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ORIGINAL PAPER

A study of changes in levator muscle in congenital ptosis

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Abstract

Purpose To study microscopic and ultrastructural changes of levator palpebrae superioris (LPS) muscle in congenital ptosis.

Methods In this prospective observational study, LPS muscle was studied in 77 eyelids with congenital ptosis; 35—simple congenital ptosis (SCP), 12—Marcus Gunn jaw winking phenomenon (MGJWP), and 30—blepharophimosis epicanthus inversus syndrome (BPES). Light microscopy, enzyme histochemistry, immunohistochemistry and electron microscopy were performed, and results were analyzed.

Results Muscle fibers were detected in 83.33% of MGJWP, 22.86% of SCP and 16.67% of BPES eyelids. Fibers were detected significantly more in individuals with moderate ptosis, LPS action > 4 mm, present eyelid crease and eyelid fold. Severe endomysial and perimysial fibrosis was seen significantly more in individuals with MGJWP. Fat infiltration and nuclei internalization were seen in all three groups. The absence of degenerating or regenerating fibers and inflammatory cells, normal staining pattern on immunohistochemistry and absence of accumulation of any abnormal substance were found in all three groups. Abnormal mitochondrial staining pattern was seen occasionally in three groups. On electron microscopy, muscle was detected in 1 SCP eyelid and 8 MGJWP eyelids out of which 4 had myofibrillary disruption. All other eyelids where muscle fibers were not detected had only fibrocollagenous tissue.

Conclusion Fibrocollagenous tissue predominated in all the cases, and muscle fibers detected correlated inversely with the severity of ptosis. The absence of degenerating, regenerating fibers and inflammatory cells supported the theory of dysgenesis of muscle. However, internalization of nucleus seen in all the subtypes is a feature favoring dystrophy.

Keywords Levator palpebrae superioris · Histology · Histochemistry · Electron microscopy · Dystrophy · Dysgenesis

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Introduction

True simple congenital ptosis (SCP) is the commonest type of congenital ptosis. Rarely congenital ptosis may be associated with blepharophimosis epicanthus inversus syndrome (BPES) or Marcus Gunn jaw winking phenomenon (MGJWP). Etiology-wise, the former two have been categorized as myogenic and latter as neurogenic. The pathological description of levator palpebral superioris (LPS) in true SCP as dystrophy or dysgenesis is still not clear [1]. While some authors have described changes of LPS muscle as dystrophic [2–4], others have reported as dysgenetic [1, 5–7]. The scarce availability of affected and normal LPS muscle along with associated artifacts on the histopathological stains produced by fixation and embedding techniques has led to considerable confusion regarding the basic pathogenesis of congenital ptosis.

Clinically, dystrophy is described as an inherited disease with progressive muscle wasting while dysgenesis as a non-progressive and non-inheritable defect in the muscle. In skeletal muscle dystrophies, characteristic histological features described include variable fiber size, hypertrophy, fibrosis of endomysial connective tissue, regenerating or degenerating muscle fibers and increased numbers of internalized nuclei [8]. Distortion of tubular system and sarcolemma, loss of cross-striations and mitochondrial alterations are features found on electron microscope [2]. Features characteristic of dysgenesis includes decrease in the number of muscle fibers, endomysial and perimysial fibrosis, dense fibrous connective tissue replacement and no features of inflammation or necrosis [5–7, 9]. Abnormal extracellular material has been reported on electron microscopy [5]. Clinically, SCP falls in the category of dysgenesis as it is a stationary non-inheritable disorder. Studies on histopathology also support the hypothesis of dysgenesis [1]. However, whether LPS muscle pathology in congenital ptosis is dystrophy or dysgenesis is still debatable.

Materials and methods

This was a prospective observational study conducted at a tertiary care eye center. Institutional Ethics Committee approval was obtained, and informed consent was taken in accordance with the principles of Declaration of Helsinki. Cases of congenital ptosis admitted for surgery over the period of May 2015–August 2016 were recruited. Cases with history of previous eyelid surgery or presence of ocular surface disease were excluded. In SCP cases, the LPS muscle resected above the Whitnall ligament was sent for study or else a biopsy of LPS muscle was sent in eyelids where the LPS resection was below the Whitnall ligament. In all MGJWP cases, the LPS excision was done above Whitnall ligament and the muscular portion of the excised LPS was sent for study. In BPES cases, open method sling was performed and a biopsy of 6 mm × 6 mm was obtained above the Whitnall ligament.

