

Case Report

Primary hypergonadotrophic hypogonadism, alopecia totalis, and müllerian hypoplasia: A clinical study

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Abstract

Two sisters with primary hypergonadotrophic hypogonadism associated with alopecia totalis, streak ovaries, absent or rudimentary uterus and markedly hypoplastic internal and external genitalia are presented. Their parents were first cousins.

Introduction

Syndromes with alopecia and hypogonadism are rare and genetically heterogeneous. Patients with both features have been reported with other clinical abnormalities of the skin and eyes, ataxia, deafness, or diabetes. If the parents are consanguineous, autosomal recessive inheritance of the syndrome is likely.

Two sisters born of a consanguineous marriage with features resembling those described by Al-Awadi¹ in 1985 and Mégarbané² in 2003 are presented.

To the best of our knowledge and supported by an intensive literature search, this is the third reported case on this entity.

Case Report

Two Muslim sisters, resident of Quetta presented with primary amenorrhea at the National Institute of Diabetes and Endocrinology [NIDE] Karachi. Menarche had not been attained till the age of 22 and 23 years respectively.

They were born by normal vaginal delivery with no prenatal and postnatal complications. Milestones had been reached appropriate to age. The past history was unremarkable. Both the girls were studying at a local college and apparently had no mental deficiencies. There were no complaints of heat or cold intolerance, palpitation, oral thrush, muscular weakness or ability to smell. Their drug history and personal history were insignificant.

The elder sister was of 23 years age with a height of 178 cm and weight of 55 kg. Her vitals were stable and physical examination showed temperature of 98.4°F, blood pressure 115/75 mmHg with a regular pulse rate of 82/min. Respiratory rate was 16/minute. She had fine sparse hair on scalp with absent eye brows but had normal eye lashes.

Her pubic and axillary hair were downy and

glandular tissues of the breasts were not developed. On physical examination of her genitalia, we found that her labia majora were underdeveloped while labia minora were absent. Her neurological, ophthalmologic, cardiac and respiratory examinations were all unremarkable.

The younger sister was 22 years of age with a height of 174 cm and 44 kg weight. Her physical appearance was similar to the elder sister, with sparse scalp hair and absent eye brows. There was also no development of secondary sexual characteristics. External genitalia were also underdeveloped. Her vitals were stable. She was afebrile with blood pressure of 120/80 mm Hg and pulse 72/min. regular. Respiratory rate was 18/min. No abnormality was detected on systemic examination.

Pelvic ultrasound revealed absent uterus in the elder sister and under-developed infantile uterus in the younger sister. Streak ovaries were visualized in both the cases.

Complete blood count, blood glucose, urinalysis and thyroid function studies were all in the normal range. Hormonal findings revealed a hypergonadotrophic hypogonadism with high FSH levels at 49.9 mIU/L and 43.7 mIU/L, in the older and younger sister respectively, (normal FSH in adult females: Follicular=4to13, Luteal=2to13, Midcycle=5to22, Menopausal=20 to138 mIU/ml). The estradiol levels were 10pg/ml and 12pg/ml respectively, for the two sisters (Normal values for estradiol in adult females: Early follicular= 30-100 pg/ml, Late follicular=100-400 pg/ml, Luteal phase=50-150 pg/ml) Prolactin and cortisol levels were in the normal range for age. There were no circulating antimicrobial and antithyroglobulin antibodies. Chromosome studies revealed a normal 46, XX karyotyping for both sisters.

Their parents were first cousins. There was no history of any other significant inherited disorder in the family.

Discussion

The significant characteristics of the two sisters were primary hypergonadotrophic hypogonadism, alopecia totalis, streak ovaries, and Müllerianhypoplasia. Autoimmune Polyglandular Syndrome (APS) was excluded as antibodies like antimicrobial and antithyroglobulin were not

detected. There was no evidence of pernicious anaemia, type 1 diabetes mellitus, mucocutaneous candidiasis and autoimmune adrenal insufficiency. An important characteristic present in both sisters was Müllerian duct hypoplasia manifested as hypoplastic and absent uterus which is not a part of APS.

Streak or absent ovaries with malformed uterus, and

ovaries, and Müllerian hypoplasia. An exaggerated dorsal kyphosis, lumbar lordosis, and malformed 5th lumbar vertebra were observed in one sister. Their parents were also first cousins.

The clinical findings of the family presented in this study are very similar to the two cases reported by Al-Awadi and Mégarbané (Table), and it may be suggested that this is

Table: Comparison between the presented case and two other similar published case reports.

	1st Case Report Megarbane ² 2002		2nd Case Report Al-Awadi ¹ 1985			Our Case Report Zaman 2008	
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2
Sex	F	F	F	F	M	F	F
Age of examination (year)	18	17	18	16	22	22	23
Microcephaly	+	+	-	-	-	-	-
Scalp alopecia	+	+	+	+	+	+	+
Eyebrows	Sparse	Sparse	Normal	Normal	Normal	Absent	Absent
Eyelashes	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Axillary and pubic hair	Absent	Absent	Sparse	Sparse	Normal	Sparse	Sparse
Hypergonadotropic hypogonadism	+	+	+	+	+	+	+
Müllerian hypoplasia	+	+	+	+	+	+	+
Absent/streak ovaries / testes	+	+	+	+	+	+	+
Back deformities	+	-	+	-	-	-	-
Parental consanguinity	+	+	+	+	+	+	+

hypoplastic fallopian tubes had been previously reported in different kindred, but, in these families mental retardation and abnormal karyotyping was not detected.³⁻⁵

Most of the entities described with alopecia and hypogonadism were excluded in the presented cases because of the absence of retinitis pigmentosa, deafness, ataxia, diabetes, or mental retardation.⁶⁻⁹

In 1979 Salti and Salem¹⁰ described a Lebanese family with four sons and three daughters with fine sparse scalp hair and absent facial, axillary and pubic hair. But hypogonadotropic hypogonadism was also present. Streak ovaries, hypoplastic uterus, or microcephaly were also reported in these siblings.

In 1985 Al-Awadi,¹ reported three siblings, one male and two females, born to consanguineous Jordanian parents living in Kuwait. The male child aged 22 years, had a normal penis but small soft testes. His testicular biopsy revealed no germinal elements. The females presented with primary amenorrhea. Both had partial alopecia especially on the temporo-parietal regions of the cranium. Their eyebrows and eyelashes were intact. They had streak ovaries. There was no visible cervix, uterus and fallopian tubes. One female had back deformities.¹

Mégarbané² in 2003 reported a similar case of two sisters from Lebanon who presented with primary hypergonadotropic hypogonadism associated with microcephaly, flat occiput, partial alopecia, absent or streak

the report of a 3rd family with a similar clinical presentation. In contrast to the patients reported in the earlier studies, the present cases did not have back deformities and microcephaly. They had alopecia totalis, with sparse scalp hair and absent eye lashes.

Earlier reported families were from the Middle East, while our cases are from the South Asia, so the impression presented in the second report by the authors, that a founder mutation is present in the Middle-Eastern population for this entity, is now questionable.

These three reports may have a fortuitous association. But it would only have a significant value, if more familial cases are reported to support the hypothesis. The cases presented may be a part of the syndrome, or an allelic entity, the etiology of which is currently unknown. Identification of more cases with similar clinical and biochemical features, will help to understand the genesis of this pathology, and further promote appropriate management and counseling.

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