**Review** paper

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# Technical aspects and current clinical applications of the skin and skeletal muscle biopsy in neurological diagnostics: an overview

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**Abstract**

*This short overview recalls the basic principles and technical aspects of skin and skeletal muscle biopsies in humans with paying special attention to the stages of these procedures essential for further correct morphological diagnosis. Some of these principles may also be useful in animal experimental studies. The authors emphasize the important role of proper thickness of the skin fragment, proper orientation of muscle fibres and a scalpel during skin biopsy, and proper concentration of fixatives. They recommend avoiding anaesthesia of the skeletal muscle itself and using forceps carefully so as not to crush the epidermis.*

***Key words:*** *muscle biopsy, skin biopsy, biopsy technique.*

## Introduction

It would seem that relatively easy access to information on the principles of performing diagnostic biopsies for further morphological evaluation will reduce the amount of non-diagnostic material supplied to laboratories. Sometimes, however, the practice is far from theory, so we decided that it is worth recalling the basic principles and technical aspects of biopsy, paying special attention to those stages of the procedures that are crucial for the correct morphological diagnosis. While this practical information relates to human neurological diagnostics, some of it may also be useful in animal experimental studies.

Skin biopsy, skeletal muscle biopsy, and combined skin and muscle biopsy are the most commonly used methods in the diagnosis of the peripheral nervous system diseases. Biopsies of other organs or tissues, including peripheral nerves, are rarely performed today due to the use of other, more specific and less traumatic diagnostic methods.

## Skin biopsy

### Anatomy of the skin

Skin has three main layers: the epidermis, the dermis and the subcutaneous layer. The epidermis is an elastic external layer composing predominantly of keratinocytes and melanocytes. The dermis is the inner layer that includes hair follicles, sweat glands, sebaceous glands, collagen and smooth muscle fibres (the arrector pili muscles), fibroblasts, nerves, nerve receptors, and lymph and small blood vessels. The dermis consists of two sublayers: papillary and reticular, which merge with each other without clearly demarcating. The upper and thinner papillary layer consists of loose connective tissue. The deeper reticular layer is less cellular and consists

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of dense connective tissue (bundles of collagen fibres). The subcutaneous layer consists of connective and adipose tissue, and contains sensory neurons and vessels larger than in the dermis. The blood supply to the skin is a system of two plexuses. The first lies between the papillary and reticular layers of the dermis and the second lies between the dermis and subcutaneous layer.

Skin biopsy is used in the diagnosis of neuropathies (diabetic, inflammatory, demyelinating, vascular, hereditary) as an alternative method to nerve biopsy, especially when small fibre neuropathy is suspected. Other diseases where a skin biopsy is sometimes performed include certain systemic diseases with neurological symptoms such as systemic lupus erythematosus or systemic scleroderma, neuroaxonal dystrophy, lysosomal storage disorders (including sialidosis, Tay-Sachs disease), mitochondrial disorders (especially myoclonic epilepsy with ragged-red fibres [MERRF] syndrome) and rare diseases causing progressive myoclonic epilepsy such as Lafora body disease, neuronal ceroid lipofuscinosis, and Unverricht-Lundborg disease [4,12]. Although a skin biopsy may be useful in these conditions showing characteristic inclusions, swollen nerve endings filled with tubulovesicular structures or deposits of immunoglobulins, other diagnostic methods are more helpful.

Skin biopsy is also used in diagnostics of sensory ganglionopathies, vasculitides and cerebral microangiopathies of generalized character such us CADASIL (cerebral autosomal dominant arteriopathy with ischemic stroke and leukoencephalopathy), CARASIL (cerebral recessive dominant arteriopathy with ischemic stroke and leukoencephalopathy), CARASAL (cathepsin A-related arteriopathy with strokes and leukoencephalopathy), and others. Tissue samples obtained from a skin biopsy may also be subjected to further molecular tests allowing, among others, to identify mRNA differentially expressed in various neurological disorders [14].

