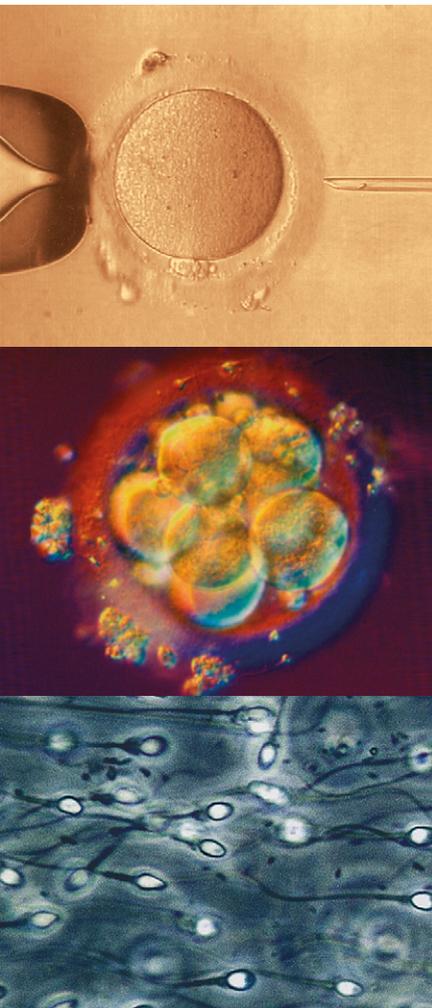


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Rare Syndromes Associated with Infertility

M. Hempel, T. Buchholz

Although rare syndromes seldomly are the reason for infertility, physicians for reproductive medicine should be aware of these syndromes. The majority of syndromes can be diagnosed clinically by thorough exploration of the personal and family histories and by extensive medical examination. To confirm a genetic diagnosis, specific tests have to be carried out. If a syndrome is detected, it often explains not only the reproductive failure but also other possible disabilities, leading to a specific therapy and accurate genetic counseling of the affected, patient and his family. **J Reproduktionsmed Endokrinol 2009; 6 (1): 24–6.**

Key words: hypogonadotropic hypogonadism, maldescended testes, primary infertility, syndromes, genetic counseling

■ Introduction

Infertility is not commonly associated with the occurrence of genetic syndromes [1]. Therefore, infertility work-up does not center on the detection of rare syndromes. However, these syndromes can be found through a detailed and targeted personal and family history examination, including a three-generation pedigree, and through an accurate clinical examination. If a syndrome is suspected, further investigations should be initiated.

More than 70 syndromes associated with infertility have been found so far. The majority of these syndromes is extremely rare and related to severe malformations and mental retardation. Due to their handicaps infertility is not their main problem because mostly these patients do not consider family planning. In some syndromes, however, infertility may be the initial obvious symptom [2]. Other symptoms can be minor and are not easily recognizable or will develop later in life.

It is not the purpose of this article to list all syndromes which are accompanied by infertility. Some examples of rare but widely recognizable syndromes are described here to illustrate the importance of the medical history and examination of the patient.

Among rare syndromes associated with infertility it is helpful to differentiate between:

- Rare syndromes associated with hypogonadotropic hypogonadism

- Rare syndromes associated with maldescended testes
- Rare syndromes associated with primary infertility.

■ Rare Syndromes Associated with Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism causes infertility, which can be successfully treated by gonadotropin stimulation. There are a few syndromes which have the leading symptom of hypogonadotropic hypogonadism.

Kallmann syndrome (olfactogenital syndrome, anosmia with hypogonadotropic hypogonadism) occurs in males with an incidence of 1:8000. Females can also be affected, but less frequently with an incidence of 1:40,000 [3]. Cardinal symptoms of the Kallmann syndrome are the inability to smell and hypogonadotropic hypogonadism. The patient has to be asked if he has difficulty in smelling

because sometimes patients with the Kallmann syndrome are not aware that they have anosmia. Additional symptoms include eunuchoidism, cleft lip/palate, reduced hearing ability, unilateral agenesis of a kidney, brachydactyly, synkinesia, and agenesis of the corpus callosum.

Autosomal dominant, X-chromosomal recessive and autosomal recessive inheritance of the Kallmann syndrome has been described (Tab. 1). In affected families, the pattern of inheritance can be distinguished according to the pedigree. Mutations in the KAL1 gene located on the short arm of the X chromosome have been found in 5–10 % of male Kallmann patients. Mutations in the FGFR1 gene have been detected in 5–10 % of autosomal dominant Kallmann syndrome patients. More infrequent mutations in the PROKR2 gene (~5 %) and the PROK2 gene (< 5 %) have also been revealed leading to the autosomal dominant Kallmann syndrome. There is at least one more gene locus suspected of

