Approach to the Interpretation of Muscle Biopsy

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1. Introduction

The history of muscle biopsy dates back to 1860 when Duchenne first performed a biopsy on a patient with symptoms of myopathy. Introduction of enzyme histochemical methods by Victor Dubowitz in 1970 revolutionised the role of muscle biopsy in the diagnosis of various primary and secondary muscle diseases. Diagnosis of various subtypes of dystrophies was further made easy with beginning of immunohistochemical methods in 1980s. Twenty first century has brought in a new spectacular progress in utility of muscle biopsy with commencement of molecular methods. Significance of muscle biopsy is rising with application of new techniques. The treatment of neuromuscular disorders is also undergoing a parallel and dramatic change with promising genetic therapeutic approaches. Accurate diagnosis of the underlying neuromuscular disease is the need of the day and muscle biopsy forms a gold standard in diagnosis of these diseases.

The indications and techniques of muscle biopsy are discussed in detail in another chapter. Close interaction between pathologist and clinician is necessary for optimal utilization of muscle biopsy sample to get diagnostic information. The muscle biopsy should be planned only after relevant clinical and family history, physical examination findings, laboratory tests including electromyography (EMG), creatine phosphokinase (CPK) and relevant biochemical or serological tests.

2. Site of muscle biopsy

It is necessary to sample a muscle which is clinically involved. This is decided by clinical examination, course of progression of disease and sometimes by imaging studies. It is imperative to biopsy a muscle which is moderately involved. Biopsy from severely affected muscle will only show fat and fibrosis and minimally involved muscle may lack diagnostic histological features. Biopsy has to be taken from muscle belly and avoided from tendon insertion site as it will show central nuclei, variation in fibre size and endomysial fibrosis mimicking myopathy. Muscle site traumatized by EMG needle, sites of recent injections and previous surgery should also be avoided.

In most of the proximal myopathies and generalised/systemic diseases; vastus lateralis is the standard muscle biopsied by international consensus. The site is suitable for biopsy as it is away from major vessels and nerves. The other muscles that are good choices for biopsy are biceps and gastrocnemius. Tibialis anterior is sampled when indicated by imaging studies. Deltoid muscle biopsy is usually avoided as it is a site for injections and may not be
involved in all diseases. It is always better to standardize the biopsy from a particular site in the laboratory as the fiber type distribution varies from each site. Biopsies obtained from unusual sites during surgery pose problems for orientation, fiber typing etc.

3. Technique of biopsy

The biopsy can be a needle biopsy or open biopsy. The needle biopsies are dealt within another chapter in detail. Though needle biopsies have largely replaced open biopsies in most parts of the world, certain laboratories still favour open biopsy technique due to feasibility of the procedure and it is usually free of any surgical complications and most importantly because a bigger piece of muscle is available for examination. The sample is kept on a saline soaked gauze piece and transported to the laboratory immediately. It should not be floating in the saline to avoid artefacts.

4. Processing of sample

Orientation of the fibers is of utmost importance since most of the information is provided by transverse sections. The biopsy should be oriented under a dissecting microscope and sample is divided as follows:

1. For electron microscopy, 2-3mm fragments are kept in cacodylate buffered glutaraldehyde and preserved at 4°C.
2. For cryosections, biopsy piece is fresh frozen in isopentane cooled in liquid nitrogen (-170 °C to -180°C) and then sections are cut in cryostat at -18°C to -20°C. These sections are stained with Hematoxylin and Eosin (H&E), Masson trichrome, Modified Gomori’s trichrome (MGT). The various enzyme histochemical stains done include myosine adenosine triphosphatase (ATPase) preincubated at pH 9.4, 4.6 and 4.3, succinate dehydrogenase (SDH) and Nicotinamide adenine dinucleotide-Tetrazolium reductase (NADH-TR). Other stains like Per-iodic acid Shiff (PAS), Oil red O, acid phosphatase, cytochrome oxidase, acid maltase and myophosphorylase are done as and when indicated.
3. A part of biopsy is used for routine processing after fixing in buffered formalin
4. For molecular biology, biochemical and genetic analysis, a small tissue is preserved in -80°C. 1,3,4
5. The fresh unfixed muscle is used for
   a. Detection and quantification of proteins by Gel electrophoresis
   b. Quantification of individual proteins to confirm a deficient or altered protein and provide a precise quantitative measurement by western blot
   c. Demonstrate gene mutations by Polymerase chain reaction (PCR), fluorescent in situ hybridisation (FISH) and others. These techniques are particularly useful in the diagnosis of muscular dystrophies.