Each LPS specimen thus obtained was divided into three parts; first part was fixed in 10% buffered neutral formalin, routinely processed and paraffin-embedded, and 5-µm-thick serial sections were cut and stained with hematoxylin and eosin (H&E) for light microscopy; second part was immediately snap-frozen in isopentane cooled in liquid nitrogen (− 70 to − 80 °C) and then sections of 8–10 µm thickness were cut on a cryostat at − 18 to − 20 °C. Various stains which included H&E, Masson trichrome, modified Gomori trichrome (MGT), periodic acid Schiff (PAS), Oil Red O stain were performed on these sections. The cryofixed sections were subjected to various enzyme histochemical stains which included adenosine triphosphatase—ATPase (PH 9.4), nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), cytochrome C oxidase (COX) with SDH and immunohistochemical stains included myosin (developmental, neonatal, fast and slow heavy chains), actin, desmin, collagen VI, laminin (Merosin), sarcoglycans, dystroglycan, dystrophin and dysferlin. The third part of muscle specimen, approximately 1 mm^3, was transferred in cacodylate-buffered glutaraldehyde, preserved at 4 °C, post-fixed in 1% osmium tetroxide at pH 7.3, dehydrated in graded ethanol and embedded in the EMbed-812 epoxy resin. After 48-h heat polymerization at 60 °C, semi-thin (0.8 µm) tissue sections were cut and stained with toluidine blue and basic fuchsin, and after selection of appropriate cross sections of muscle fibers, the epon block was trimmed for ultrathin sectioning. Ultrathin (80 nm) sections were cut with a diamond knife on ultramicrotome and stained with aqueous 2% uranyl acetate and lead citrate solutions for 10 min each. The sections were then examined under the electron microscope.

Features studied on light microscopy

Features characteristic of dystrophy These included variation in the muscle fiber size, hypertrophy of muscle, fibrosis and fat infiltration of endomysial and perimysial connective tissue, presence of regenerating or degenerating muscle fibers, necrosis and internalization of nucleus.

Features characteristic of dysgenesis These included decrease number/absence of muscle fibers, endomysial and perimysial fibrosis, dense fibrous connective tissue replacement, absence of features of inflammation or necrosis and presence of abnormal extracellular material.

Features studied on electron microscopy

This included structural cytoskeleton, mitochondrial abnormalities, matrix abnormalities or any accumulation of abnormal substances.

Statistical analysis

Data were analyzed using Strata/SE 12.1. Descriptive statistics were used for demographic characteristics; qualitative data were compared by Chi-square and Fisher's exact test. Quantitative data were compared by *t* test/Mann–Whitney/ANOVA. The intergroup comparison of various microscopic features and comparison with clinical parameters of ptosis was done.

Results

Seventy-seven eyelids with congenital ptosis were analyzed, which included SCP (35 eyelids), MGJWP (12 eyelids) and BPES (30 eyelids). Age (years) distribution between three groups was similar to mean ± SD of 12.3 ± 6.69, 13.75 ± 6.94, and 11.07 ± 6.66, respectively.

Clinical parameters

MGJWP cases had predominantly moderate degree of ptosis compared to predominant severe ptosis in SCP and BPES cases. The difference was statistically significant for all clinical parameters except for lagophthalmos (Table 1).

Histopathological findings

Features characteristic of dysgenesis

Muscle fibers were detected in 10 MGJWP eyelids (83.33%) as compared to 8 SCP (22.86%) and 5 BPES eyelids (16.67%) (p value of 0.096 and < 0.001, respectively). Remaining eyelids showed only fibrocollagenous tissue with fatty changes. All further characteristics of muscle were described from these cases where the muscle fibers were detected. The endomysial and perimysial fibrosis was seen significantly more in eyelids with MGJWP as compared to SCP and BPES (p value 0.04 and 0.031, respectively).

