, ассоциированных с развитием различных форм вторичного гипогонадизма. Верификация формы врожденного гипогонадотропного гипогонадизма возможна лишь с помощью молекулярно-генетической диагностики. Точная диагностика необходима для прогнозирования течения заболевания и выбора корректной тактики ведения пациента. Приводим описание семейного случая нормосмического гипогонадотропного гипогонадизма и позднего пубертата, ассоциированного с дефектом гена *FGFR1*. Данный случай интересен яркими фенотипическими проявлениями и их высокой концентрацией в родословной пробанда. Также интерес вызывает нетипичный для дефектов в данном гене фенотип. Молекулярно-генетическое исследование проведено методом секвенирования нового поколения с использованием авторской панели праймеров и полупроводникового секвенатора PGM (Ion Torrent). Подтверждение выявленной мутации и исследование родственника пробанда выполнено по методу Сенгера. У обоих пациентов выявлена гетерозиготная мутация в гене *FGFR1*, ранее описанная при синдроме Кальмана.

Ключевые слова: нормосмический гипогонадотропный гипогонадизм, FGFR1, полидактилия, поздний пубертат, семейный случай, клинический случай, секвенирование нового поколения.

Familial case of normosmic hypogonadotropic hypogonadism with polydactyly, associated with defect of *FGFR1* gene

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Congenital isolated hypogonadotropic hypogonadism refers to a group of predominantly monogenic diseases associated with impaired production, secretion, and/or action of the gonadotropin-releasing hormone (GnRH), which leads to a pronounced delay or absence of puberty. Clinical and genetic heterogeneity is typical of this group of diseases. To date, about 30 candidate genes associated with the development of various forms of secondary hypogonadism are known. Congenital hypogonadotropic hypogonadism can be verified only using molecular genetic diagnostics. The correct diagnosis is necessary for predicting the disease course and choosing the proper approach for managing the patient. We describe a familial case of normosmic hypogonadotropic hypogonadism and late puberty associated with a mutation in the *FGFR1* gene. The case is interesting because of pronounced phenotypic manifestations and their high concentration in the proband's family history. Also of interest is the phenotype untypical of mutations in this gene. The molecular genetic study was performed using new generation sequencing with the authors' panel of primers and a PGM semiconductor sequencer (Ion Torrent). The Sanger method was used to confirm the identified mutation and examine the proband's relative. In both patients, a heterozygous mutation in the *FGFR1* gene, previously described in Kallmann syndrome, was detected.

Keywords: normosmic hypogonadotropic hypogonadism, FGFR1, polydactyly, delayed puberty, familial case, case report, next-generation sequencing.

Topicality

Congenital hypogonadotropic hypogonadism (HH) is a group of monogenic diseases caused by mutations in more than 30 genes. Identification of the exact molecular genetic cause of the disease enables both predicting the course of the disease (because delayed spontaneous disinhibition of the hypothalamic-pituitary system can occur in some disease forms) and expecting concomitant disorders of other organs and systems.

The fibroblast growth factor receptor type 1 (*FGFR1*) gene is one of the genes, mutations in which lead to the development of HH. The FGFR1 protein encoded by this gene simultaneously participates in the development and differentiation of several organs and systems. The fibroblast growth factor (FGF) family and appropriate ligands are expressed in almost all tissues of the body and play an important role in embryogenesis, organogenesis, and cell proliferation, differentiation, and migration; in the postnatal period, they function as homeostatic (autocrine or paracrine) factors regulating metabolism [1—6]. Members of the FGF family are highly conserved molecules and differ in the level of expression in different tissues. The full protein structure is necessary for axial growth of the body in the embryonic period and development of the skeletal system and GnRH-producing neurons.

Most of the identified mutations in the *FGFR1* gene are associated with the development of Kallmann syn-

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drome (concomitant manifestations include unilateral/bilateral renal agenesis, bimanual synkinesis, tooth agenesis, gothic palate, and distal skeleton pathologies in the form of clinodactyly/polydactyly); less often, these mutations are associated with normosmic hypogonadotropic hypogonadism. The type of disease inheritance is autologous-dominant; digenic inheritance in combination with other genes is also possible.

