Case Report
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A Novel Mutation in the *FOXL2* Gene in Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome, Leucoencephalopathy and Myasthenia Gravis

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Abstract

Blepharophimosis-Ptosis-Epicanthus inversus Syndrome (BPES) is a rare autosomal dominant disease caused by *FOXL2* gene mutations, and it is clinically characterized by an eyelid malformation associated (type I) or not (type II) with premature ovarian failure. A clinical and molecular genetic investigation was performed in a woman with BPES and a complex neurological picture associating multifocal leucoencephalopathy, Myasthenia Gravis and thymic tumor. Genomic DNA was extracted, and the *FOXL2* coding region was sequenced. We identified the novel mutation c.558delC causing a premature stop codon (p.Y186X) in the *FOXL2* protein. We can hypothesize that the mutation described in our patient may be linked to the thymic tumor. Further studies will have to be conducted to confirm this hypothesis.

Keywords: *FOXL2* mutations; Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome; Myasthenia gravis; Multifocal leucoencephalopathy

Abbreviations

BPES: Blepharophimosis-Ptosis-Epicanthus inversus Syndrome; MS: Multiple Sclerosis; MG: Myasthenia Gravis; POF: Premature Ovarian Failure

Introduction

Blepharophimosis-Ptosis-Epicanthus inversus Syndrome (BPES;OMIM 110100) is a rare autosomal dominant genetic disorder with an estimated incidence of one in 50,000 [1]. It is characterized by narrow horizontal palpebral fissures, congenital ptosis, telecanthus and epicanthus inversus [2]. In addition to the ophthalmic symptoms, female BPES patients may have infertility caused by Premature Ovarian Failure (POF), classified as type I BPES, whereas those without POF are classified as type II [3]. Currently, mutations of the *FOXL2* gene are the major cause of BPES [4].

FOXL2 is a 2.7-kb gene with a single exon encoding a 376 amino acid protein, which contains a 110 amino acid DNA-binding Fork-Head Domain (FHD) and a polyalanine (poly-Ala) tract of 14 residues of unknown function. *FOXL2* is an essential transcription factor involved in normal development of the ovary and eyelid [5,6]. It has also been suggested that the gene could be involved in the regulation of cholesterol and steroid metabolism, apoptosis, reactive oxygen species detoxification and inflammatory processes [7]. *FOXL2* mutations are also implicated in other diseases, such as Polycystic Ovary Syndrome (PCOS) [8] in an Indian family with BPES. Moreover a recent Japanese genome-wide association study showed a significant association of keloid with *FOXL2* expression. It has been assumed that gonadal and steroid hormones might influence keloid formation, which is known to be regulated by expression of *FOXL2* [9]. Shah *et al.* identified a somatic point mutation (p.C134W) and considered this mutant *FOXL2* a potential driver in the pathogenesis of adult-type ovarian Granulosa-Cell Tumor (GCT) [10]. Recent studies demonstrated a correlation between lacrimal gland underdevelopment and *FOXL2* [11], especially for truncated proteins or mutations affecting the FHD.

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Thus far, 70% of BPES cases were shown to have intragenic mutations, including premature stop codons, missense mutations, expansions of the region encoding the poly-Ala tract and frameshift mutations leading to a shorter or longer proteins [7], but the correlation between mutation types and BPES types still needs to be clarified. Poly-Ala expansion mutations often lead to BPES type II, and truncations before the poly-Ala tract always lead to BPES type I [4,12]. However, the effect of mutations containing an intact FHD and poly-Ala tract remains elusive [13,14].

In our study, we identified a novel mutation (the heterozygous deletion c.558delC causing a premature stop codon (p.Y186X)) in the *FOXL2* gene in a woman with BPES and a complex neurological picture associating multifocal leucoencephalopathy and Myasthenia Gravis (MG).

Case Report

A 52 years old woman with BPES type I syndrome was admitted in April 2017 to the Neurological Clinic of Florence for progressive dysphagia. She presented blepharophimosis, surgically corrected, ptosis, telecanthus, reverse epicanthus, amblyopia in left eye and primary amenorrhea due to ovarian failure (Figure 1). The genetic analysis of *FOXL2* identified a heterozygous deletion (c.558delC) causing a premature stop codon (p.Y186X). The family history was remarkable just for a schizoaffective syndrome in the brother. Informed consent for the genetic analysis was obtained for the patient. The study received the approval of the local Ethical Committee and was performed according to the Declaration of Helsinki.

The patient past medical history was very long and complex. In 1985, at the age of 20 years, she began complaining of bilateral blurred vision. In the following years she presented episodes of diplopia and dysphagia of variable duration (ranging from minutes to several days) associated with a sense of constriction in the throat, followed by spontaneous remission. She underwent brain MRI that showed two T2-hyperintense lesions, one subcortical, localized in the subcortical white matter of the parietal region and one periventricular, localized at the level of the occipital horn of the lateral ventricle, both on the right side, no gadolinium enhancing lesion. Spinal cord MRI was normal. CSF examination documented the presence of Oligoclonal Banding (OB) at isoelectrofocusing; serological, dysimmune and thrombophilic assessments were unremarkable. A diagnosis of possible Multiple Sclerosis (MS) was initially reported.