The biochemical evaluation of muscle for respiratory enzymes and mitochondria are useful in the evaluation of mitochondrial diseases. These are dealt with in greater detail in other chapters.

5. Normal anatomy

Normal muscle is composed of a number of fascicles which are bound by epimysium and each fascicle in turn is composed of muscle fibers and wrapped by collagen, called perimysium.(Figure 1) The arterioles, nerve bundles, venules and muscle spindles are
located in the perimysium. In a child, the muscle fibers are rounded and in an adult, the fibers are polygonal opposed to each other with very little intervening stroma. Myocytes are syncitial and the nuclei are seen subsarcolemmal. However, 3-4% of internal nuclei are normal. Satellite cells are seen closely applied to the periphery of myofibers. The connective tissue within the fascicle is called endomysium and contains capillary sized blood vessels.

Fig. 1. (A) Fascicular architecture of the muscle with endomysium, perimysium. (H&E X40) (B) The polygonal muscle fibers with subsarcolemmal nuclei (H&E X200)

The interpretation of muscle biopsy will be dealt with according to the type of stain used. The summary of stains and their interpretation is given in Table 1.

| Stain                              | Use                                          |
|------------------------------------|----------------------------------------------|
| Hematoxylin and Eosin              | General architecture and histology           |
| Masson Trichrome                   | Collagen, fibrosis                           |
| Modified Gomori’s trichrome        | Red ragged fibers, nemaline rods, nuclei, myelinated fibers |
| Picrocidic acid Schiff             | Glycogen                                      |
| Oil red O                          | Neutral lipid                                |
| Acid Phosphatase                   | Lysosomal enzymes, necrotic fibers           |
| Crystal violet                     | Amyloid                                       |
| ATPase PH 9.4                      | Type 1 fibers pale                           |
|                                   | Type 2 fibers dark                           |
| ATPase 4.6                         | Type 1 fibers dark                           |
|                                   | Type 2 fibers pale                           |
| NADH                               | Sarcoplasmic structural details              |
| SDH                                | Oxidative enzyme activity                    |
| Cytochrome C Oxidase               | Mitochondrial enzyme activity                |

Table 1. Summary of various stains used in interpretation of muscle biopsy
6. Histochemistry

6.1 Hematoxylin and eosin

This stain helps in evaluation of general architecture of the muscle and variation in the morphology of individual fibers.

H&E is basically used to look at the following changes in muscle:

1. Variation in fascicular architecture
2. Variation in fiber size and shape
3. Necrosis and degeneration of muscle fibers
4. Nuclear characteristics
5. Type and distribution of inflammatory infiltrate
6. Interstitial changes

The architecture of muscle fascicles is assessed on a scanner and the adipose tissue infiltration and fibrosis are noted. The pathological changes if any are noted. Diffuse pattern of involvement is seen in dystrophy, focal in neurogenic and patchy in inflammatory myopathies. Extent of adipose tissue infiltration and fibrosis depend upon the duration of disease and degree of muscle fiber atrophy and contribute to loss of fascicular architecture.

In a normal muscle, there is minimal variation in fiber size which depends on age, gender and muscle. The fiber type variation may be atrophy or hypertrophy and it may selectively involve type 1 or type 2 fibers. The involvement may be diffuse or focal.

