Primary ovarian insufficiency associated with variants or mutation of the luteinizing hormone-receptor gene

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Primary ovarian insufficiency (POI) is defined as an ovarian failure installed before the age of 40. The etiology of POI remains unknown in about 90 percent of cases. About 10 percent of cases appear to be familial. We describe here the cases of hypergonadotropic hypogonadic patients: 3 referred for secondary amenorrhea being 36, 24 and 14 years old respectively and one 35 year-old referred for primary amenorrhea and absence of breast development.

All the patients had female external genitilia.

In the patients referred for secondary amenorrhea, the karyotypes were 46,XX. The presence of the SRY gene and FMR1 premutations was excluded. The DNA sequencing of the LH-receptor gene revealed 4 genetic variants. The c.872 A>G variant (p.Asn291Ser) is the only one mentioned in the literature. In vitro tests have shown that this variant would decrease the receptor sensitivity to LH however this variant has also been found in asymptomatic patients. Surprisingly, 2 patients out of the 3 had a genetic variant in common (c.148 T>C). The c.606-5 C>T variant is close to the splicing site and could have a functional impact. The c.1360 G>A variant could have an effect on the protein function (p.Val454Ile).

In the patient referred for primary amenorrhea, pelvic ultrasonography and magnetic resonance imaging revealed the absence of uterus and gonads localized in the inguinal regions. The karyotype was 46,XY. The SRY gene was unmutated and there were no FMR1 premutations. The DNA sequencing of the LH-receptor gene revealed a homozygous deletion of guanine at nucleotide 1850 (c.1850delG). This deletion is responsible for a premature stop codon.

Conclusion

We report here the cases of 4 hypergonadotropic hypogonadic patients, who were referred for primary or secondary amenorrhea before 40. Several genetic variants or mutation of the LH-receptor gene have been found in these patients highlighting how gonadotropin receptor sequencing is important. Further research is needed to establish whether these variants play a role in the etiology of POI, which remains unknown in most cases.