This article presents a rare familial case of puberty impairment with varying degrees of penetrance (delayed puberty or normosmic hypogonadotropic hypogonadism) in combination with bilateral polydactyly of the hands and feet caused by a mutation in the *FGFR1* gene.

CASE REPORT

The patient was referred to the Endocrinology Research Center (ERC) for the first time at the age of 17.5 years due to complaints of underdeveloped external genitalia and delayed puberty. There were no complaints of hyposmia. An early medical history was normal; there were no traumas and surgery of the head or genitalia.

The proband' parents and available 2nd degree relatives were apparently healthy; however, the maternal grandfather and his siblings (great uncles of the patient) had a history of delayed puberty and bilateral polydactyly of the hands and/or feet. At the age of 17 years, the grandfather was examined for low growth and lack of puberty; he received hormone replacement therapy for 1 year, which had no effect; at the age of 20 years, there was spontaneous growth spurt and the onset of puberty. The grandfather's brothers were also known to have delayed puberty (18—20 years).

On examination of the patient, the height was 160.5 cm (SDS=−2.11); the body weight was 46 kg (SDS BMI=−1.75); he had a eunuchoid body build: a trunk length of 81.7 cm (SDS=−3.49) and a lower limb length of 78.8 cm (SDS −0.57). The phenotype was unusual, with multiple stigmas of dysembryogenesis: macrotia, a prominent position combined with dysplasia of the auricles, a wide neck, a long medial cleft, hypoplasia of the zygomatic bones, moderate micrognathia, scoliosis, abnormal bite, bilateral polydactyly of the hands and feet in medical history (at the time of examination, surgical scars were present at the sites of removed extra fingers), brachydactyly, and flatfoot. Sexual maturation: Tanner (G1, P2); micropenis; testicles in the scrotum, d=s=3—4 mL. The patient's maternal grandfather had a similar phenotype with multiple small developmental anomalies.

According to laboratory-instrumental tests, the patient's bone age was 12 years; the LH level was reduced to 0.2 U/L (reference interval, 2.5—10.0); the FSH level was reduced to 0.5 U/L (2.0—9.2); the testosterone level was 0.25 nmol/L (12.1—30.0); levels of other tropic pituitary hormones were normal. On the basis of these data, we excluded hypopituitarism and supposed, at the time of patient's examination, the presence of hypogonadotropic hypogonadism. To confirm secondary hypogonadism, a GnRH analogue test was performed, during which the maximum rise of LH and FSH was 4.5 U/L and 28.1 U/L, respectively. On the one hand, these data confirmed the diagnosis, but on the other hand, the high FSH rise might indicate a later onset of puberty, especially given the significant bone age delay.

Given the family history (combination of delayed puberty with bilateral polydactyly and multiple small developmental anomalies in the maternal grandfather and grand uncles), a monogenic disease with autosomal dominant inheritance was suggested. The patient was subjected to molecular genetic tests for a panel of genes associated with the development of hypogonadotropic hypogonadism. Molecular genetic testing was carried out using high-throughput parallel sequencing with a primer panel developed in a laboratory of the Department of Hereditary Endocrinopathies of the ERC (Ion Ampliseq Custom DNA Panel, Life Technologies, USA). The panel includes coding regions of the following genes: *CHD7*, *DNMT3L*, *DUSP6*, *FGF17*, *FGF8*, *FGFR1*, *FLRT3*, *GNRH1*, *GNRHR*, *HS6ST1*, *IL17RD*, *INSL3*, *KAL1*, *KISS1*, *KISS1R*, *LHB*, *NELF*, *POLR3B*, *PROKR2*, *RBM28*, *SEMA3A*, *SPRY4*, *TACR3*, *WDR11*, *GREAT*, *TAC3*, *KAL4*, *NR0B1*, *POLR3A*, and *MKRN3*. Sequencing was performed on a PGM semiconductor sequencer (Ion Torrent, Life Technologies, USA). Bioinformatic processing of the sequencing data was performed using the Torrent Suite 4.1 software (Ion Torrent, Life Technologies, USA) and Annovar package software (version 2014 Nov 12) (http: /www.openbioinformatics.org/annovar/) [Wang K, Li M, Hakonarson H. ANNOVAR: Functional annotation of genetic variants from next-generation sequencing data Nucleic Acids Research, 38: e164, 2010]. A heterozygous mutation c.304G>Ap.V102I in the *FGFR1* gene was identified, which had been described in Kallmann syndrome [7]. Sanger direct sequencing revealed a similar mutation in the proband's maternal grandfather.

