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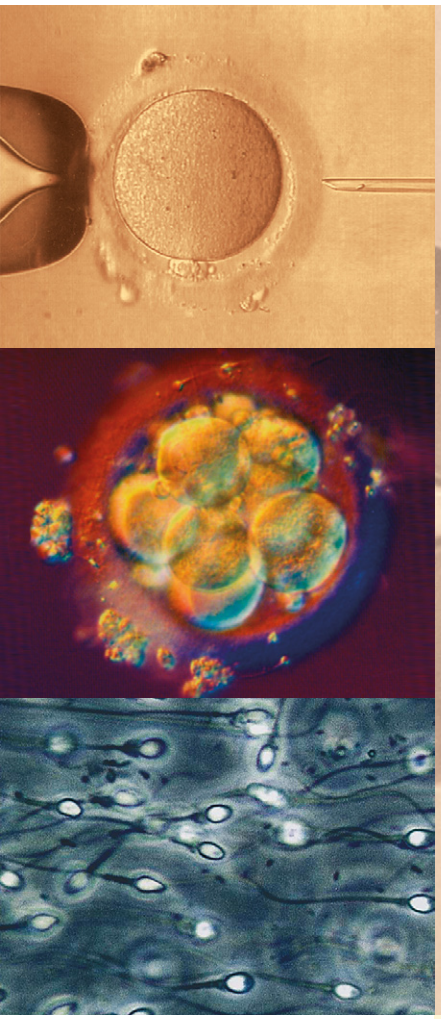

Genetic Aspects of Premature Ovarian Failure

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Genetic Aspects of Premature Ovarian Failure

P. Wieacker

Premature ovarian failure (POF) is characterized by the combination of amenorrhea before age 40 years and hypergonadotropic hypogonadism. The prevalence is approximately 1 %. Genetic causes of POF include chromosome aberrations and monogenic defects. Furthermore, polygenic-multifactorial inheritance can be assumed in a subset of cases. **J Reproduktionsmed Endokrinol 2009; 6 (1): 17–8.**

Key words: premature ovarian failure, chromosome aberrations, gene mutations

Introduction

Premature ovarian failure (POF) is characterized by the onset of amenorrhea before age 40 years combined with tonically increased levels of gonadotropins and hypoestrogenism (hypergonadotropic hypogonadism, ovarian insufficiency WHO group III). Premature ovarian failure affects approximately 1 % women by age 40, 1:1000 by age 30, and 1:10000 by age 20 [1].

POF is a heterogeneous disorder caused by non-genetic (infections, radiotherapy and chemotherapy) and genetic factors, including chromosome aberrations, monogenic defects and polygenic-multifactorial dispositions. Chromosome aberrations can be detected in approximately 9 % [2], including Triple X syndrome, Turner mosaics, deletions of the X chromosome and X; autosome as well as Robertsonian translocations.

Analysis of deletions of the X chromosome delineated three critical regions: POF1 region in Xq27.2-q27.3 (OMIM311360) including FMR1, POF2 region in Xq13.3-q22 (OMIM300511) including DIAPH2, and a third region in Xp11 including BMP15. There is some evidence that POF caused by rearrangements in the POF2 region is due rather to oocyte-specific position effects than to haploinsufficiency of specific genes of this genomic sequence regions [3].

Furthermore, ovarian dysgenesis, in which ovaries are completely depleted of follicles before puberty, can be seen as the most severe POF manifestation. The phenotype includes primary amenorrhea, lack of breast development, poor pubes and axillar hair growth, hypoestrogenism and elevated gonadotropins. Ovaries are degenerated and only streak gonads can be detected, in contrast to entities characterized by arrests of follicle development, which also show hypoestrogenism, amenorrhea, and elevated gonadotropins (Fig. 1).