Skin biopsy can be performed by many methods such as shallow biopsy (shave biopsy), scoop biopsy with the use of a surgical spoon, punch biopsy, traditional incisional and excisional biopsy with the use of a scalpel, and others. The choice of a technique depends primarily on the suspected pathology and the desired slice thickness. A shallow biopsy (3-4 mm) is sufficient to examine the nerve fibres of the epidermis, while a deeper biopsy (6-8 mm) additionally allows for the assessment of sweat glands, hair follicles and arteriovenous anastomosis [9].

In neurology, punch and incisional biopsy is recommended for diagnostic purposes.

## Punch biopsy

A punch biopsy is an easy procedure that can be performed by a physician, nurse, or physician's assistant. To obtain a full thickness sample of skin, a punch, a single-use stainless type of a tube with sharp edges at one end is used. The blade size can vary from 2 to 6 mm in diameter, but the most commonly used blades are 3 and 4 mm in diameter. Smaller diameter punches should be avoided due to the risk of over-manipulation and tissue crushing.

Before the biopsy, the area of skin where the biopsy is to be performed is sanitized with an alcohol swab. Next, skin is topically anesthetized. Lignocaine is the most commonly used local anaesthetic agent, however, topical anaesthesia with eutectic mixture of local anaesthetics (EMLA) can be also used. The clinician holds the circular punch perpendicularly to the skin with three fingers – the thumb and the middle finger support and rotate the punch while the index finger stabilizes and exerts pressure on the punch [17]. The skin is stretched in a direction perpendicular to the resting skin lines and the skin sample is collected by rotating the punch around its long axis (Fig. 1A). At this point, the patient may experience a pressure and twisting sensation but no pain. The physician uses the forceps to grab the dermis of the cored skin, pulls up the core to

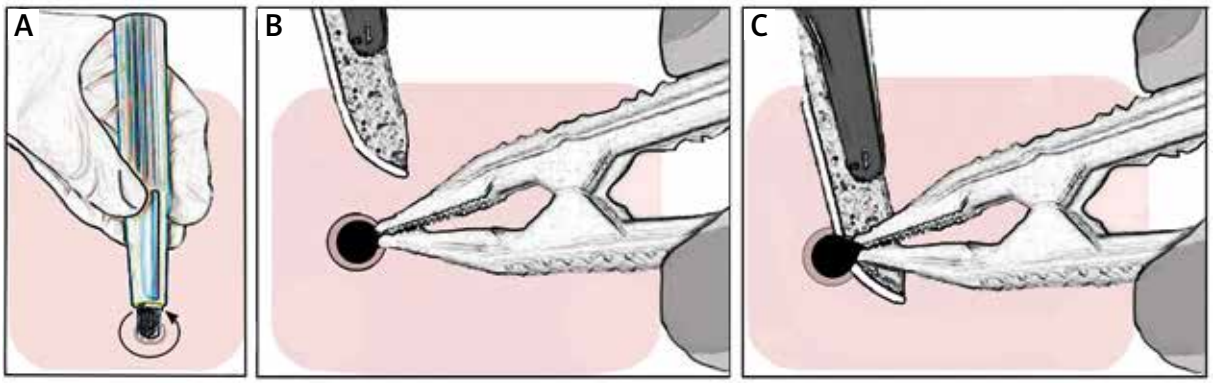


**Fig. 1.** Technique of the punch biopsy.

reveal all its layers (Fig. 1B), and then using the scalpel, in one or two cutting motions cut the cored skin free (Fig. 1C). During the excision process, the position of the scalpel is important – the scalpel should be placed under the forceps and moved in the opposite direction of the forceps pulling on the dermis. Great care should be taken not to damage the epidermis by crushing it with forceps. Blood collected on and around the biopsy specimen should be washed with normal saline. Washing the excess of blood is important as the presence of blood can sometimes give the false impression of extravasation of red blood cells [17].

After washing, the skin specimen should be immediately fixed in fixative. Usually no suture is required and the biopsy wound heals on its own. The most common but very rare side effect of the punch biopsy is a mild infection of the wound.

## Incisional biopsy

The use of a scalpel blade allows for the collection of larger and deeper fragments of the skin, therefore incisional biopsy is useful when the pathological process involves medium-sized blood vessels or subcutaneous fat.