Feature characteristic of dystrophy

Marked variation in muscle fiber size was observed more in MGJWP (80%) and BPES (80%) as compared to SCP (37.5%), but this difference was not statistically significant (Fig. 1a, b). Nuclei internalization was seen in all three groups (Fig. 1c). Degenerating fiber characterized by homogenized appearing pale eosinophilic cytoplasm and pyknotic nuclei was seen in one case of SCP and regenerating fiber characterized by the presence of basophilic cytoplasm with vesicular nucleus, and a prominent nucleolus was seen in one case of MGJWP. Atrophy was a predominant feature seen in all three groups, while hypertrophy was observed more in eyelids with MGJWP (60%) as compared to SCP (12.5%) and BPES eyelids (40%). Fat infiltration was observed in all three groups (SCP: 50%; MGJWP: 70%; and BPES: 60%) (Fig. 1d).

Correlation of clinical parameters with histopathology findings

In overall analysis of 77 eyelids with congenital ptosis, it was found that the presence of muscle fibers in LPS was inversely related to severity of ptosis. The eyelids in which muscle fibers were detected had moderate ptosis as compared with severe ptosis. Similarly, the presence of muscle fibers was found in significantly more number of cases where eyelid crease and eyelid fold were present as compared to when they were absent (Table 2). On comparing other histopathological features with the clinical parameters, no significant correlation was found.

Table 1 Clinical parameters within subtypes of ptosis

	SIMPLE	MGJWP	BPES	*p* value (overall between three groups)
Number of eyelids	35	12	30	
Grade of ptosis				
Moderate	4 (11.43%)	7 (58.33%)	2 (6.67%)	**< 0.001**
Severe	31 (88.57%)	5 (41.67%)	28 (93.33%)	**< 0.001**
LPS action				
≤ 4 mm	23 (65.71%)	5 (41.67%)	28 (93.33%)	**< 0.001**
> 4 mm	12 (34.29%)	7 (58.33%)	2 (6.67%)	**< 0.001**
Frontalis overaction				
Present	32 (91.43%)	9 (75.00%)	30 (100%)	**< 0.001**
Lid crease				
Present	27 (77.14%)	11 (91.67%)	4 (13.33%)	**< 0.001**
Lid fold				
Present	25 (71.43%)	11 (91.67%)	4 (13.33%)	**< 0.001**
Lid lag				
Present	20 (57.14%)	9 (75.00%)	30 (100%)	**< 0.001**
Lagophthalmos				
Present	13 (37.15%)	2 (16.67%)	17 (56.67%)	0.058

p value < 0.05 is considered as significant

Histochemistry findings

On enzyme histochemistry, 5 LPS showed abnormal staining with NADH-TR and/or COX and RRF. Two cases of SCP showed irregular staining pattern on NADH-TR and COX stains with red ragged fibers (RRF) on MGT stain (Fig. 2a–c). In MGJWP, 1 case showed irregular intense staining pattern on NADH-TR and RRF on MGT stain, while 1 case showed irregular staining pattern on NADH-TR but no RRF. Normal COX staining pattern was seen in all MGJWP cases. In BPES, 1 LPS muscle showed vacuolated staining pattern on NADH-TR and COX stain. Normal staining pattern was seen on SDH. ATPase stains in the entire three groups showed normal checker board pattern representing both type 1 and 2 fibers. Lipid accumulation was seen on Oil Red O stain in 14 eyelids (4 SCP, 7 MGJWP and 3 BPES). No excessive glycogen accumulation was seen on PAS stain in any case.

Immunohistochemistry findings

On immunohistochemical staining with myosin, actin, desmin, collagen VI, laminin (Merosin), sarcoglycans, dystroglycan, dystrophin and dysferlin, no abnormal staining pattern or loss of staining was seen in any case.

