GENDER-SPECIFIC HORMONAL FEATURES ASSOCIATED WITH COL1A1 rs1800012 GENOTYPES IN PRIMARY EMPTY SELLA SYNDROME

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ABSTRACT

Primary empty sella syndrome (PESS) may be accompanied by variable endocrine disturbances resulting from anatomical and functional changes in the hypothalamic-pituitary system. The present study evaluated hormonal characteristics associated with different genotypes of the COL1A1 rs1800012 polymorphism in women and men with PESS. The analysis included 26 women and 10 men with available molecular-genetic and hormonal data. Among women, 13 had the G/G genotype, 9 the G/T genotype, and 4 the T/T genotype. The most pronounced genotype-related differences involved prolactin. Its concentration was 38.7±4.6 in G/G carriers, 20.9±4.6 in G/T carriers, and 46.0±7.5 in T/T carriers; significant differences were observed between G/T and G/G as well as between T/T and G/T groups ($p<0.05$). Among men, the T/T genotype was associated with a significantly lower FSH level compared with G/T carriers (2.07±0.10 vs 2.70±0.10; $p<0.05$), while LH and testosterone also tended to be lower. No consistent genotype-dependent differences were found for TSH or free T4. The results indicate that the association between COL1A1 rs1800012 and the hormonal phenotype of PESS may differ between sexes, involving prolactin predominantly in women and gonadotropic function in men.

Introduction

Primary empty sella is not exclusively a neuroradiological finding. In a proportion of patients, it is associated with disturbances in pituitary hormone secretion. The hormonal phenotype is heterogeneous and may involve hyperprolactinemia, gonadotropin deficiency, growth hormone deficiency, and, less commonly, abnormalities of the thyroid or adrenal axes [1].

A systematic review by Auer et al. demonstrated a substantial frequency of pituitary dysfunction among patients with primary empty sella and emphasized the importance of neuroendocrine assessment even when the neuroradiological finding is incidental. More

recent clinical studies have also shown that endocrine abnormalities are more frequently detected in patients with more pronounced morphological changes of the pituitary gland. In the study by Akkuş et al., hypopituitarism was particularly common among patients with total empty sella.

However, the mechanisms determining why patients with apparently similar morphological changes develop different hormonal abnormalities remain unclear. One possible contributor may be genetically determined differences in connective-tissue structure. The COL1A1 gene encodes the α1 chain of type I collagen, while the rs1800012 polymorphism affects an Sp1 binding site and can alter COL1A1 expression and collagen composition [2].

The aim of this study was to evaluate hormonal profiles according to COL1A1 rs1800012 genotype separately in women and men with primary empty sella syndrome.

Main Part

The analysis included patients with PESS in whom both hormonal and genetic data were available. Twenty-six women were evaluated: 13 women carried the G/G genotype, 9 carried G/T, and 4 carried T/T.

The most prominent genotype-associated differences in women involved prolactin. Mean prolactin concentration was 38.7±4.6 in women with the G/G genotype and decreased to 20.9±4.6 in G/T carriers; this difference was statistically significant ($p<0.05$). In women with the T/T genotype, prolactin concentration reached 46.0±7.5, being significantly higher than in the G/T group ($p<0.05$).

The other hormonal parameters showed less consistent genotype-dependent changes. TSH levels were 1.97±0.20, 1.49±0.27, and 1.50±0.50 in the G/G, G/T, and T/T groups, respectively. Free T4, FSH, LH, and estradiol also varied between genotypes, but the differences were not statistically significant.

Thus, in women with PESS, prolactin appeared to be the hormonal parameter most closely related to the rs1800012 genotype.

A separate analysis was conducted in 10 men with PESS. Four patients had the G/G genotype, three had G/T, and three had T/T.

The most pronounced differences in men involved the gonadotropic axis. FSH concentration in T/T carriers was 2.07±0.10, significantly lower than the 2.70±0.10 observed in G/T carriers ($p<0.05$).

A similar direction was observed for LH and testosterone, although these differences did not achieve statistical significance. LH decreased from 1.90±0.20 in G/G carriers to 1.20±0.20 in the T/T group. Testosterone was 2.60±0.20 in G/G carriers, 2.70±0.30 in G/T carriers, and 2.27±0.30 in T/T carriers.

TSH and free T4 concentrations were generally comparable between male genotype groups, and no clear relationship with rs1800012 was identified. Prolactin levels also did not demonstrate significant differences between genotypes in men.

The different pattern observed in women and men is of particular interest. In women, genotype-related hormonal changes were mainly associated with prolactin, whereas in men they were more clearly reflected in gonadotropic function. These findings may indicate that the phenotypic expression of genetic susceptibility in PESS is modified by sex-specific endocrine mechanisms.

At the same time, these findings should be interpreted cautiously because the genotype subgroups, especially the T/T groups, were small. Therefore, the results primarily identify a direction for further investigation rather than establish a definitive genotype-hormone causal relationship.

Conclusion

The analysis demonstrated sex-related differences in the hormonal profile associated with COL1A1 rs1800012 genotypes in patients with primary empty sella syndrome.

In women, the most pronounced genotype-related changes were observed in prolactin concentration: G/T carriers had lower prolactin levels, while women with the T/T genotype showed the highest values. In men, the association was more evident for gonadotropic function, with significantly lower FSH in T/T carriers compared with the G/T genotype and parallel tendencies toward lower LH and testosterone levels.

No consistent genotype-dependent association was identified for TSH and free T4 in either sex.

These results suggest that the relationship between COL1A1 rs1800012 and the endocrine phenotype of primary empty sella syndrome may be sex-specific. In women it may be manifested predominantly through changes in prolactin secretion, whereas in men it may involve the gonadotropic axis. Larger studies are required to confirm these preliminary associations..

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