After sterilizing the skin with an alcohol swab, the biopsy area is anaesthetized with a subcutaneous injection of the lidocaine solution. The injection should be continued until a bleb formed under the skin is greater than 3 mm in diameter. The injection of lidocaine may burn slightly due to a pH difference between the skin and the solution, however, the burning will quickly subside and the site will become numb. The area to be biopsied should be checked to ensure that the skin is properly anesthetized. For this purpose, the area around the periphery of the bleb is lightly poked with the tip of the syringe. Pressure sensation is normal and expected but there should be no pain. If the area requires more anaesthesia, another injection with a new syringe is made until the patient is comfortable. Then, the skin is stretched with the non-dominant hand, while with the other hand, tissue samples are taken using a scalpel, scissors or flexible blade. After the incisional skin biopsy, sutures are usually not required, however, a suture may be used to close a bigger wound or in the event of bleeding.

## Skin biopsy in diagnostics of small fibre neuropathies

Diagnosis of small fibre neuropathies (SFN) is a challenge because clinical and neurophysiologic investigations usually do not show involvement of small myelinated nerve fibres. Due to rich autonomic innervation of the skin, this biopsy method enables the morphometric and qualitative evaluation of somatic and autonomic nerve fibres. It allows not only the diagnosis of SFN, but also allows the identification of early and even subclinical stages of fibre damage. To evaluate myelinated fibres, it is recommended to obtain hairy skin biopsies from the distal part of the leg (10 cm above the lateral malleolus). The diagnosis of SFN from a unilateral leg skin biopsy is believed to be reliable [7], but sometimes a skin biopsy is performed from the calf, paraspinal and upper lateral thigh (20 cm below the anterior iliac spine) or, in upper limbs, from the lateral part or from the tip of the index or middle finger [8]. To reveal a unilateral neural process or for comparison of the innervation density, skin biopsy can be performed in other body sites. When biopsy is taken from other body site, a control biopsy from a similar non-affected region should also be taken.

Routinely, when evaluating a biopsy with suspected SFN, antibodies against the protein gene product 9.5 (PGP 9.5), collagen IV, vasoactive intestinal peptide (VIP) and dopamine β-hydroxylase (Dβh) are used. PGP 9.5 is a neuronal form of the ubiquitin carboxyl terminal hydroxylase transported by the slow component of axonal transport, while VIP and Dβh are selective cholinergic and noradrenergic markers, respectively. In addition to the qualitative analysis, a quantitative analysis of the skin specimen can be performed. The intraepidermal nerve fibre density (number of fibres per linear mm) is calculated on 4 non-consecutive sections stained with the PGP 9.5 or double stained with PGP 9.5 and collagen IV. The sensitivity of skin biopsy in SFN is up to 94% and the specificity is up to 97% (references in [6]).

## Skin biopsy in diagnostics of cerebral microangiopathies

A full-thickness skin biopsy is required in the diagnostics of cerebral microangiopathies. Skin biopsy is diagnostic only in the case of generalized angiopathies, and only a positive biopsy result is of practical importance. The main indications for a skin or combined skin-muscle biopsy are: relatively young age of the patient (30-50 years), the presence of hyperintense magnetic resonance imaging (MRI) lesions of unknown origin in the cerebral white matter, and a positive history of early-onset dementia or recurrent strokes in the patient or in his/her family [10,21].

In suspicion of microangiopathy, there are no recommendations concerning location of the skin biopsy. The location depends mainly on the patient's preferences but not on the distribution of symptoms. During the biopsy procedure, it is necessary to control the thickness of the skin fragment. In the study on a large group of CADASIL patients, Tikka *et al.* [21] showed that the most diagnostically valuable samples should contain

blood vessels from the deepest layers of the skin (on the border with the subcutaneous tissue) because they have the appropriate diameter. In CADASIL, the sensitivity of the skin biopsy is 45-50% while its specificity is 100% [11] but in other than CADASIL microangiopathies these values are unknown. It is worth remembering that a nosological diagnosis of angiopathy is often impossible due to the lack of pathognomonic morphological changes. In such cases, descriptive diagnoses are used (i.e., endoteliopathy, pericytopathy, basement membrane disease, etc. [1]) because even such general biopsy results may be helpful in guiding genetic testing.

