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TYPE OF ARTICLE: Case Series

TITLE: Blepharophimosis Ptosis Epicanthus-inversus Syndrome (BPES) - A Rare Cause of Primary Ovarian Insufficiency, Case Series of three Cases

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Short Running Title: BPES

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SUMMARY
Primary ovarian insufficiency (POI) is defined as amenorrhea, hypoestrogenism, and elevated serum gonadotropins in a woman less than 40 years of age. More than 4 months of amenorrhea and two serum FSH levels of >40 mIU/mL obtained more than 1 month apart in a woman aged <40 years are the suggested criteria for diagnosing Primary ovarian insufficiency. 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. 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 Gynaecology Out Patient Department (OPD) of AIIMS Rishikesh over a period of six months.
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 search for. Treatment becomes incomplete. For instance first 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 hypo estrogenic complications. Ultimately she came to us with primary infertility and advanced hypo estrogenic complication which should be entirely preventable if proper diagnosis was made in correct time.
So we can safely conclude that though BPES is a rare disease, timely diagnosis should be made in all cases. Ophthalmologist and Gynaecologist should be aware of this entity.
TITLE: Blepharophimosis Ptosis Epicanthus-inversus Syndrome (BPES) - A Rare Cause of Primary Ovarian Insufficiency, Case Series of three Cases.

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. 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 Gynaecology 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: 28 years lady presented with dimness of vision since early childhood primary infertility and secondary amenorrhea for 10 years, hot flush for last 5 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: 36 years lady with visual dimness, secondary infertility and secondary amenorrhea for 8 years, hot flush for last 5 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.
supplementation and offered corrective ocular surgery. She responded to the
treatment.

Case 3: An 11 years 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 increase among clinicians.

Keywords: Blepharophimosis ptosis epicanthus-inversus syndrome (BPES),
Primary ovarian insufficiency, secondary amenorrhoea, Ptosis, Early menopause
TITLE: Blepharophimosis Ptosis Epicanthus-inversus Syndrome (BPES) - A Rare Cause of Primary Ovarian Insufficiency, Case Series of three Cases.

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 mille International Unit/mille Littre (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 amenorrhoea is 10%–28%; in those with secondary amenorrhoea, 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].

POI 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. 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. 50% 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
28 years nulligravida presented with dimness of vision since her early childhood, amenorrhoea for last 10 years, inability to conceive in her 5 years of married life and hot flushes for last 3-4 years. Her menarche was at 16 years. She had oligomenorrhoea followed by amenorrhoea 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 Height was 5 feet 2 inch, weight 40 kilogram. Facial feature revealed bilateral Blepharophimosis, under corrected bilateral Ptosis (right eye moderate and left eye severe) with poor Levator Palpabral Supperiolis (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 gynaecological examination the uterus was small in size without any pelvic and abdominal mass. Serum FSH levels were raised (40mIU/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. Counselling 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 Mustarde’s VY plasty and transnasal wiring followed by frontalis suspension procedure bilaterally.

Case 2
36 years old presented with dimness of vision since early childhood, inability to conceive for 8 years after birth of her 1st baby 10 years back, amenorrhoea for last 6 years, hot flush lack of sleep at night and backache for last 5 years. She attained menarche at 15 years initially cycle length & flow was normal, gradually she developed oligomenorrhoea with scanty flow followed by amenorrhoea 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 gynaecological examination the uterus was small in size and no mass in the pelvis or abdomen was felt. Serum FSH levels were raised (40mIU/ml) on two occasions. Serum prolactin and thyroid hormones were within normal range. Ultrasound pelvis shows 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 counselled for in vitro fertilization with donor embryo transfer but due to
economic constrain and as she already has 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
Eleven year 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 blepharphimosis, 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 gynaecological consultation.
Her 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 Gynaecology OPD to address to
her future menstrual problem and fertility aspect. She was also advised genetic
analysis to determine type of BPES.

DISCUSSION
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 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 are 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 uridyltransferase (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 shares 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 decreased activity of the protein product [10].

Several other newer mutation has 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 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 search 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 hypo estrogenic complications. Ultimately she came to us with primary infertility and advanced hypo estrogenic 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 not a diagnostic criteria of BPES and even it does not help to differentiate 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 Gynaecologist and Ophthalmologist. Goals of the treatment are fertility preservation by cryopreservation of ovarian tissue and prevention 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

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

CONFLICT OF INTEREST

Authors declare no conflict of interest in this study.

AUTHOR’S CONTRIBUTIONS

Niharika Dhiman
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

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REFERENCES


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A novel insertion mutation in the \textit{FOXL2} gene is detected in a big Chinese family with blepharophimosis–ptosis–epicanthus inversus.


\textbf{FIGURE LEGENDS}

Figure 1: Ocular features of Case 1 BPES.

Figure 2: Ocular features of Case 2 BPES.

\textbf{FIGURES}

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)