Electron microscopy findings

Muscle fibers were identified in 9 of 77 (12%) eyelids, 1 with SCP and 8 with MGJWP. Of these 9 cases, 4 cases of MGJWP showed myofibrillary disruption (Fig. 2d), and rest showed normal staining pattern. Fibrocollagenous tissue was seen in all other cases. No abnormal mitochondria or inclusions in the mitochondria were seen. Abnormal glycogen accumulation or any other abnormality was not noted.

Discussion

Most studies on LPS muscle in true SCP have demonstrated a primary defect in the muscle with fibrosis and decreased numbers of muscle fibers [2, 3, 5, 10]. Various authors have noted an inverse correlation between the severity of ptosis and the number of muscle fibers [6, 9–12]. Variation in the size and frequency of the muscle fibers with predominant hypoplasia has been documented in congenital blepharoptosis [1–4, 7, 10, 12]. However, this

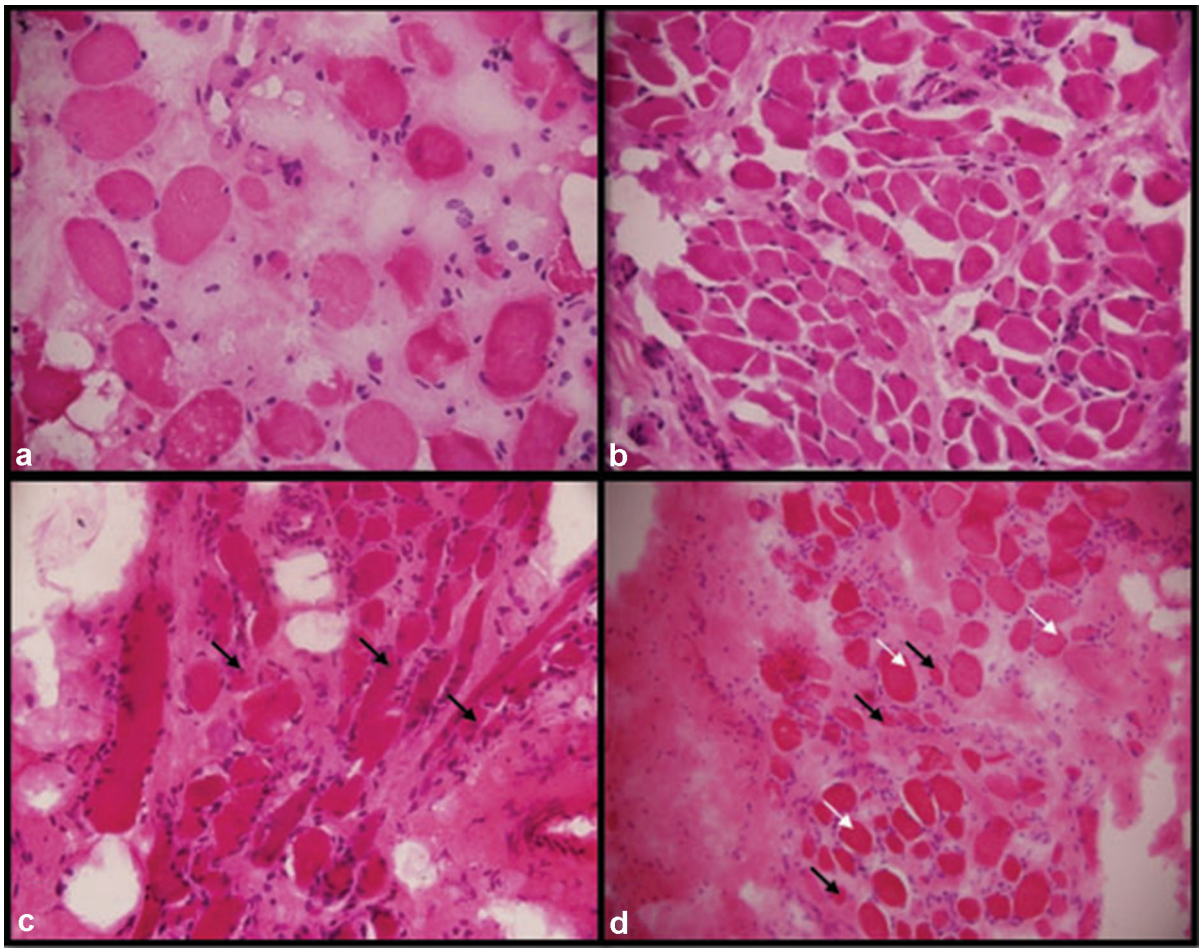

Fig. 1 Case of BPES showing marked variation in fiber size (**a**; H&E, ×200). Case of simple ptosis showing mild variation in fiber size (**b**; H&E, ×100). Case of Marcus Gunn showing internalization of nuclei (black arrow) (**c**; H&E, ×200) along with hypertrophic (white arrow) and atrophic (black arrow) fibers (**d**; H&E, ×200)

variation in muscle fiber diameter is similar to that found in individuals with no ptosis as reported in another study [7]. Fat infiltration in the muscle in cases with congenital ptosis as reported by some authors is possibly a degenerative change found in both congenital and acquired ptosis [3, 12, 13].

In the present study, muscle fibers were detected in a significantly higher number of MGJWP eyelids as compared to SCP and BPES. Specimens from all other eyelids showed only fibrocollagenous tissue with fatty infiltration suggestive of dysgenetic LPS. In cases where muscle fibers were detected, marked variation of muscle fibers size was seen in MGJWP and BPES as compared to SCP, though not statistically significant. Hypertrophy was seen more in cases with MGJWP as compared to BPES and SCP, while atrophy was a predominant feature seen in all MGJWP and BPES eyelids and 75% eyelids with SCP. Also, severe endomysial and