## Skeletal muscle biopsy

### Anatomy of the skeletal muscle

The skeletal muscle is made of muscle fascicles and each fasciculus contains bundles of muscle fibres. The skeletal muscle is surrounded by a connective tissue sheath known as epimysium or fascia. Each fasciculus is covered by the connective tissue sheath called perimysium while muscle fibres are separated from each other by the innermost sheath known as endomysium. Every skeletal muscle is richly supplied by the axons of somatic motor neurons and by blood vessels. The main artery supplying blood to the skeletal muscle courses parallel to the longitudinal axis of the muscle fibres and gives off feed arteries running perpendicularly to the primary artery and perimysium. The feed artery branches into primary arterioles which, after branching, gives rise to transverse arterioles, then to terminal arterioles, and finally to capillary vessels. The capillaries are present within the endomysium and travel parallel to the longitudinal axis of the muscle fibre.

The main indication for skeletal muscle biopsy is the clinical suspicion of muscular disease due to the presence of symptoms such as muscle weakness, myalgia, exercise intolerance, increased creatine kinase activity, myoglobinuria or rhabdomyolysis. The presence of isolated symptoms, such as pain or muscle atrophy, is not an indication for a muscle biopsy due to its low diagnostic value e.g. in isolated muscle pain, a biopsy reveals specific changes only in about 2% of cases [3]. Muscle biopsy is also a method that offers a high diagnostic yield in patients with vasculitic neuropathy [18].

The main limitation of skeletal muscle biopsy is a nonspecific character of many pathological changes. It is also worth remembering that sometimes normal results of biopsy examination do not exclude neuromuscular processes [16]. Therefore, before performing a biopsy, all other less invasive studies should be done to confirm the diagnosis including: creatine kinase activity, electromyography (EMG) and MRI of the muscles.

In skeletal muscle biopsy, it is possible to assess the hypertrophy or atrophy of muscle fibres (selective, grouped, perifascicular), their splitting and regeneration, the location of cell nuclei, the presence of grouping of various types of fibres, as well as the presence of vacuoles, ragged-red fibres and various types of inclusions. Immunohistochemical tests allow to evaluate expression of the normal (e.g. dystrophin, emerin, A/C lamin, desmin) and pathological (e.g. β-amyloid, tau) muscle proteins. Ultrastructural examination enables the diagnosis of various types of structural myopathies and can confirm the diagnosis of inclusion body myositis, mitochondrial myopathy, glycogenoses and others.

A skeletal muscle biopsy should be prepared according to the latest recommendations of the European Reference Network EURO-NMD Neuromuscular Pathology Working Group from 2019 [2]. The selection of the muscle for biopsy is based on clinical examination using Medical Research Council (MRC) strength scale, results of skeletal muscle MRI and EMG. If a pathological process is chronic, moderately affected (grade 4/5 MRC) muscle should be selected for biopsy because diagnostically useless atrophic changes dominate in the muscle with severe involvement [5]. In the case of an acute disease, biopsy material should be taken from the muscle showing the most severe clinical symptoms. When choosing a muscle for a biopsy, the cosmetic effect after the procedure related to the formation of a scar should also be taken into account. The patient's right – or left-handedness also plays a role in choosing the muscle because it is recommended to limit the load and use of the limb for several hours after the biopsy to avoid complications. In addition, a muscle that has recently been assessed by EMG, has been injured or has been given an injection should not be selected for examination.

A muscle biopsy should not be performed less than one month after an episode of myoglobinuria. In patients with myoglobinuria and rhabdomyolysis, the biopsy may be performed only after the resolution of acute symptoms which means the delay even up to 8 weeks [22].

If it is possible, a muscle biopsy should be performed before starting any treatment, especially with glucocorticosteroids, which may interfere with its outcome. Sometimes, a combined skin and muscle biopsy is performed. Since in such case two different tissues are examined, this method is theoretically more sensitive than either biopsy separately and may be useful when vasculitis or generalized microangiopathy is suspected.

A muscle biopsy is usually performed using a needle or a scalpel (open biopsy).

