Insights Into Levator Muscle Dysfunction in a Cohort of Patients With Molecularly Confirmed Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome Using High-Resolution Imaging, Anatomic Examination, and Histopathologic Examination

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Objective: To study the basis of defective levator palpebrae superioris (LPS) function in blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), an autosomal dominant eyelid malformation sometimes associated with ovarian dysfunction.

Methods: Eight patients with molecularly proved BPES underwent high-resolution surface-coil 3-T magnetic resonance imaging before surgical intervention. The features of LPS muscle and adjoining connective tissue were compared with an age-matched control subject. During LPS resection for ptosis repair, detailed anatomic examination of the LPS was performed. Histopathologic characteristics were compared with normal control samples from a cadaver and a patient with simple severe congenital ptosis.

Results: The most striking feature shown on magnetic resonance imaging was the thin, long anterior part of the LPS. During the operation, this consisted of a disorganized, thin, long aponeurosis. However, in the posterior part of the LPS, there was an organized thick structure suggestive of a muscle belly. Histopathologic examination revealed posteriorly well-formed striated muscle fibers in all patients with BPES but not in the control sample from the patient with simple severe congenital ptosis. These striated muscle fibers were comparable to those of the normal control tissue but were more intermixed with collagenous tissue and little fatty degeneration.

Conclusions: The presence of striated muscle fibers in LPS of patients with BPES contrasts with the fatty degeneration in patients with simple severe congenital ptosis. To our knowledge, this is the first study providing novel insights into the pathogenesis of the eyelid malformation in BPES through extensive imaging, anatomic study, and histopathologic testing in a unique cohort of patients with molecularly proved BPES.

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The blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) is a complex eyelid malformation characterized by 4 major abnormalities that are present at birth: blepharophimosis, ptosis, epicanthus inversus, and telecanthus. In addition, lateral displacement of the inferior punctum, another important anatomic hallmark of BPES, is present in all patients. The inheritance of this syndrome is most often autosomal dominant, and it is the result of mutations in the FOXL2 gene (OMIM *605597), which encodes a forkhead transcription factor.

The diagnosis of BPES is based primarily on clinical findings. However, molecular genetic testing revealing a FOXL2 mutation is important to confirm the clinical diagnosis. Management of BPES requires multidisciplinary care, including an oculoplastic operation. Surgical correction of the eyelid malformation in BPES is recommended not only for cosmetic reasons but also because of functional implications, including amblyopia, strabismus, and refractive errors. Surgical management traditionally involves a medial canthoplasty for correction of blepharophimosis, epicanthus inversus, and telecanthus in children aged 3 to 5 years, followed approximately 1 year later by ptosis correction.

Most patients with molecularly proven BPES have severe congenital ptosis with poor LPS function. The pathophysiologic factors underlying this defective LPS function in BPES remains largely unexplained. Until now, this was commonly attributed to dysplasia or even absence of the levator palpebrae superioris (LPS). A re-
cent study demonstrated that supramaximal LPS resection resulted in a significant increase in LPS function, which is not the case when conventional ptosis repair using a frontalis suspension procedure is performed in this condition.

To provide an anatomic substrate for our earlier findings, we set out to study the basis of defective LPS function in BPES through extensive use of magnetic resonance imaging (MRI) with surface coils, anatomic examination, and histopathologic testing in a unique cohort of patients with molecularly proved BPES.

**METHODS**

**PATIENTS**

Eight consecutive patients with molecularly proved BPES were included in this study. The patients’ parents or guardians provided informed consent, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with formal ethics committee approval. In general, presence of the 4 major criteria (blepharophimosis, ptosis, epicanthus inversus, and primarily telecanthus) was initially used for a clinical diagnosis of BPES. In addition, a fifth anatomic hallmark (ie, lower eyelid malpositioning) was present in all patients. Mutation screening of the FOXL2 gene was performed as previously described to confirm the diagnosis.