Table 1: Molecular genetics and phenotypic association in the Kallmann syndrome

X-linked recessive Kallmann syndrome	Autosomal dominant Kallmann syndrome	Autosomal recessive Kallmann syndrome
Mutation in KAL1 gene (5–10 %) Deletion of KAL1 gene (infrequent)	Mutation in FGFR1 gene (5–10 %) Mutation in PROKR2 gene (5 %) Mutation in PROK2 gene (< 5 %)	Gene loci unknown
Delayed pubertal development, micropenis, maldescended testes, synkinesia, unilateral renal agenesis	Cleft lip/palate, oligodontia, digit malformation, synkinesia, agenesis of corpus callosum	

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From the Institut für Humangenetik, Technische Universität München, Germany

Correspondence: Dr. med. Maja Hempel, Institut für Humangenetik, Technische Universität München, D-81675 München, Trogerstraße 32; e-mail: hempel@humangenetik.med.tu-muenchen.de

Table 2: Testing algorithm in the Kallmann syndrome**In family cases***In X-linked pattern of inheritance*

1. Sequencing of KAL1 gene
2. Deletion screening of KAL1 gene

In autosomal dominant pattern of inheritance

1. Sequencing of FGFR1 gene
2. Sequencing of PROKR2 and PROK2 gene

In isolated cases*Male*

1. Sequencing of KAL1 gene
2. Sequencing of FGFR1 gene
3. Sequencing of PROKR2 and PROK2 gene

Female

1. Sequencing of FGFR1 gene
2. Sequencing of PROKR2 and PROK2 gene

contributing to this syndrome, especially for the autosomal recessively inherited Kallmann syndrome [3–5]. The algorithm for genetic testing depends on the inheritance pattern and gender (Tab. 2). In males with sporadic Kallmann syndrome or patients with suspected X-linked inheritance, the KAL1 gene should be sequenced first. In females with the sporadic Kallmann syndrome and patients with an autosomal dominant pattern of inheritance, KAL1 gene analysis can be omitted. Instead, the order of gene sequencing should be as follows: first the FGFR1 gene, secondly the PROKR2 gene, and thirdly the PROK2 gene. This is also recommended for males with the sporadic Kallmann syndrome in whom no KAL1 gene mutation was found [6].

The following further examples of syndromes associated with hypogonadotropic hypogonadism are usually recognized early in infancy, but these patients can reach reproductive age.

Prader-Willi syndrome is suspected in the first weeks of life due to feeding problems and severe muscular hypotonia. Later in life patients display short stature, obesity, and mental retardation.

Pseudohypoparathyroidism is characterized by low calcium and high phosphorus serum levels, short stature, and short metacarpal IV. Depending on the severity of the metabolic disturbance, different types of pseudohypoparathyroidism have been classified.

Bardet-Biedl syndrome patients usually suffer from obesity, retinitis pigmentosa, and renal malformation. Most patients show postaxial polydactyly. The clinical

variability of Bardet-Biedel syndrome is very high.

■ Rare Syndromes Associated with Maldescended Testes

There are a number of syndromes associated with maldescended testes. One example is the Noonan syndrome in males (pterygium colli syndrome, male Turner syndrome). This syndrome is characterized by a congenital heart defect (especially pulmonary valvular stenosis, dysplastic pulmonary valve, and hypertrophic cardiomyopathy), short stature, and a typical sternum malformation (pectus carinatum in cranial and pectus excavatum in the caudal part of the sternum). Furthermore, these patients exhibit a typical facial dysmorphism including hypertelorism, ptosis, down-slanting palpebral fissures, deep-set and posterior rotated ears, short and broad neck, and low posterior hair line. Some, but not all patients suffer from mild to moderate mental retardation, depending on the underlying genetic defect [7–9]. Infertility is not the leading symptom of Noonan syndrome but may occur as a result of untreated maldescended testes. With an incidence of 1:1000 to 1:2500 in newborns, Noonan syndrome is one of the more common syndromes and therefore a male Noonan patient is more likely to be found in a consultation for infertility.

Noonan syndrome is inherited in an autosomal dominant pattern. Mutations in four genes have been identified so far: the PTPN11 gene (50%), SOS1 gene (10–15%), KRAS gene (5%), and RAF1 gene (3–17%). At least one more gene is likely to contribute to this syndrome. If Noonan syndrome is suspected in a patient with infertility, genetic testing is required, starting with PTPN11 gene sequencing, followed by SOS1, KRAS and RAF1 gene sequencing. There is a genotype-phenotype correlation. The majority of patients with an SOS1 gene mutation shows a normal development and growth in contrast to patients with a PTPN11 gene mutation who mostly display the full phenotype [7–9].

Other syndromes with maldescended testes leading to infertility are Cleido-

cranial dysostosis (hypoplasia of the clavulae, craniosynostosis), Bloom's syndrome (short stature, teleangiectatic erythematous skin lesions, high risk for malignancies), and Russel-Silver syndrome (short stature, relative macrocephaly, distinctive face, hemihypertrophy) [10]. These syndromes are usually detected early in infancy. However, because these patients are not severely handicapped, they may desire children and therefore seek reproductive counseling for infertility problems.