## Needle muscle biopsy

In a needle biopsy, a piece of muscle is removed with a needle, sometimes with the use of vacuum. The technique with the accompanying video has been described in detail by other authors [19]. The amount of material for diagnosis is small, but it can be increased by repeated punctures or changing the needle position without changing the puncture site. Using a needle biopsy, diagnostically useful material can be obtained from 96% to 99% of cases [13,19]. This method can be used not only for diagnostic purposes, but also to monitor the course of the disease. The advantage of a needle biopsy, especially compared to the open method, is the smaller size of the wound and therefore less scar and less complications, especially pain. The disadvantage is the greater risk that in the case of disseminated lesions it will not be possible to collect the pathologically changed fragment of the muscle. There is also no possibility to control the arrangement of the muscle fibres in the collected samples. For this reason, and due to the small size of the sample, the material from the needle biopsy can be unreliable for evaluation in histochemical and immunohistochemical studies.

## Open muscle biopsy

Open muscle biopsy is a simple surgical procedure that requires only short-term local anaesthesia. The tissue sample is collected from the venter of the muscle, remote from its attachment to the bone or the transition to the tendon. There is no cauterization or ligation of vessels during the procedure, and no clamps are applied. The biopsy material should have a shape similar to a cylinder with a long axis along the muscle fibres and be collected in the manner as little traumatic as possible in order to avoid mechanical destruction of the structure of tissues. The size of the sample depends on the nature of the expected changes (focal, diffuse or dispersed) and the number of methods to be used in the histopathological examination.

The main contraindication to an open muscle biopsy is allergy to drugs used for local anaesthesia or conditions associated with blood coagulation disorders [5]. Complications are rare and include: local pain, pain or numbness due to cutting through a superficial sensory nerve (but the risk of damaging the motor nerve is extremely rare), bleeding or local hematoma, local infection, dehiscence of sutures, muscle invagination into the biopsy hole in the case of improperly sutured fascia, reactions to local anaesthetics (adrenalin-related arrhythmia and allergic reactions), and skin scar enlargement in the long term.

## Open skeletal muscle biopsy technique

The muscles most often chosen for biopsy are the quadriceps and biceps muscles. When the muscle biopsy is taken from various sites in the body, to evaluate the unilateral process, a control biopsy should be performed from a similar unchanged muscle.

To collect a section from the biceps muscle (medial head, Fig. 2A), the patient is placed with his/her hand fixed on the operating table. When biopsy is taken from the quadriceps muscle of the thigh (medial head, Fig. 2B), the patient is placed in the supine position. The procedure is performed under local anaesthesia of the skin with a 2% lignocaine solution without the use of coagulation. The local anaesthetic is administered subcutaneously to distribute the drug around the site of a section. The muscle itself should not be anesthetized because the structure of the muscle may be damaged both by the pressure generated during the injection and by the drug itself.

After a thorough examination of the biopsy site for visible intra – and subcutaneous vessels and other skin lesions (moles, wounds, purulent lesions), the patient

