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Premature ovarian Insufficiency: a case report of a particular syndromic association

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Context:

Premature ovarian insufficiency (POI) is a clinical syndrome characterized by loss of ovarian function before the age of 40 years and concerns 1% of women. This disorder presents a marked heterogeneity and remains idiopathic in the large majority of cases. The most Known etiologies of non-iatrogenic POI are chromosomal abnormalities, FMR1 prémutation and autoimmune causes. POI is also described in numerous rare inherited pleiotropic syndromes.

Objective:

To present a case of POI associated with mitochondrial dysfunction, auto-immunes affections suggestive of polyendocrine autoimmune syndrome (APS) and probably Blepharophimosis-ptosis-epicanthus syndrome (BPES).

Patient and Method:

A 35 years old woman consulted for POI with secondary amenorrhea and elevated FSH levels. The patient has medical histories of Biermer anemia, Hashimoto hypothyroidism, hypertrophic cardiomyopathy and myopathies due to a deficiency in Complex 4 of the respiratory chain and has been operated for congenital eyelids abnormalities. The patient's paternal grandmother presented POI and the father have also eyelids abnormalities.

Interventions:

To better understand the etiologies of POI in this patient we have looked for further potential genetic and auto-immune contribution by performing firstly karyotype, FMR1 premutaion, anti-ovarian and anti-adrenal antibodies analysis. The karyotype and FMR1 were normal, the anti-adrenal antibodies were positive. We have secondary checked the adrenal and parathyroid function which were normal and performed array-CGH to look for the presence of submicroscopic chromosomal abnormalities (CNV) and a gene panel (GP) of candidate genes of POI (including FOXL2 and AIRE genes) by Next generation sequencing(NGS).

Main Outcome:

POI evaluation showed absence of cytogenetic abnormalities. GP showed the absence of FOXL2 and AIRE mutations, which excludes the diagnostic of BPES and APS type 1 but not APS type 2. We identified by GP, very rare mutations in 4 candidate genes of POI which are CDKN1B, LHCGR, NTRK1 and POR. These mutations are estimated to be deleterious by at least one of the different software predicting the impact of a gene mutation.

Conclusions:

We have presented a complex POI case that may be due to different etiologies including mitochondrial dysfunction, APS type 2 and mutations of 4 candidate genes of POI estimated to be deleterious and/or probably damaging by in silico analysis.

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