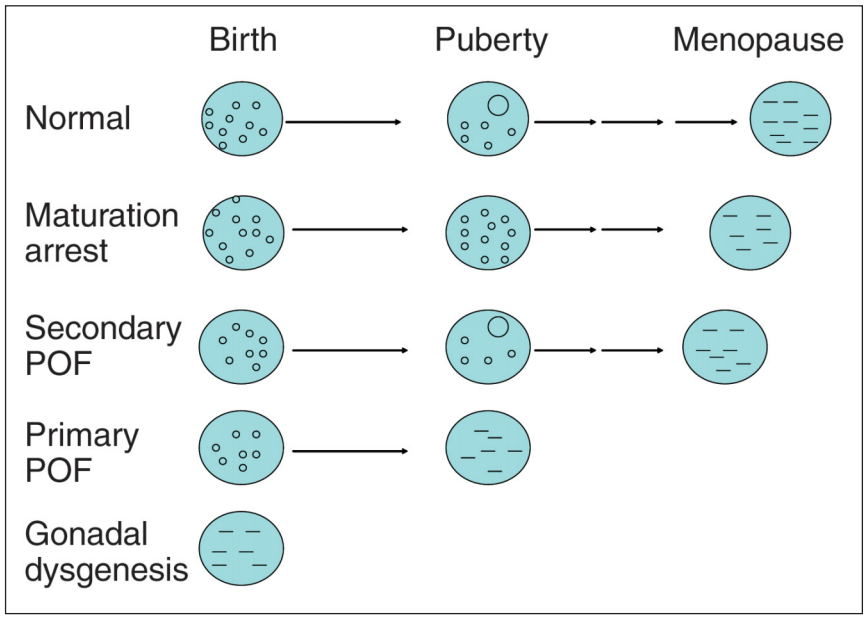

Figure 1: Possible mechanisms of hypergonadotropic hypogonadism in females. (A) In normal ovaries maturation of follicles is beginning at the time of puberty. (B) In case of maturation arrest only primordial or primary follicles are present. Basic estradiol production of granulosa cells makes breast development possible, but there is a primary amenorrhea. FSHβ-, FSHR- or LHR-mutations can cause such a condition. (C) In secondary POF, maturation of follicles at puberty makes menarche and breast development possible, but early depletion of follicles causes secondary amenorrhea. Such a condition can be caused by Turner mosaicism. (D) In primary POF, depletion of follicles before the puberty causes primary amenorrhea. Breast development is not possible. (E) In gonadal dysgenesis degeneration of the follicles occurs during fetal life. In the rule, primary POF and gonadal dysgenesis cannot be delineated clinically.

In the last decades an increasing number of genes involved in POF could be identified. Mutations of these genes can lead to a non-syndromic POF with POF as isolated disorder or to a syndromic POF in the case of pleiotropic effects of the involved genes.

Non-Syndromic Monogenetic POF Caused by Gene Mutations

The underlying etiology of non-syndromic POF is poorly defined. FSHR mutations have been described almost exclusively in the Finnish population [4]. Mutations of the LH receptor gene (LHR) in females are associated with primary amenorrhea, but normal breast

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development and normal or elevated LH concentrations as well as normal FSH level. A mutation of the X-linked gene POF1B has been reported in only one family [5]. Di Pasquale et al. [6] described a mutation in the X-linked gene BMP15 in two sisters affected by POF, and afterwards several mutations in BMP15 and its autosomal paralog GDF9 have been detected [7]. However, caution is required in the interpretation of many of these mutations because functional in vitro analyses of these mutations were not available [8]. In 2007, Recently, Qin et al. [9] reported on mutations of NOBOX, an oocyte-specific homeobox gene, in a small subset of patients (approximately 1 % of POF patients) affected by non-syndromic POF. Furthermore, mutations of FIGLA, a gene expressed in all oocyte stages, may be causal for about 2–4 % of non-syndromic POF cases [10].

Recently, skewed inactivation of the X chromosome was detected in a part of patients with primary POF [11]. Skewed inactivation of the X chromosome may be the consequence of selection processes against cells carrying microdeletions or specific gene mutations on the active X chromosome. Furthermore, it cannot be excluded that skewed inactivation of the X chromosome in POF is a general feature of premature aging because it is well known that skewed X inactivation is more frequent in older women than in young women.

Syndromic POF Caused by Gene Mutations

Approximately 3–4 % without and 10–15 % with a family history of ovarian failure carries a FMR1 premutation allele [12]. After female meiosis premutations can expand to full mutations causing Fragile X Mental Retardation Syndrome (FRAXA). Because carriers of FMR1 premutations are at high risk for children with mental retardation, it is important to detect carriers of FMR1 premutations in a diagnostic context of POF. Carriers of FMR1 premutations are not affected by mental retardation. Nevertheless, in this review FMR1 has been included in the category of syndromic POF because of the high risk of mental retardation in offspring of female premutation carriers.

Further genes involved in syndromic POF are AIRE (mutated in APECED), FOXL2 (mutated in BEPS-I), GALT (mutated in galactosemia), mitochondrial POLG (mutated in progressive ophtalmoplegia), PMM2 (mutated in CDG syndrome type I) and EIF2B2, EIFB4 and EIFB5 (mutated in ovarioleukodystrophy). A syndromic form of POF, associated with eyelid malformation, has been mapped to chromosome 3q22-q23 [13].

Ovarian Dysgenesis as the Most Severe POF Phenotype

Ovarian dysgenesis is also a very heterogeneous disorder including chromosome aberrations and XX gonadal dysgenesis caused by monogenic defects and – in most cases – unknown factors. From a clinical point of view, non-syndromic and syndromic forms of XX gonadal dysgenesis can be delineated. Familial occurrence in sibs suggests autosomal recessive inheritance of XX gonadal dysgenesis. However, Meyers et al. [14] determined a recurrence risk of 16 % in sibs of an affected patient. Therefore, autosomal recessive inheritance can be expected in only a subset of patients affected by non-syndromic XX gonadal dysgenesis.

In syndromic XX gonadal dysgenesis, mutations in genes involved in early gonadal differentiation have been identified, such as WT1 mutations in Denys-Drash syndrome associated with renal failure or SF1 mutations associated with adrenal failure. Further syndromes have been described including Perrault syndrome characterized by gonadal dysgenesis and deafness or Marinesco-Sjögren syndrome.

Furthermore, disorders of DNA repair are associated with gonadal dysgenesis in females, as it is the case for Ataxia teleangiectasia, Nigmegen breakage syndrome, Bloom syndrome, Werner syndrome or Cockayne syndrome. Chromosomal instability has also been detected in a woman with non-syndromic gonadal dysgenesis [15]. It can been suggested that in these cases of chromosomal instability gonadal dysgenesis is due to impaired reparation of double strand breaks occurring in crossing over during meiosis.

Practical Aspects

Currently, about 15–20 % of cases can be explained at a chromosomal or molecular level. Genetic testing should begin with chromosome analysis. FMR1 testing should be performed. In syndromic POF genetic testing depends on the patient's phenotype. An increasing number of genes could be identified in non-syndromic POF, each gene contributing only to a small subset of cases.

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