

Blepharophimosis ptosis epicanthus inversus syndrome (BPES): A rare cause of primary ovarian insufficiency

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ABSTRACT

Introduction: Most common cause of primary ovarian insufficiency is idiopathic (80–90%). Other causes are chromosomal, genetic, autoimmune, metabolic, infectious, and iatrogenic. Blepharophimosis ptosis epicanthus-inversus syndrome (BPES) is a rare genetic cause of primary ovarian insufficiency. It mainly affects development of eyelids and has autosomal dominant inheritance. The BPES is of two type, type I and II. Both of which include the eyelid malformations and other facial features. Type I is associated with primary ovarian insufficiency in women. We studied three cases who presented with BPES in Gynecology OPD of AIIMS Rishikesh over a period of six months.

Each case was unique, representing different clinical features and treatment requirements. Thus this case series will expose readers about varied spectrum of BPES and treatment protocol. **Case Series:** Case 1: A 28-year-old lady presented with dimness of vision since early childhood primary infertility and secondary amenorrhea for 10 years, hot flush for last five years. On examination she had bilateral blepharophimosis, under corrected bilateral ptosis, epicanthus inversus and telecanthus. Her clinical and biochemical feature suggested primary ovarian insufficiency. So she was a case of BPES type I. She was advised hormone replacement therapy and calcium supplementation and offered corrective ocular surgery. She responded to the treatment. Case 2: A 36-year-old lady with visual dimness, secondary infertility and secondary amenorrhea for eight years, hot flush for last five years. On examination she had bilateral blepharophimosis, bilateral ptosis, epicanthus inversus and telecanthus. Her clinical and biochemical feature suggested primary ovarian insufficiency. So she was a case of BPES type I. She was advised hormone replacement therapy and calcium supplementation and offered corrective ocular surgery. She responded to the treatment. Case 3: An 11 years and girl with bilateral Blepharophimosis, bilateral ptosis, epicanthus inversus and telecanthus. She was clinically diagnosed as BPES and offered corrective ocular surgery. **Conclusion:** Consciousness about clinical presentation of BPES along with importance of early diagnosis, counseling, prompt treatment of infertility and hypoestrogenic state and corrective ocular surgery should be should be increase among clinicians.

Keywords: Blepharophimosis ptosis epicanthus-inversus syndrome (BPES), Primary ovarian insufficiency, Ptosis, Early menopause, Secondary amenorrhea

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INTRODUCTION

The definition of primary ovarian insufficiency (POI) is amenorrhea, hypoestrogenism, and elevated serum gonadotropins in a woman less than 40 years of age [1]. More than 4 months of amenorrhea and two serum FSH levels of more than 40 mIU/ml obtained more than 1 month apart in a woman aged <40 years are the suggested criteria for diagnosing primary ovarian insufficiency [2]. Primary ovarian insufficiency affects 1 in 10,000 women by age 20 years, 1 in 1,000 women by age 30 years, and by age 40 years 1 in 100 women [3]. The prevalence of POI in women with primary amenorrhea is 10%–28%; in those with secondary amenorrhea, POI occurs in 4–18% [2]. Isolated and familial cases have been described; however, studies demonstrate that familial POI can vary between 4% and 35% [4–6].

Primary ovarian insufficiency is a heterogeneous disorder with many potential causes. In most of the cases cause is idiopathic (80–90% of the cases). Other causes are chromosomal, genetic, autoimmune, metabolic, infectious, and iatrogenic.

This case report describes three patients with BPES as a cause of primary ovarian insufficiency.

Blepharophimosis ptosis epicanthus-inversus syndrome (BPES) is a rare autosomal dominant disorder which manifests as eyelid malformation. The BPES is of two type, Type I and Type II. Type I is associated with premature ovarian failure in the affected female. Vignes in 1887 first associated blepharophimosis with ptosis and epicanthus inversus. This disease is characterized by four features: [7]

- (1) Bilaterally shortened horizontal palpebral fissure (blepharophimosis) [7].
- (2) Severe impairment of the superior palpebral levator function (ptosis) [7].
- (3) A vertical skin fold arising from the lower eyelid, which inserts medially in the upper lid (epicanthus inversus) [7].

- (4) An increased inner canthal distance with a normal outer canthal distance (telecanthus) [7].

The mutations causing BPES are found in the FOXL2 gene which is a forkhead transcription factor, located in 3q23. Fifty percent patients with blepharophimosis ptosis epicanthus-inversus syndrome have an affected parent and 50% of cases are sporadic.

A diagnosis of BPES can be made by combination of typical facio-ocular features with clinical and biochemical features of primary ovarian insufficiency. So for diagnosis purpose detailed genetic analysis is not needed and it is not in diagnostic criteria.