■ Rare Syndromes Associated with Primary Infertility

Primary Ciliary Dyskinesia (PCD) is a rare entity caused by congenital defects in cilia, which includes the immotile cilia syndrome, Kartagener syndrome, ciliary dysmotility, and primary orientation defects. Main symptoms of PCD are recurrent and persistent rhinitis, nasal polyps, recurrent ear infections, tympanosclerosis, bronchiectasis, and infertility. Situs inversus occurs in 50% of patients with PCD, named Kartagener syndrome. Additionally, PCD patients may suffer from ceratoconus, glaucoma, and myopia as well as from malformations of the brain, skeleton, and kidney [11]. The prevalence has been estimated between 1:3000 and 1:20,000 depending on the inclusion criteria of the PCD definition [12, 13].

The inheritance of PCD is autosomal recessive in the majority of cases. Linkage analyses have discovered at least nine gene loci up to now. Five of those have been identified so far: DNAH5 (30%), DNAI1 (10%), TXNDC3 (two case reports), DNAH11 (one patient and one family report), and DNAI2 (three case reports). Defects in these genes result in loss of function of the primary ciliary apparatus which leads to an abnormal ciliary structure and function, frequently followed by the symptoms described above. For diagnosis of PCD, a biopsy of the respiratory epithelium is necessary to detect specific ciliary ultrastructural defects and/or impairments of the ciliary motility using transmission electron microscopy and high-speed videomicroscopy. In the case of abnormal ciliary ultrastructure and/or ciliary beat frequency, testing for DNAH5 and DNAI1 mutations is recommended [14]. But in

Table 3: Phenotype and molecular genetics of Myotonic Dystrophy 1

	Mild DM1	Classic DM1	Congenital DM1
Symptoms	Mild myotonia Cataract Infertility Diabetes mellitus	Myotonia Muscle weakness Cataract Cardiac arrhythmia Frontal balding Infertility Diabetes mellitus Others	Muscle hypotonia Respiratory insufficiency Facial muscle weakness Mental retardation Symptoms of classic DM1 in adults
Age of onset	20 to 70 years	10 to 30 years	Birth
CTG repeat expansion	50 to ~200	~100 to ~1000	> 2000
Life expectancy	60 years to normal	45–55 years	45 years

60 % of PCD patients, the gene defect cannot be identified.

Males with myotonic dystrophy 1 (Morbus Curschmann-Steinert, Dystrophia myotonica 1, DM1) may also suffer from primary infertility. In some patients, this even is the initial obvious symptom [1]. DM1 is a multisystem disorder affecting the skeletal and smooth muscles, the heart, the eyes, and the endocrine and central nervous systems. According to the phenotype, three partially overlapping types have been classified: mild, classic, or congenital DM1 (Tab. 3). The main symptoms of all types of DM1 are myotonia (sustained muscle contraction) and posterior subcapsular cataract. The majority of patients show a typical myopathic and expressionless face [15]. Muscular weakness, frontal balding, cardiac arrhythmias, fatigue, dysphagia, constipation or diarrhea, and diabetes mellitus are additional symptoms which may occur in all types of DM1, but less frequently in the mild type. Congenital DM1 is the most severe phenotype characterized by muscular hypotonia and respiratory problems already present in the neonatal period. Surviving children develop mental retardation and symptoms of classical DM1 [16].

DM1 follows an autosomal dominant pattern of inheritance. The underlying genetic defect is based on the expansion of CTG repeats in the DMPK gene. More than 50 CTG repeats result in DM1. The expansion correlates with the phenotype (Tab. 3). An increased CTG repeat expansion is associated with the severity of the disease and an earlier onset of symptoms. Alleles may expand during gametogenesis resulting in transmission of an increased CTG re-

peat expansion from generation to generation. DM1 can be suspected by a detailed query of medical personal and family history and an accurate medical examination. To confirm the diagnosis molecular testing of the CTG repeat expansion in the DMPK gene is mandatory [17].

Conclusion

These examples of rare syndromes associated with infertility show that they can be detected by a detailed medical history and through medical examination. The history should include the personal history (including development, education, etc.), medical data (operations, frequent infections, etc.), associated disabilities (hearing loss, inability to smell, etc.), and a family history with a three-generation pedigree. Clinical investigations by and/or consultations of a human geneticist help to clarify the speculated syndrome and lead to a diagnosis.

Although these syndromes are rare in patients with infertility, awareness is very important for physicians of reproductive medicine so that the affected patients and their families can be adequately counseled by human geneticists. Genetic consultation should comprise detailed information about the respective syndrome, the availability of specific therapies and programs for preventive care. This should also include counseling about the possible risk for family members and the risk for own affected children. Treatment of these patients mostly requires close cooperation between several professions like reproductive specialists, geneticists, endocrinologists, and others.

Practical Aspects

Awareness of rare syndromes is very important in patients with unexplained infertility. Rare syndromes can be detected by a detailed medical history including personal history, medical data, associated disabilities, family history, and medical examination. Consultations of a human geneticist help to clarify the speculated syndrome. The diagnosis can often be confirmed or ruled out by specific genetic testing. The care for these patients needs close cooperation between several specialists.

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