perimysial fibrosis was found to be significantly more in MGJWP as compared to SCP and BPES. Thus, muscle fibers identified in cases with MGJWP were more, but the fibers had marked variation in size associated with severe endomysial and perimysial fibrosis and also hypertrophied and atrophied fibers. Fat infiltration was seen in 50% SCP, 70% MGJWP and 60% BPES eyelids. Thus, fat infiltration was a feature seen in all three groups.

In MGJWP, various theories about the etiology of this entity have been proposed. This included existence of abnormal connections between the third and fifth nerves which has been postulated to be at different levels of central nervous system [14]. In a

Table 2 Comparison of muscle fibers detected with clinical parameters in all cases with ptosis

Clinical parameters	Present	Absent	Total	*p* value
Grade of ptosis				
Moderate	7 (53.85%)	6 (46.15%)	13	**0.038**
Severe	16 (25.00%)	48 (75.00%)	64	
LPS action				
> 4 mm	10 (47.62%)	11 (52.38%)	21	**0.037**
≤ 4 mm	13 (23.21%)	43 (76.79%)	56	
Eyelid crease				
Present	19 (45.24%)	23 (54.76%)	42	**0.001**
Absent	4 (11.43%)	11 (88.57%)	15	
Eyelid fold				
Present	19 (47.50%)	21 (52.50%)	40	**< 0.001**
Absent	4 (10.81%)	33 (89.19%0	37	
Lid lag				
Present	19 (32.20%)	40 (67.80%)	59	0.418
Absent	4 (22.22%)	14 (78.78%)	18	
Lagophthalmos				
Present	8 (25.00%)	24 (75.00%)	32	0.431
Absent	15 (33.33%)	30 (66.67%)	45	

p value < 0.05 is considered as significant

study, authors have reported variation in the muscle fiber diameter with overall tendency of atrophy of muscle fibers and compensatory hypertrophy of remaining muscle fibers on the affected side in cases with MGJWP. They also found fewer fibers with both atrophic and hypertrophic forms in the contralateral clinically normal levator muscle. Thus, it is concluded that the process underlying the MGJWP is a neurogenic atrophy with aberrant innervation and is a bilateral process with one side being severely affected than the clinically normal side [11]. In MGJWP, this atrophied muscle fiber associated with fibrosis suggests some muscular abnormality while hypertrophic fibers would be representative of the abnormally innervated muscle fibers.