**MAGNETIC RESONANCE IMAGING**

Detailed history and clinical evaluation was carried out in all patients to rule out any contraindication for MRI. All patients underwent high-resolution 3-T MRI with surface coil before the operation to correct ptosis. The MRIs were acquired using a 3-T scanner (Trio; Siemens, Erlangen, Germany). The scanning protocol included a sagittal and coronal T2-weighted sequence and a sagittal T1-weighted sequence. Both sequences had a field of view of 100 mm and an in-plane resolution of 0.4 mm. The images were taken with both eyes closed (resting position in slight downgaze). The features of the LPS muscle and adjacent connective tissue were studied. These were compared with findings of a high-resolution 3-T MRI scan with surface coil in a healthy, age-comparable control individual. The MRI findings were correlated with intraoperative anatomic and postoperative histopathologic findings.

**ANATOMIC ANALYSIS**

The ptosis operation was performed in all patients with BPES between the ages of 4 and 13 years. All patients had severe ptosis with poor LPS function (ranging from 0-4 mm). During the operation, using supramaximal LPS resection, detailed anatomic examination of the LPS was performed.

**HISTOPATHOLOGIC EXAMINATION**

Histopathologic examination was performed on the resected tissue using hematoxylin-eosin, desmin, and smooth muscle actin staining. The histopathologic findings were compared with those from examination of a normal control sample taken from a cadaver as well as a sample from a patient with simple severe congenital ptosis, also having an LPS function less than 4 mm and undergoing the same type of operation.

Data on the FOXL2 mutation screening, each patient’s age at the time of the ptosis operation, and LPS aponeurosis length measured on the sagittal T2-weighted high-resolution surface-coil MRI scan are listed in the Table.

**MRI FINDINGS**

Representative MRI findings are depicted in Figure A (healthy control) and B (patient with BPES). In a sagittal T2-weighted high-resolution surface-coil MRI of a healthy individual (Figure 1A), several distinct structures could be observed in an anterior-posterior direction, starting with the thin skin and subcutaneous tissue. The preseptal part of the orbicularis oculi has an intermediate to hypointense signal intensity in T2-weighted images. The preseptal fat pad appears as a hypointense structure, and the orbital septum forms a hypointense bandlike structure descending from the superior orbital rim and fusing with the LPS aponeurosis. The preaponeurotic fat is seen as a hypointense structure and is identified just posteriorly to the orbital septum. The LPS splits into Muller muscle (which runs more posteriorly) on one side and into the aponeurosis on the other side. The aponeurosis attaches to the upper part of the tarsal plate after fusing with the orbital septum. Posteriorly, the aponeurosis fuses with the superior rectus muscle and a few connective septa between these two are observable on the image. The anterior, bandlike component of the common sheath between the LPS and superior rectus muscle is called the transverse superior fascial expansion and is seen as a hypointense structure below the aponeurosis. Whitnall’s ligament is identified as a hy-
pointense V-shaped structure at the highest point of the LPS. From that point, the LPS changes direction and descends apically.

Figure 1B shows a sagittal T2-weighted high-resolution MRI in a representative patient with BPES. To facilitate comparison with the age-matched control depicted in Figure 1A, the same numbering has been applied to both figures.

In all patients with BPES examined, there were several notable differences found compared with the healthy control. The volume of the preaponeurotic fat pad was increased in all patients. Whitnalls ligament appeared to be stretched, and the transverse superior fascial expansion was thinned or absent. The most striking feature was the thin aponeurosis of the LPS muscle, which was seen in all patients. This thinned aponeurosis was also much longer than in the control participant. The mean LPS aponeurosis length measured in our 10 patients with BPES was 24.9 mm (range, 21–28 mm). Because of the loss of signal intensity as the probe is placed deeper into the orbit, a muscle belly could not be discerned in the patients compared with the control participant.

ANATOMIC FINDINGS

During the ptosis operation using the supramaximal LPS resection, the LPS aponeurosis was consistently seen as a thin, very long, disorganized structure. On dissecting further posteriorly, the aponeurosis was replaced by a much thicker and well-organized structure suggestive of a muscle belly (Figure 2). The junction between the disorganized aponeurosis and organized musclelike structure was located 20 to 25 mm from the anterior insertion of aponeurosis on the tarsal plate (black arrows).