CASE SERIES

Case 1

A 28-year-old nulligravida presented with dimness of vision since her early childhood, amenorrhea for last 10 years, inability to conceive in her five years of married life and hot flushes for last 3–4 years. Her menarche was at 16 years. She had oligomenorrhea followed by amenorrhea since 18 years of age. On pedigree analysis no similar facial or menstrual abnormality and infertility were found in first and second degree relatives. She had history of prior surgery for ptosis 16 years back.

On clinical examination her height was 5 feet 2 inch, weight 40 kilograms. Facial feature revealed bilateral blepharophimosis, under corrected bilateral Ptosis (right eye moderate and left eye severe) with poor levator palpebrae superioris (LPS) muscle action with frontal over action with lid scars, epicanthus inversus, and telecanthus. Best corrected visual acuity: right eye 6/18, left eye 6/24 with both eyes mixed astigmatism with meridional amblyopia (Figure 1). She had breast atrophy with normal pubic and axillary hair growth. On gynecological examination the uterus was small in size without any pelvic and abdominal mass. Serum FSH levels were raised (40 mIU/ml) on two occasions. Serum prolactin and thyroid hormones were within normal range. Ultrasound pelvis shows uterus smaller in size, endometrial thickness 4 mm.

From the combination of her typical facio-ocular features with clinical and biochemical features of primary ovarian insufficiency her diagnosis was confirmed to be BPES Type I. DNA polymerase chain reaction study (PCR) and genetic sequencing not done as it was not required for diagnosis and she could not afford it.

Counseling of the couple regarding infertility and adverse effects of early menopause were done. Possibility of pregnancy by embryo transfer was discussed with her but as her family was not affording she went for adoption instead. She was prescribed menopausal hormone therapy in form of cyclical conjugated oestrogen 1.25 mg 21 days in a month and medroxyprogesterone (progesterone) 10 mg daily last 10 days of cycle. She was also prescribed calcium and vitamin D3 supplement daily. Regarding

her ophthalmic findings, she was advised Mustard's or VY plasty and transnasal wiring followed by frontalis suspension procedure bilaterally.

Case 2

A 36-year-old female presented with dimness of vision since early childhood, Inability to conceive for eight years after birth of her 1st baby 10 years back, amenorrhea for last six years, hot flush lack of sleep at night and backache for last five years.

She attained menarche at 15 years initially cycle length and flow was normal, gradually she developed oligomenorrhea with scanty flow followed by amenorrhea at the age of 30 years.

On pedigree analysis no similar facial or menstrual abnormality and infertility were found in 1st and 2nd degree relatives.

On clinical examination her height was 5 feet 2 inch weight 56 kg.

Facial examination revealed bilateral blepharophimosis, bilateral severe ptosis with poor LPS action with frontalis over action, epicanthus inversus, telecanthus (Figure 2).

On gynecological examination the uterus was small in size and no mass in the pelvis or abdomen was felt. Serum FSH levels were raised (40 mIU/ml) on two occasions. Serum prolactin and thyroid hormones were within normal range. Ultrasound pelvis showed uterus smaller in size, endometrial thickness 4.2 mm.

From the combination of her typical facio-ocular features with clinical and biochemical features of primary ovarian insufficiency her diagnosis was confirmed to be BPES Type I. DNA PCR and genetic sequencing not done as it was not required for diagnosis and she could not afford it.

Patient was counseled for in vitro fertilization with donor embryo transfer but due to economic constrain, and as she already had a living issue she was not interested. She was prescribed menopausal hormonal therapy and calcium supplementation as previous case. She was advised multi staged surgery with correction of epicanthus followed by ptosis surgery later.

Case 3

An eleven-year-old girl presented to the eye OPD with complaints of droopy eyelids since birth. She had best corrected visual acuity of 6/18 both eyes with astigmatism with meridional amblyopia. Her lid and adnexal examination revealed bilateral severe ptosis along with poor LPS action with blepharophimosis, epicanthus-inversus and telecanthus. Pedigree analysis revealed her father was a diagnosed case of blepharophimosis syndrome. In view of these findings diagnosis of BPES was confirmed and to classify the syndrome as type 1 or type 2, the girl was referred from eye OPD for a gynecological consultation.

The patient's ophthalmologist prescribed spectacles for her refractive error along with advice to undergo a multi-staged surgery for correction of epicanthus inversus and telecanthus followed by ptosis surgery along with a trial of occlusion therapy for amblyopia. She was advised regular follow up in gynecology OPD to address to her future menstrual problem and fertility aspect. She was also advised genetic analysis to determine type of BPES.

DISCUSSION

The BPES is a rare autosomal dominant disorder caused by mutation in the FOXL2 gene, a forkhead transcription factor, located in 3q23.

Zlotogora et al. showed that penetration was 100% in type I and it was transmitted by males only and affected females are infertile. In type II penetration is 96.5% and transmission occurs through both sexes. Zlotogora et al. also found there was a deviation from the normal sex ratio among children of affected fathers in both types. In type I, most of the children were males and most of the male offspring were affected, in contrast in type II, most of the children were females and most of the female offspring were affected [8].