In a normal muscle fiber, the nucleus is at the periphery. Internalization of nucleus is a morphological marker of dystrophy [8, 15]. It could be present in less than 3% of the normal muscle fibers [16]. To the best of our knowledge, no other study has documented nucleus internalization in cases of congenital ptosis. In our study, we found nucleus internalization in all BPES, 80% MGJWP and 50% SCP eyelids. Normal muscle is devoid of inflammatory cells. Necrotic muscle fibers invaded by mononuclear cells are seen in almost all dystrophies [15]. While the presence of inflammatory cells in cases of congenital ptosis was observed in some studies [10, 17], others have found no inflammatory cells [5, 18]. Similarly, regenerating and degenerating features have been documented by few authors [2, 5]. Amorphous extracellular material in some cases of congenital ptosis has been documented [5]. In our study only one case of SCP had degenerating fibers and one case of MGJWP had regenerating fibers. Amorphous extracellular material or features of inflammation were not seen. Thus, the absence of degenerating or regenerating fibers, abnormal extracellular material or inflammatory cells point against the theory of dystrophy.

In the literature, it has been emphasized that the detection of muscle fibers correlated with the degree of ptosis and levator muscle function (LMF) [1, 3, 6, 9]. In the present study also, we found that muscle fibers were detected significantly more in cases with moderate ptosis as compared to severe ptosis and also it had direct correlation with the presence of eyelid crease and eyelid fold. No correlation has been reported in the literature between amount of fat in LPS and congenital or acquired ptosis, degree of ptosis or LMF [19].

Histochemistry aids in identification of abnormal enzymes or structural proteins. In a study, authors reported abnormal extracellular material in 4 cases with congenital ptosis and immunohistochemical