HISTOPATHOLOGIC FINDINGS

Tissue of the LPS obtained during the ptosis operation in patients with BPES was subjected to histopathologic examination. Hematoxylin-eosin staining of the anterior part of the LPS (insertion on the tarsal plate) revealed smooth muscle fibers suggestive of Muller muscle and dense disorganized fibrous tissue representing the aponeurosis (Figure 3A). The posterior part showed the junction of the fibrous tissue of the aponeurosis into an area of well-formed striated muscle fibers. The striated muscle fibers were round to oval, with minimal variation in diameter. These findings suggest the presence of a LPS muscle belly in BPES. Some scattered areas of fatty degeneration were found (Figure 3B and C).

For comparison, a sample from a patient with severe congenital ptosis with very poor LPS function, as well as a normal cadaver LPS specimen, were examined. The congenital ptosis specimen showed a similar histopathologic anterior aspect of the LPS as seen in the BPES specimen, with Muller muscle and disorganized fibrous tissue representing the aponeurosis (Figure 3A). However, in the posterior part, striated muscle fibers were absent, contrary to the finding in the BPES specimen. There were also extensive areas of fatty degeneration and dense, disorganized fibrous tissue (Figure 3E and F). These find-
ings indicate the absence of an LPS muscle belly in patients with simple severe congenital ptosis.

The normal control specimen showed, in the anterior part of the LPS, a very similar structure of collagenous tissue, representing the normal aponeurosis, and a smooth muscle, representing Müller muscle, compared with the BPES and congenital ptosis specimens (Figure 3G). The posterior part of the normal control sample showed striated muscle fibers comparable to those seen in BPES, with round to oval shape and little variation in diameter. However, the muscle belly in the normal control differed from that in the BPES specimen because the muscle belly was denser, with much less connective tissue and almost no fatty degeneration (Figure 3H and I).

One of the cardinal features of the complex eyelid malformation in BPES is severe ptosis with almost no LPS muscle function. However, the pathophysiologic factors underlying LPS dysfunction in BPES remain largely unexplained. It is commonly suggested that poor LPS function could be attributed to dysplasia or even absence of the LPS. However, in a recent study, our group was able to demonstrate an increase in LPS function after supramaximal resection during ptosis repair of BPES.

We suggested an anatomic substrate for these findings and, in an attempt to provide more insight into the basis of LPS dysfunction in BPES, we performed high-
resolution surface-coil 3-T MRI before the ptosis opera-
tion in 8 patients.

High-resolution MRI with surface coils is currently the
optimal way to visualize the minute structures of the or-
bit and periorbita. Surface coils significantly improve the
signal to noise ratio, allowing thinner sections and in-
creased spatial resolution compared with conventional im-
aging. The role of surface coils in delineating nor-
amal orbital structures has been demonstrated in various
studies.

The MRI findings in patients with BPES have previ-
ously been discussed in only 2 reports. Dollfus et al17 per-
formed MRI of the LPS muscle in 5 affected members of a
family with molecularly proven BPES. Absence of the LPS
muscle was reported in 4 of the patients, and a very thin
LPS muscle was noted in the fifth patient. The authors,
however, had not used surface coils in their scanning pro-
tocol; this might explain the nonvisualization of the LPS
muscle. Tronina et al18 performed similar preoperative MRI
without surface coils in patients with BPES. Contrary to
Dollfus et al, Tronina et al noted the presence of an LPS
muscle. However, BPES was not molecularly confirmed
in the latter study, and no detailed description of the mor-
phologic characteristics of the LPS muscle was given.