Fig. 2. (A) Large group atrophy H&EX40 (B) Small group atrophy H&EX40 in neurogenic lesions
The atrophic fibers may involve entire fascicle (large group atrophy), small groups of muscle fibers (small group atrophy) or as single fibers. Sometimes all the fibers may be atrophic. These patterns are seen in neurogenic atrophy. (Figure 2) When the atrophic fibers are distributed at the periphery of a fascicle, it is called perifascicular atrophy which is characteristically seen in dermatomyositis, especially juvenile type. (Figure 3) Diffusely distributed atrophic fibers are seen in dystrophies. Atrophy involving selectively type 1 fibers is seen in congenital myopathies, myotonic dystrophy and rheumatoid arthritis.

Fiber hypertrophy is seen in athletes and as compensatory phenomenon in neurogenic atrophies also. They are important findings in dystrophy, especially Limb girdle muscular dystrophy (LGMD). Hypertrophy beyond a particular size leads to splitting. Fiber splitting result in a group of small fibers may be mistaken for small group atrophy. (Figure 4)

6.2 Fiber shape
In normal adult muscle, the muscle fibers are polygonal and in an infant the fibers are rounded. In infants and children there is very little endomysial connective tissue. The fibers become rounded in muscular dystrophies and become angulated and atrophic in denervation.

6.3 Position and number of nuclei
In a normal muscle, nuclei are subsarcolemmal. They are small, oval and dark staining. However, about 3% of fibers in transverse section may show internal nuclei. Large number
of internal nuclei suggests a myopathy and transverse section is best to assess the same. Dystrophies show about 10-30% internal nuclei and myotonic dystrophy is characterized by profuse number of internal nuclei of about 60%.

Myotubular/centronuclear myopathy shows more than 30% of fibers showing single centrally placed nuclei. (Figure 5) Chronic neuropathies like Charcot-Marie-Tooth disease also shows large number of central nuclei. Not only increase in number, the character of nuclei may also vary in various conditions. Vesicular nuclei with prominent nucleoli and transparent nucleoplasm are seen in regenerating fibers, in myopathies and in central nucleus of myotubular/centronuclear myopathy. Tigroid nuclei with granular and clumped chromatin are usually seen in neuropathies and in myotonic dystrophy. Pyknotic nuclei which are dark staining and shrunken are seen in groups with clumping of chromatin. These are seen in neurogenic atrophies and limb girdle dystrophies.

6.4 Necrosis, degeneration and regeneration

A necrotic fiber is pale stained on H&E and infiltrated by phagocytes. This is called myophagocytosis. (Figure 6) This is usually seen in myopathies especially dystrophies like Duchenne muscular dystrophy (DMD). These fibers are highlighted by acid phosphatase and esterase reactions. Sometimes necrotic fibers are seen in inflammatory myopathies, paraneoplastic necrotizing myopathies, after rhabdomyolysis and in acute neuropathies.
Fig. 5. (A) Muscle fibers showing central nuclei (B) The longitudinal section of the muscle showing central row of nuclei

Fig. 6. (A) Myophagocytosis H&EX200 (B) Hyaline fibers H&EX200
A hyalinised fiber is a fiber which has lost its cross striations, has homogenous pale cytoplasm. (Figure 6) Usually these fibers are rounded. They are usually seen in dystrophies. They are highlighted on MGT and Masson trichrome stains.

The granular fiber on H&E shows a coarse granular bluish cytoplasm and represents the ragged red fibers of mitochondrial myopathy on MGT.

Splitting of fibers is seen when a hypertrophic fiber crosses a particular size limit. The nuclei first migrate along the split and large fiber results in a number of small fibers. Fiber splitting is seen normally at tendinous insertion. It is a feature of LGMB and other myopathies and some chronic neuropathies like Charcot-Marie-Tooth disease.