For the purpose of masculinization and improvement of psychosocial adaptation of the patient, testosterone replacement therapy at a half-age dose was prescribed. The chosen treatment approach and refusal of gonadotropins were related to possible spontaneous pubertal development at a later age (given the results of GnRH analogue tests and spontaneous delayed puberty of the grandfather carrying a similar mutation).

DISCUSSION

Mutations in the *FGFR1* gene leading to complete loss of the protein function were first described in patients with Kallmann syndrome in 2003 [8]. The same study reported mutations characteristic of craniosynostosis, which did not lead to loss of the protein function. The authors supposed that X-linked *KAL1* encoding anosmin-1 actively participated in FGF-mediated signal

transduction; this may explain a higher prevalence of the disease among males. Pitteloud et al. [9] studied the *FGFR1* gene structure in seven unrelated patients with normosmic hypogonadotropic hypogonadism; three of them were detected with heterozygous mutations leading to the loss of protein function. Two of these patients had relatives with isolated anosmia and midline defects of the palate. Seminara et al. [10] examined two sisters with normosmic hypogonadotropic hypogonadism, and both had combination of a heterozygous missense mutation in the *FGFR1* gene with previously identified heterozygous mutations in the *GNRHR* gene. A similar defect of *FGFR1* was detected in their father who had a history of delayed puberty. In 2007, Pitteloud et al. [11] found the identical heterozygous missense mutation in the *FGFR1* gene in a proband with Kallmann syndrome, his father (history of delayed puberty, pronounced anosmia), mother (clinodactyly, Duane syndrome), sisters (midline defects of the palate), and brother (clinodactyly) [11]. This finding clearly demonstrated the variability of phenotypic manifestations associated with a single genetic defect. In a study by Raivio and co-workers [12], out of 134 patients with normosmic isolated hypogonadotropic hypogonadism, heterozygous mutations in the *FGFR1* gene were detected in 9 (7%) cases, with 5 of them having digenic defects (involving *GNRHR*, *PROKR2*, and *FGF8*).

To date, 153 defects in the *FGFR1* gene have been described, most of which are missense mutations (n=116); there are also a small number of splicing defects (n=12), various deletions (n=14), and insertions (n=8). The vast majority of defects are associated with Kallmann syndrome (n=110), and a much smaller number (n=30) are associated with normosmic isolated hypogonadotropic hypogonadism [13]. Phenotypic manifestations of hypogonadism range from delayed puberty to severe GnRH insufficiency that manifests, since birth, as underdeveloped external genitalia, anosmia, and lack of spontaneous puberty. There is no correlation between the mutation type as well as severity of hypogonadism and the presence of concomitant defects. The phenotype can significantly vary within a single genotype. A distinctive feature is combination of hypogonadism with limb development defects, in particular with clinodactyly and polydactyly. Also, a number of rare phenotypes are associated with defects in this gene: Hartsfield syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, osteoglophonic dysplasia, encephalocraniocutaneous lipomatosis, and trigonocephaly 1 [14]. All these are autosomal dominant inherited syndromes.

The mutation identified in the present study had been earlier described for a family case of Kallmann syndrome [7]. However, that study did not report accompanying developmental anomalies (distal skeletal defects) revealed in our patient. The described case demonstrates the importance of genetic counseling of families with any monogenic nosology. The risk of having children with this pathology in patients with mutations in the *FGFR1* gene is 50%. In this regard, patients should be informed about consequences of genetic disorders and all possible clinical manifestations of the disease.

ADDITIONAL INFORMATION

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Consent of the patient. The patients provided voluntary consent for publication of personal medical information in an impersonal form in the journal Problems of Endocrinology.

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