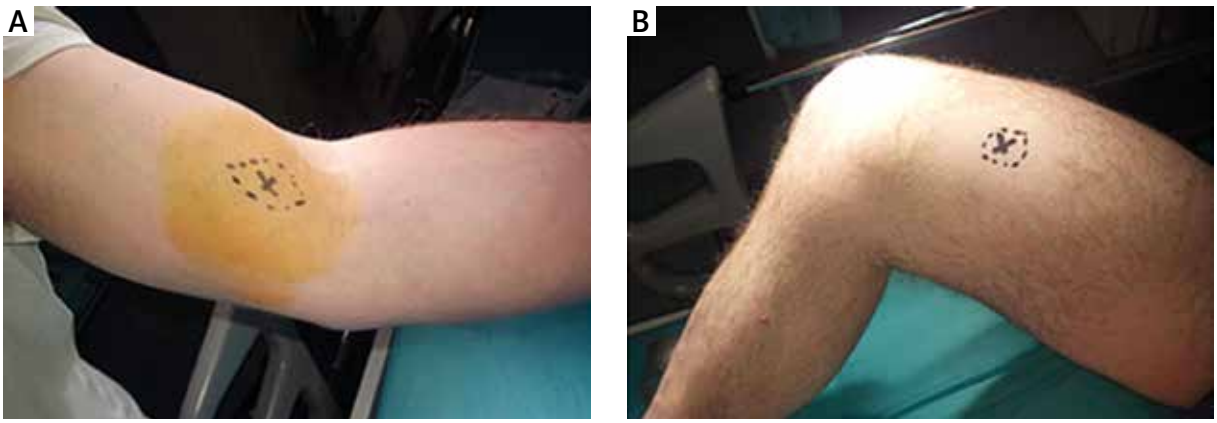


**Fig. 2.** The site of specimen collection for the biopsy of the biceps brachial muscle (medial head) (**A**) and the quadriceps muscle of the thigh (medial head) (**B**).

should be asked to actively contract the muscle to roughly determine the depth of the muscle under the skin and mark a potential cut line. When making a skin incision, it is necessary to pay attention to the correct spatial orientation of the cut line in relation to the limb axis, taking into account the basic determinants of skin tension, i.e. Langer's lines and dynamic wrinkle which affect the functional state of the scar and its cosmetic effect. A skin fragment in the shape of an ellipse (lens), about 1 cm wide and up to about 2-3 cm long, should be taken. Then, after incising the fascia along the muscle fibres, visualizing the muscle and cutting along the visible fibres, a muscle fragment with an oblong cubic shape and a volume of about 0.5 $cm^3$ should be collected and then be placed on sterile gauze soaked in sterile saline.

In the event of bleeding, the bleeding vessel should be punctured or, if the bleeding site is not visible, local gentle pressure should be applied. The fascia is usually left unattached because when cut along the fibres its edges come closer by themselves. In the case of severe hyperaemia and swelling of the muscle, it is recommended to incise the fascia wider to prevent the intra-fascial tightness syndrome. If, during contraction, the muscle fibres penetrate into the fascia's opening, or when the fascial opening disturbs the axis of movement of the fibres, the fascia should be sewn together with absorbable sutures. The skin is sutured with the best possible cosmetic effect and a sterile dressing is placed over the wound.

In the upper limb biopsy, the limb should be immobilized for 24 hours in a triangular sling or an orthosis. After the lower limb biopsy, the patient should be transported to the bed in a wheelchair and a bed regimen and no strain on the limb should be applied for 24 hours.

The biopsy wound should be monitored for possible exudate or bleeding, and analgesic treatment dosed according to the patient's needs should be given.

The handling of the specimen for the purpose of its morphological evaluation has been thoroughly discussed in the work of other authors [5,15].

## Combined skin-muscle biopsy

A combined skin-muscle biopsy, as opposed to a skin or solely muscle biopsy, seems to be beneficial in the diagnosis of some systemic diseases, which at some stage may manifest mainly or solely by symptoms from the central nervous system. It is necessary to remember that larger vessels are easier to find in a deep skin biopsy, while capillaries in a muscle biopsy. In addition, the skeletal muscle has several times more vessels per unit volume than the skin, while the vessels in the skin are less numerous but more clustered. These different properties of the biopsy material are of particular importance in microangiopathies, which do not affect all types of vessels equally and are often focal in nature [20]. In such cases, the evaluation of the combined skin-muscle biopsy material may increase the sensitivity of the method and the probability of making a diagnosis.

Regardless of the biopsy method used, for the material to be suitable for morphological evaluation, particular attention should be paid to:

- checking the thickness of the skin fragment,
- avoiding damage to the epidermis by crushing it with forceps,
- avoiding anaesthesia of the skeletal muscle itself,
- proper orientation of the scalpel during skin biopsy (the scalpel should be placed under the forceps and moved in the opposite direction of the forceps pulling on the dermis),
- proper orientation of the muscle fibres so as to obtain fibre cross not longitudinal sections during cutting,
- proper concentration of fixatives (for fixation, the concentration of formalin should be 10% while the commercially available formalin is 40% and has to be diluted with water in a ratio of 1 : 4).

## Disclosure

The authors report no conflict of interest.

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