6.5 Interstitial changes

In a normal muscle, the fibers are opposed to each other with very little connective tissue in the endomysium. In muscular dystrophies following myophagocytosis, there is pericellular fibrosis. Fibrosis occurs due to a variety of extracellular matrix proteins and fibrosis occurs in all types of dystrophies, some form of neurogenic atrophies and central core disease also. Adipose tissue infiltrates usually occurs after muscle atrophy. It is more common in DMD but occurs in other dystrophies and late stages of neurogenic atrophies and congenital myopathies. The degree of fibrosis is well brought out by Masson trichrome stain. (Figure 7)

![Fig. 7. Pericellular fibrosis highlighted by Masson trichrome. MTX100](www.intechopen.com)
6.6 Inflammatory cell infiltrates

Normal muscle is devoid of any inflammatory cells. Cellular infiltrates are seen in inflammatory myopathies like dermatomyositis, inclusion body myositis (IBM). (Figure 8) Necrotic muscle fibers are invaded by mononuclear cells which are seen in almost all dystrophies. Inflammatory cells can occur in toxic, necrotizing and dystrophic muscle diseases especially fasioscapulohumeral dystrophy (FSHD), DMD, dysferlinopathy and other LGMDs apart from inflammatory myopathies.

The infiltrate is composed of B cells, CD4 positive cells and dendritic cells in dermatomyositis; CD8 positive cells, dendritic cells and macrophages in polymyositis and IBM which can be demonstrated by immunohistochemistry.

The modified Gomori’s trichrome (MGT) stain is useful to stain the red ragged fibers; the hallmark of mitochondrial myopathy. (Figure 9) Red ragged fibers are also seen in other conditions like dystrophies (LGMD), dermatomyositis, older individuals and Zidovudine associated myopathy in HIV patients. 5,6

Tubular aggregates and cytoplasmic bodies are nonspecific and are seen with MGT as red. (Figure 10) Tubular aggregates are seen in periodic paralysis, dysferlinopathy, exertional myalgia etc. Cytoplasmic bodies are seen in collagen vascular disease, IBM and others.

Fig. 8. (A) Inflammation around non necrotic fibers in IBM H&EX40 (B) Perivascular inflammation in dermatomyositis. H&EX40
Fig. 9. Red ragged fibers of mitochondrial myopathy MGTX200

Fig. 10. Tubulofilamentous inclusions MGTX400
Rod bodies characteristically stain red with MGT. (Figure 11) The rods are delicate and accumulate subsarcolemmal. They stain negative with ATPase, NADH and SDH as they lack myosin and mitochondria. Rods are characteristic of nemaline myopathy but also seen in central core disease and various other diseases which include neurogenic disorders (amyotrophic lateral sclerosis, spinal muscular atrophy, undefined), inflammatory myopathies (dermatomyositis, polymyositis, periarteritis nodosa), metabolic myopathy (mitochondrial myopathy), muscular dystrophy (LGMD) and some undefined myopathies.

Fig. 11. Rod bodies seen in subsarcolemmal and perinuclear position in a case of nemaline myopathy. MGTX400

MGT also stains nuclei and myelinated fibers.

The per-iodic-acid Schiff (PAS) and Oil red O demonstrate glycogen and neutral lipid respectively. (Figure 12) These two stains are useful for metabolic myopathies. Acid phosphatase identifies lysosomal enzymes and hence identifies necrotic fibers. Masson trichrome is useful to demonstrate fibrosis and fibrinoid necrosis. Congo red and crystal violet stains demonstrate amyloid.

