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HYPERGONADOTROPIC HYPOGONADISM IN 46,XX ADOLESCENTS WITHOUT GONADOTOXIC THERAPY: CLINICAL FEATURES AND MOLECULAR ETIOLOGIES

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Background

- **Hypergonadotropic hypogonadism (HH) in females results from primary gonadal failure related to;**
  - **Genetic defects affecting ovarian development and function**
  - **Pathogenic variants in single genes, chromosomal abnormalities such as Turner syndrome**
  - **Acquired gonadal damage**
- **Over 75% of cases do not have a clear molecular diagnosis.**
- **Limited knowledge exist regarding underlying genes involved or potential gene environment interactions responsible for disease trait manifestations.**

Method

- **24 females (23 families) with 46,XX HH from a single pediatric endocrinology center**
- **Patients with gonosomal chromosomal abnormalities and gonadal failure secondary to chemotherapy/surgery were excluded.**
- **Ascertainment was based on characteristic clinical and laboratory features.**
- **Potential molecular genetic etiologies were investigated by family based genomics to gain insights into disease biology.**

Results

Table 1. **Clinical features of the patients**

Age at diagnosis (years) mean±SD	**15.1±2.3**
Consanguinity n (%)	**20 (71.4)**
A family member with HH n (%)	**7 (25.0)**
Clinical presentations	**n (%)**
• **Primary amenorrhea**	**19 (67.9)**
• **Secondary amenorrhea**	**5 (17.9)**
• **Short stature**	**3 (10.7)**
• **Breast underdevelopment with irregular menstrual cycles**	**1 (3.5)**
Height SDS	**0.8±1.1**
BMI SDS	**0.6±1.5**
Breast Tanner stage n(%)	
I	**7 (25.0)**
II-III	**9 (32.1)**
IV-V	**12 (42.9)**
LH (mIU/ml)(N:2.4-12.6) mean±SD	**27.1±9.7**
FSH (mIU/mL)(N:3.8-8.8) mean±SD	**82.2±30.8**
BMD Z-score with DXA (Lumbar spine)	**1.8±1.1**
BMD Z-score <-2.0 (%)	**12 (42.9)**
Final height SDS	**-0.2±1.0**
Midparental height SDS	**-0.5±0.9**

Table 2. **Comparison of primary amenorrhea (PA) and secondary amenorrhea (SA) groups**

	PA	SA	p
Age at diagnosis (years) mean±SD	**15.7±1.5**	**15.4±1.0**	**ns**
Height SDS	**-0.7±1.1**	**-0.4±0.7**	**ns**
BMI SDS	**0.5±1.5**	**1.7±1.1**	**ns**
LH (mIU/ml)(N:2.4-12.6) mean±SD	**25.2±9.8**	**31.7±9.6**	**ns**
FSH (mIU/mL)(N:3.8-8.8) mean±SD	**80.8±25.0**	**81.1±28.9**	**ns**
Length of the uterine long axis (mm) mean±SD	**34.6±11.8**	**54.6±13.0**	**0.004**
Median time from initiation of estrogen to combined hormone replacement therapy (months)	**18.1**	**1.1**	**0.012**

- **Likely damaging pathogenic variants were identified in 14 patients (50%)**
- **Multi-locus pathogenic variation was detected in 2 cases.**
- **Patients with galactosemia (*GALT*) presented with PA, and their urinary reducing substance levels were normal.**

- ***SOHLH1 (n:2)***
- ***NOBOX***
- ***PAD16***
- ***MRPS22***
- ***GALT (n:2)***
- ***CYP17A1***
- ***MSH5***
- ***MCM9***
- ***MCM8***
- ***C3***

Conclusions

✓ **At least 50% of HH cases have a molecular diagnosis in a gene that contributes to gonadal development and maintenance, participates in estrogen biosynthesis, or has been implicated in diminished ovarian reserve.**

✓ **Additionally, standard laboratory screening can fail to identify galactosemia.**

Reference

1. Jolly A, Bayram Y, Turan S et al. Exome sequencing of a primary ovarian insufficiency cohort reveals common molecular etiologies for a spectrum of disease. J Clin Endocrinol Metab. 2019 Aug 1;104(8):3049-3067.