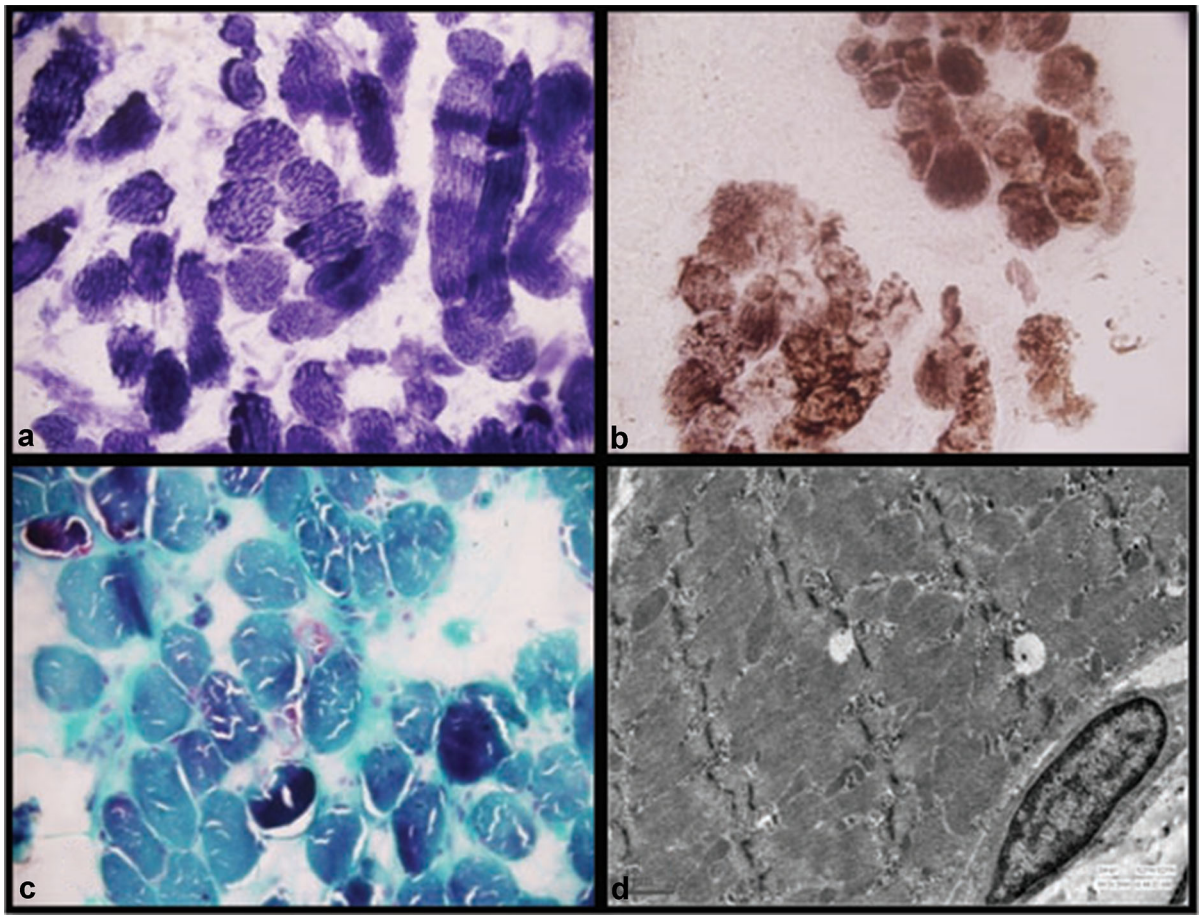

Fig. 2 Enzyme histochemistry showing irregular NADH-TR (**a**; ×200) and COX (**b**; ×200) staining in a case of simple ptosis. MGT stain showing ragged red fibers in another case of simple ptosis (**c**; ×200). Ultrastructural examination shows myofibrillar disruption in a case of MGJWP (**d**)

stains showed the presence of collagen type III and fibronectin. Authors proposed that this material could have been synthesized by dysfunctional myocytes during dysgenesis of the levator complex [5]. In another study authors have found grouping of fibers on ATPase staining and no abnormal staining pattern with NADH-TR in congenital ptosis suggesting neurogenic origin [8]. Some studies have supported theory of dysgenesis and reported homogenous fibers with no immunoreactivity to antibodies against muscle proteins (actin, myosin and myoglobin), amyloid A, collagens II and IV and laminin and positive immunoreactivity to fibronectin [5, 12]. Studies in cases with MGJWP using MGT, ATPase, NADH-TR, nonspecific acid phosphatase and acetyl cholinesterase have found no abnormal staining pattern, lysosomal accumulation within fibers, presence of macrophages in the perimysium or any synapses supporting neurogenic basis [11]. In our study, abnormal mitochondrial staining was noted in 5 eyelids with congenital ptosis, 2 of which had MGJWP. Staining for Oil Red O was positive in 14 eyelids. No accumulation of glycogen was noted on PAS stain or abnormal staining pattern was seen with other histochemical enzymes, i.e., SDH and ATPase or immunohistochemical stains.

In a study on ultrastructural changes in the LPS muscle in congenital ptosis, mitochondrial alterations such as megamitochondria, mitochondrial matrix alterations and abnormal cristae, similar to CPEO, were seen in 8 of 11 cases. However, no statistically significant correlation was observed between mitochondrial alteration and levator function [18]. Others have also documented correlation between electron microscopic changes in LPS muscle in patients with

congenital ptosis and clinical severity of ptosis [2, 12]. In the present study, on electron microscopy myofibrillary disruption was seen in 4 MGJWP cases but was inconclusive because of the absence of muscle fibers in the samples studied.

Limited number of cases in each subgroup, mild variation in area of sample collection and availability of muscle were the limitations of this study. However, all surgeries were done by single experienced surgeon keeping the area of LPS sampling consistent. To conclude, most of the histopathology features supported the theory of dysgenesis; however, internalization of nucleus seen in all the subtypes is a feature favoring dystrophy. Abnormal mitochondrial enzyme staining pattern was observed on histochemistry in few patients and ultrastructural examination was inconclusive due to scarcity of muscle fibers seen. In the current scenario, with inclusion of ptosis in congenital cranial dysinnervation syndrome [20], these findings delineate the pathological changes in LPS muscle in various types of congenital ptosis. However, further studies with larger sample size, detailed evaluation including imaging and genetic studies are needed to understand the underlying mechanism.

Compliance with ethical standards

Conflict of interest No financial interest or conflicts involved.

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