Vacuoles

Vacuoles are of two types- one type contains some material within and the other appears as just empty spaces. The former are called as rimmed vacuoles and on H&E they contain basophilic granular material and on MGT they appear as having red granules. (Figure 13) They appear in number of conditions like IBM, distal myopathies, oculopharyngeal muscular dystrophies, myofibrillar myopathies and others. In glycogen storage disease, vacuoles appear on H&E. The vacuoles are seen in acid maltase deficiency of childhood (Pompe’s disease) and adulthood (McArdle’s disease) and Glycogenses V.
Fig. 12. (A) Vacuolated cytoplasm in glycogen storage disease. H&EX100. Inset: Intracellular glycogen content. PASX200 (B) Small vacuoles in the sarcoplasm of muscle fibers in lipid storage myopathy. Inset: lipid droplets stained red by Oil Red O. Oil Red OX200

Fig. 13. (A) Rimmed vacuoles showing basophilic rimming. H&EX200 (B) Rimmed vacuoles showing red granular rimming. MGTX400
The diagnosis can be established by demonstrating absence of acid maltase and phosphorylase respectively. Excess glycogen accumulation in vacuoles and in the fibers can be demonstrated by PAS stain in glycogenoses. Similarly, lipid accumulation is demonstrated in vacuoles or in the fibers in carnitine deficiency or in disorders of mitochondrial beta oxidation. They show cytochrome C oxidase enzyme deficiency.

7. Enzyme histochemistry

ATPase: In myosine ATPase preincubated at PH 9.4, type 1 fibers are pale and type 2 fibers are dark. At PH 4.6 and 4.3, the reaction is reversed and type 1 fibers are dark and type 2a and 2b fibers are light with variable intensity. Owing to these staining characteristics on ATPase, this stain is used to demonstrate abnormalities in fiber types and distribution of the two types of fibers. (Figure 14)

Fig. 14. ATPase at PH 9.4 showing checkerboard pattern with pale Type 1 fibers and dark Type 2 fibers. ATPX100

In muscles like vastus lateralis, type 1, 2a and 2b are one third each. Type 1 and 2 fibers are intermixed in a checkerboard pattern. Type 1 fibers of more than 55% is said to be type 1 predominance and similarly type 2A and type 2B each of 55% constitute predominance of that fiber subtype. Type 2 predominance is called when type 2 fibers are more than 80%.

Type 1 predominance indicates a myopathy; either dystrophy or congenital myopathy whereas type 2 predominance in motor neuron disease.

Type 1 predominance is normally seen in gastrocnemius and deltoid and hence caution should be exercised in interpreting biopsies from these sites.
In addition to type predominance, fiber type grouping which is characteristic of neurogenic lesions is also best assessed on ATPase stain.

Atrophy of particular type of fibers is also evaluated by ATPase. Selective type 1 fiber atrophy is seen in congenital myopathies and myotonic dystrophy. Selective type 2 atrophy is common and is seen in many conditions. These include steroid myopathy, disuse, polymyalgia rheumatica, collagen vascular diseases, pyramidal tract disease, mental retardation, myasthenia gravis etc. Type 2 atrophy usually involves type 2B or both type 2A and type 2B; however only type 2A atrophy is uncommon.

Fiber specific hypertrophy is very uncommon.

Subtle changes in fiber size are best made out by plotting histograms.

**SDH and NADH**

These enzyme histochemical stains bring about various structural abnormalities of muscle fibers and being oxidative enzymes are important in diagnosis of mitochondrial myopathies.

The abnormal fibers of mitochondrial myopathy are seen as “blue ragged fibers” on SDH and NADH and they are the counterpart of red ragged fibers on MGT. (Figure 15) COX is a mitochondrial enzyme and its activity is absent in mitochondrial myopathy or abnormalities. A combination of COX-SDH brings about more number of abnormal fibers in mitochondrial myopathy.

Fig. 15. (A) Blue ragged fibers of mitochondrial myopathy. SDHX100 Inset: The same fibers on higher magnification. SDHX400 (B) The same muscle showing more abnormal fibers on COX-SDHX40
NADH-TR highlights the sarcoplasmic reticulum and oxidative enzyme activity. Structural abnormalities like cores, targets, whorles, lobulated fibers are best seen on NADH-TR. SDH is an oxidative enzyme and mitochondrial abnormalities are highlighted by SDH. Cores and lobulated fibers are also seen on SDH. (Figure 16) Acid maltase, myophosphorylase are done as and when indicated clinically (glycogen storage diseases). The myofibrillar abnormalities include central/minicores, target, targetoid fibers, ring fibers, whorled fibers and lobulated fibers.