According to some investigators, POI could be explained by two basic mechanisms, early decrease in number of ovarian follicles or dysfunction of follicles. Follicular depletion can be from decreased number



Figure 1: Ocular features of Case 1 BPES. (Patient had given informed consent which is attached).



Figure 2: Ocular features of Case 2 BPES. (Informed consent added).

of primordial follicles from beginning or an early and increased rate of follicular atresia of the initial follicular endowment.

In the last two decades multiple genetic and chromosomal anomalies associated with POI had been described. Among the chromosomal causes, X-linked alterations like Turner's syndrome, X trisomy, and X mosaicism have been responsible for a large proportion of primary ovarian insufficiency (POI) cases [4].

Most frequent POI related genes in the X chromosome are the fragile site mental retardation 1 gene (FMR1) and the bone morphogenetic protein 15 gene (BMP15) [4].

Mutations in autosomal chromosomes are also responsible in many cases of POI. Some of the responsible genes are FSH receptor (FSHR), luteinizing hormone receptor (LHR), galactose-1-phosphato uridytransferase (GALT), guanine nucleotide binding protein, a-stimulating activity polypeptide 1 (GANS), cytochrome P450c17a (CYP17), aromatase (CYP19), carbohydrate-deficient glycoprotein (CDG), and forkhead transcription factor L2 (FOXL2) have been associated with POF [4].

Foxl2 was first identified in 1998 as a new member of the winged helix family or forkhead family of transcription factors in a screen for genes involved in mouse pituitary gland development. They share a common DNA binding domain of up to 110 amino acids whose helix–turn–helix structure resembles a butterfly hence the alternative name “winged helix” [9].

In human, the forkhead family consists of 39 members, which influence a diverse range of biological processes. They are necessary for the establishment of the body axis, for the development of tissues from all three germ layers, for metabolic processes as well as cell cycle control [10]. Eight different human developmental disorders have been associated with mutations in forkhead genes. Forkhead gene mutation leads to ophthalmic features of BPES.

Two types of disease can be caused by different mutations of same protein. In type I BPES, mutations cause stop codons in the FOXL2 gene creating a truncated protein product with significant loss of function. In type II BPES, there is in-frame duplication within the FOXL2 gene which results in addition of 10 more alanine residues to the polyalanine domain, which results in decreased activity of the protein product [10].

Several other newer mutations have been discovered. Recently a novel insertion mutation in the 3'UTR of FOXL2 was discovered in a big Chinese family, which is the first reported case of a close correlation between the 3'UTR mutation and BPES [11].

Three cases of BPES were studied within six months of study period and each case had special clinical presentation and posed unique therapeutic challenges. First two cases were example of sporadic onset of disease from germline mutation and third case was example of genetic transmission of disease from affected parents. First two cases are clinically and biochemically BPES I

but presentation in different period of reproductive life changed the goal of treatment. Importance of 3rd case was that early diagnosis can help to preserve fertility by cryopreservation of oocytes.

Women patients with BPES generally consult ophthalmologist first due to typical facio-ocular features. As it is very rare genetic disorder and similarity of the facial feature with mongoloid face, most often diagnosis is not made and complete spectrum of the disease manifestation is not searched for. Treatment becomes incomplete. For instance 1st patient of our case series consulted ophthalmologist at the age of 14 years and had surgical correction of ptosis her typical facial features was confused with mongoloid facies and diagnosis was missed. So she was not referred to higher center for fertility preservation and prevention of hypoestrogenic complications. Ultimately, she came to us with primary infertility and advanced hypoestrogenic complication which should be entirely preventable if proper diagnosis was made in correct time.

In the case series, we did not study genetic anomaly of the patients as diagnosis of typical genetic anomaly is not a diagnostic criteria of BPES and even it does not help in differentiating type of the disease. Also it does not help in management. So we did not waste our poor patients' resources over costly genetic study.

Early diagnosis and treatment are very important in case of BPES. These are possible with multidisciplinary approach involving both gynecologist and ophthalmologist. Goals of the treatment are fertility preservation by cryopreservation of ovarian tissue and prevention of long term side effects of hypoestrogenic state and by early corrective surgery of eyelid prevention of amblyopia. Hormone replacement therapy in higher dose should be continued till age of menopause to prevent hypoestrogenic state. Proper counseling regarding disease to the patient and her family should be done.

CONCLUSION

Blepharophimosis ptosis epicanthus-inversus syndrome (BPES) is a rare disease that is not difficult to diagnose as it has typical clinical features. Therefore, awareness should be increased among both ophthalmologists and gynecologists about this condition as early diagnosis is the key factor in improving the long-term prognosis.

Author Contributions

Dhiman Niharika – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Chowdhuri Sandipan – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Gupta Vinita – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Chaturvedi Jaya – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Mundhra Rajlaxmi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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