Genetic Aspects of Premature Ovarian Failure

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Finden Sie in der Rubrik „Tipps und Tricks im Gyn-Ultraschall“ aktuelle Fallbeispiele von Univ.Prof. Dr. Christoph Brezinka, Innsbruck.
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 haplinsufficiency 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 axillary 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).

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 Monogenic 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...
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 GDF9 and BMP15, 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.

### Syndrome 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 pre-mutations can expand to full mutations causing Fragile X Mental Retardation Syndrome (FRAXA). Because carriers of FMR1 premutations are at high risk for mental retardation and autism, the risk of skewed X-chromosome inactivation is associated with premutation carrier status. Furthermore, disorders of DNA repair and DNA recombination are associated with gonadal dysgenesis in females, as it is the case for Ataxia telangiectasia, Nigmegon 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 be 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.

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 ophthalmoplegia), PMM2 (mutated in CGD syndrome type I) and EIF2B2, EIF2B4 and EIF2B5 (mutated in ovarioulkedystrophy). A syndrome 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 may 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 Marinosco-Sjögren syndrome.

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### Practical Aspects

Currently, about 15–20% of cases can be explained at a chromosomal or molecular level. Genetic testing should begin with chromosomal 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.

References:

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