Our study, using 3-T MRI with surface coil, revealed
detailed information on the anatomy of the LPS and its ad-
joining structures in normal controls and patients with
BPES. By using surface coils in our scanning protocol, we
could identify the LPS and follow its entire course in all
patients, up to its fusion with the superior rectus. We were
able to describe detailed anterior structures of the LPS (Mul-
ler muscle and aponeurosis) as well as its surrounding con-
nective tissues (Whitnalls ligament and transverse su-
perior fascial expansion). At a more posterior site, it was not
possible to distinguish the LPS from the closely related su-
perior rectus muscle. This was the result of a too close con-
nection between the LPS and the superior rectus in its pos-
terior part as well as diminished resolution as the probe
moved further from the surface coil. The most striking find-
ing was the very thinned and elongated aponeurosis in all
patients with BPES, with a mean length of 24.9 mm, being
much longer than the 9 mm in our control participant and
reported measurements ranging between 8 and 14 mm.

Because of loss of MRI signal activity, no muscle belly could
be identified.

These MRI findings were completed by detailed ana-
tomic examination during surgery and histopathologic anal-
ysis of the resected tissue. The anatomic examination
confirmed the MRI findings by revealing a thin, very long,
disorganized aponeurosis. In addition, anatomic examina-
tion of further maximal resection showed a rather well-
organized muscle belly. The muscle belly was located 20
to 25 mm from the tarsal plate insertion in all patients with
BPES, explaining why it could not be demonstrated on MRI.

Histopathologic examination of the resected part of the
LPS further corroborated our MRI and anatomic find-
ings. The anterior part of the resected sample from pa-
tients with BPES showed a normal appearance of Müller
muscle. However, the aponeurosis was replaced by dis-
organized connective tissue. Even more notably, histo-
pathologic analysis confirmed the presence of well-
formed striated muscle fibers in the posterior part of the
resected specimen. The anterior part of the LPS muscle in
the BPES sample resembled the findings in the con-
trol sample of severe simple severe congenital ptosis. How-
ever, striated muscle fibers are absent in simple severe
congenital ptosis, and present in BPES. In 1955, Berke
and Wadsworth21 reported the presence of loose areolar
tissue and complete absence of striated muscle fibers in
patients with simple severe congenital ptosis. This was
later confirmed by other groups.22 The absence of stri-
ated muscle fibers explains the poor LPS function in pa-
tients with simple severe congenital ptosis. The striated
muscle found in patients with BPES contained more con-
nective tissue and fatty degeneration than what was seen
in a normal cadaveric control specimen.

Because we observed well-formed striated muscle fi-
bers in patients with BPES, there must be a different ra-
ationale for the poor LPS function seen in these patients.
Combining results from the MRI, anatomic, and histo-
pathologic evaluations, we provide an anatomic sub-
strate for the LPS dysfunction seen in BPES. There is a
rather well-formed muscle belly, but the fact that it is lo-
cated too deeply in the orbit, in combination with a poor
connection to the tarsal plate through a very long and
thin aponeurosis, might explain the poor LPS function.
This anatomic substrate also explains why supermaxi-
mal resection in BPES results in increased LPS function,
as we previously demonstrated.10

In conclusion, to our knowledge, this is the first study
combining high-resolution surface-coil MRI, anatomic,
and histopathologic examinations, allowing extensive eval-
uation of the LPS muscle in patients with molecu-
larly confirmed BPES. Our study provides new insights
into the pathophysiologic characteristics of its dysfunc-
tion and offers a rationale for using distinct ptosis repair
techniques in BPES operations.

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Fukala (344, “What Is to Be Done When the Anterior Chamber Is Not Reformed After an Iridectomy for Glaucoma?”) spoke of the sad cases of glaucoma in which the anterior chamber is not restored and the vision is thereby lost. He recommends to anesthetize the eyeball and then to cauterize the wound throughout its entire extent with the electric cautery. Elsching (346, “Cyclodialysis”) has tried cyclodialysis on 109 eyes and concludes from his experiences that the operation is one to be tried in simply and fresh inflammatory glaucoma. The results are fairly good. A discussion arises concerning the term cured; he thinks that it should mean that the tension became normal or subnormal without the use of miotics.

Knapp (347, “The Operative Treatment of Glaucoma by Cyclodialysis”) has performed the operation of Heine 18 times. . . . Cyclodialysis seems to be of value in the advanced stages of chronic glaucoma especially when iridectomy has failed.