Genetic pathogenesis of Perrault Syndrome

Perrault Sendromunun genetik patogenezi

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Dear Editor,

Premature ovarian insufficiency (POI) is defined as the occurrence of hypergonadotropic hypoestrogenic amenorrhea in women under the age of 40 years and it is part of well described autosomal recessive syndromes (Perrault, Richard Rundle, Alstrom, Wolfram syndromes and Mitochondriopathies) (1). The association of hypergonadotropic hypogonadism (HH) in females and sensorineural hearing loss (SNHL) in females and males was described as Perrault syndrome (PS). Some patients also have neurological manifestations, but their exact frequency cannot be ascertained since several reports did not include a description of a neurological examination. More recent studies have investigated whether the neurological signs in some of the patients are a coincidental finding or part of the syndrome. Some researchers proposed a possible classification of PS to type I, without neurological disease, and type II or AAHH (The association of ataxia, hypergonadotropic hypergonadism and hearing loss), with progressive neurological disease (2, 3).

Previously, partial deficiency of the mitochondrial enzyme cytochrome c oxidase and muscle coenzyme Q10 (CoQ10) deficiency was reported in cases with PS (4, 5). Recently, mutations in 17 beta-hydroxysteroid dehydrogenase type 4 (also known as D-bifunctional protein (HSD17B4/DBP)) which is also involved in Zellweger syndrome, one of three leukodystrophies and mitochondrial histidyl tRNA synthetase (HARS2) also implicated, in the leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), have been proposed as the genetic causes of PS (6-8). The “ovarioleukodystrophies” comprise a group of rare leukodystrophies associated with POI. Some of the patients have a variant of “vanishing white matter disease“ with mutations in subunits of eukaryotic initiation factor 2B (EIF2B) (9).

Although HSD17B4, mitochondrial histidyl tRNA synthetase (HARS2) and EIF2B should be examined in other cases, it may be time to classify PS type II under the leukodystrophies. The report of Pierce et al. (8), represents a valuable contribution, because recent findings in genetic research have suggested that a large number of genetic disorders are highly related in the genotypical root. For example; Alstrom syndrome has begun to be classified as a ciliopathy (10). The late-onset form of GAII and the myopathic form of CoQ10 deficiency are allelic diseases and chylomicron retention disease and Marinesco-Sjogren syndrome are related (11, 12).

We suggest that, before proceeding with further laboratory investigations, clinical and neurological examinations must be fully performed and a correct diagnosis of the cases made as there are many syndromes sharing several findings. Long term follow up is very important, since some clinical manifestations appear later in life. Pierce et al. (8) evaluated the sisters MK and LK, whose clinical manifestations had been thoroughly described previously by Fiumara et al. (13) and Mc Carthy and Opitz (14). Therefore, these sisters are the only cases who have such a detailed clinical history, multidiciplinary approach and long term follow up. At the end, a causative mutation was discovered (6). This simple approach will provide an opportunity to recognize associated syndromes and evidence requiring the initiation of further laboratory investigations.

Before making high cost molecular analysis; simple blood tests for glucose, vitamin E, folate and B12 levels, alpha-feto-protein, very long chain fatty acids and phytic acid, lysosomal enzymes, amino and organic acids, serum ammonia, arterial pH levels, and X-ray of the skeleton could be carried out. Performing ECG, muscle biopsy, MRI, measurement of mitochondrial enzyme cytochrome c oxidase and CoQ10 levels and DNA analysis for trinucleotide expansions at the SCA 1, 2, 3, 6, 7 and Friedreich’s Ataxia loci, mutations analysis of FMR1, HSD17B4/DBP, mitochondrial HARS2 and EIF2B for a number of similar cases will give valuable information about the pathogenesis of PS (3, 15).

PS type II seems to be caused by both a malfunction of the mitochondria and of myelination. The question remains whether there is one gene or at least two different genes responsible for two different clinical entities.
References

1. Sarikaya E, Ensert CG, Gulerman HC. Hypergonadotropic hypogonadism, progressive spinocerebellar ataxia and late onset sensorineural hearing loss: Case report and literature review. BJMG 2011; 14: 77-88. [CrossRef]