Fig. 16. Central cores in a case of central core disease. SDHX100

Central cores are seen as pale areas of staining on oxidative enzyme staining like NADH and SDH. The cores are usually single and central but may be eccentric and multiple. They are not seen on H&E, ATPase, MGT but seen on phosphorylase. The rim of the core is devoid of mitochondria and hence lacks oxidative enzyme activity. Central cores are seen usually in type 1 fibers. Central cores are seen in many fibers in central core disease. Central cores are not limited to central core disease as they are seen in hypertrophic cardiomyopathy associated with missense mutations in the beta myosine heavy chain gene, MHY7, autosomal dominant myopathy associated with ACTA1 gene mutations. Multiple minicores seen on oxidative enzyme reactions both in transverse and longitudinal...
sections are seen in multiminicore disease (MmD) and it is a histopathologic continuum with central core disease. Many cases of MmD are caused by recessive mutations in the selenoprotein NI (SENPI) gene\textsuperscript{11} and same due to recessive RYRI mutations.\textsuperscript{12,13}

Target fibers are characterised by three distinct zones where central zone is devoid of oxidative enzyme activity, middle zone of intense activity and outer zone of intermediate activity. They are usually seen in type 1 fibers when the three zones are not clearly demarcated, the target fibers resemble central cores and they are called targetoid fibers. Target fibers are a feature of chronic neuropathies.

Moth eaten fibers show irregular disruption of myofibrillar network. These are seen on NADH or SDH and may be mistaken for minicores or cores. Moth eaten fibers are seen in dystrophies including LGMD, congenital muscular dystrophy and various myopathies including dermatomyositis. (Figure 17)

Fig. 17. (Left) Moth eaten fiber on H&E X400 and (Right) on SDHX200

Ring fibers and whorled/coiled fibers are due to various patterns of disarray of myofibrils. They are seen in various dystrophies. (Figure 18) Ring fibers are seen in myotonic dystrophy whereas whored fibers are seen in LGMD and chronic neuropathies.
Fig. 18. Whorled fibers in a case of limb girdle muscular dystrophy H&EX200. Inset: The same fiber on SDHX400

Lobulated fibers show intense oxidative enzyme activity at the periphery of the fiber and usually involve type 1 fibers. They are nonspecific and are seen in many conditions which include LGMD particularly calpainopathy, congenital muscular dystrophy, mitochondrial myopathy and others.

8. Conclusion

Muscle biopsy is essential for accurate diagnosis and treatment. Optimal utilization of the sample with appropriate stains and study of the pathologic features is important for making a diagnosis. Accurate interpretation of muscle biopsy guides appropriate immunohistochemical and molecular genetic studies.

9. References

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Investigation of muscle diseases has changed dramatically with the understanding of genetic basis of a wide range of muscle diseases. Muscle biopsy has become a powerful tool not only to provide diagnosis but to make tissue available for genetic studies and to basic scientists for biomedical research. Accurate interpretation of muscle biopsy to detect cell dysfunction/damage/death or absence/abnormality of a protein or genetic defect by the sophisticated technologies is important to guide treatment of various muscle diseases. In this book on muscle biopsy various chapters deal with the procedure and interpretation of muscle biopsy, its use in the culture of myotubes and membrane transport studies. Muscle biopsy is an important technique to investigate mitochondrial dysfunction and the mitochondrial DNA integrity in oxidation. Phosphorylation in various metabolic diseases like obesity, type 2 diabetes mellitus and peripheral vascular disease is explored in the other chapters with detailed descriptions on methodology. This book provides the advances in the basic techniques of muscle biopsy for a neuroscientist.

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