As the symptomatology had a fluctuating course and brain MRI showed no appearance of new T2 or gadolinium enhancing lesions during the follow-up period, she underwent a new diagnostic work-up in the suspicion of Myasthenia Gravis (MG), including the search of anti-Ach-R and anti-Musk antibodies, anti calcium and potassium channels, autoantibody set-up study for LAC that showed normal values. EMG with repetitive stimulation resulted in a negative Desmedt test but showed pseudotetania at the hyperpnea-ischemia test. Visual evoked potentials revealed bilateral abnormalities more marked in the left eye. A therapeutic attempt with pyridostigmine and prednisone was made but resulted to be ineffective. In the following years, due to the persistence of symptoms, the above laboratory and neurophysiological investigations were repeated periodically, remaining unchanged. In this context, in 2010 a mediastinic CT showed a thymoma: since during the first surgical attempt the patient developed a Takotsubo Syndrome, the neoplasm was effectively removed with robotic surgery only in 2016. In the following years,

Figure 1: A picture of the patient showing eyelid malformations.

due to the development of chronic widespread pain and a heightened pain response to pressure a diagnosis of fibromyalgia was formulated.

Moreover, in 2015 she developed a cutaneous lesion in the right arm for which she performed dermatological evaluation with histological examination and diagnosis of "sclerosing dermatitis with Morfea". The Dosage of autoantibody anti-dsDNA and anti-ENA was normal.

In 2017, a brain and spinal cord MRI was repeated, showing the same two lesions at brain MRI, no gd-enhancing lesion, C3-C4 and C4-C5 discopathy with large radius osteoporosis bars and a posterior-paramedian herniation in C6-C7 on the right side. A cystic septic and a C7 hemangioma were reported as occasional findings. Another EMG with Desmedt test turned out to be positive for post-synaptic alterations limited to the left orbicular muscle of the eye; also the Single Fiber Electro Myo Gram (SFEMG) was positive for neuromuscular plaque dysfunction.

The neurological examination showed bilateral ptosis and blepharophimosis on the left side, not worsened by fatigue tests. The remaining examination was normal: in particular, strength deficits were absent, even after tests of fatigue, ocular movements were normal and there was no appearance of diplopia even after tests of fatigue. Subjectively she complained of pain to the right lateral surface of the neck, bilateral shoulders and of painful paresthesias to the lateral surface of the upper limbs; moreover, of blurred vision in the primary position of gaze, that worsened in the lateral gaze, with appearance of “white stripes surrounded by black spots” in the right eye. Standard assessment of visual fields was normal.

The dosage of antititin, anti-LPR, anti-ryanodine R antibodies was normal.

Intravenous Immune globulins (IVIg) were administrated (0.4 gr per Kg of body weight daily for five days), with reported clinical benefit on dysphagia.

Discussion

We described, for the first time, a novel mutation in the *FOXL2* gene associated with a complex neurological picture whose main elements are represented by an antibody negative myasthenic syndrome and leucoencephalopathy with oligoclonal bands.

The diagnosis of MG was supported by EMG data, by the finding of thymoma and by the good response to IVIg.

This picture of leukoencephalopathy meets the current criteria

for spatial dissemination and the presence of OB that of temporal dissemination [15]. The demyelinating picture also seems to be supported by the finding of PEV. However, a definitive diagnosis of MS in our opinion remains challenging due to the atypical clinical course, the stability of the MRI findings over several decades and the possibility of an existing better explanation. Pictures of "aspecific" leukoencephalopathy at MRI have been described in the literature concomitantly with myasthenia gravis as well as cases of co-existence of the two dis (auto) immune pathologies [16,17]. The genetic analysis of *FOXL2* identified the heterozygous deletion c.558delC causing a premature stop codon (p.Y186X). What could be the pathogenic link between the mutation and myasthenia gravis or with the thymic tumor? *FOXL2* encodes a fork-head transcription factor that plays important roles in the ovary during development and in postnatal, adult life. In line with other fork-head transcription factors, its constitutional genetic defects and a somatic mutation lead to developmental disease and cancer, respectively. More than 100 unique constitutional mutations and regulatory defects have been found in BPES, a complex eyelid malformation associated (type I) or not (type II) with POF. In agreement with the BPES phenotype, *FOXL2* is expressed in the developing eyelids and in fetal and adult ovaries. An intact *FOXL2* function is not only crucial during development but is also needed throughout the lifetime of a female to prevent ovarian dysfunction, somatic transdifferentiation and tumor formation. Granulosa Cell Tumors (GCTs) represent less than 5% of all ovarian cancers and have been associated with a somatic *FOXL2* missense mutation c.402C>G (p.C134W) [10]. We can hypothesize that the mutation described in our patient may be linked to the thymic tumor. Further studies will have to be conducted to confirm this hypothesis.

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