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HOW I DO IT - PERIPHERAL NERVES

Fluorescein-guided resection of plexiform neurofibromas: how I do it

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Abstract

Background Plexiform neurofibromas (PN) can determine pain, nerve function impairment, and, when extremely large, also deformity. Surgical is often partial, with possible recurrence, and the risk of malignant transformation.

Method We describe the surgical strategy in a case of huge multiple plexiform neurofibromas of the left arm. We attempted to achieve a safe resection under the intraoperative guidance of fluorescein, with a dedicated microscope filter (*YELLOW560*). This technique can be also applied to other locations.

Conclusion Fluorescein-guided surgery, coupled with intraoperative neurophysiological monitoring, increases the safe resection rate, considering the risks of neurological deficits and the possible malignant transformation.

Keywords Fluorescein · Neurofibromatosis · Peripheral nervous system tumor · Plexiform neurofibroma · YELLOW560 filter

Relevant surgical anatomy

The brachial plexus comprises ventral roots from C5 to C8-T1. C5, C6, and rarely C4 roots give rise to the upper trunk (Fig. 1). C7 originates the middle trunk, while C8 and T1 (sometimes T2 too) compose the lower trunk. At clavicle, the trunks divide into anterior and posterior branches. The anterior divisions of the upper and middle trunks lead to the lateral cord, while from the anterior branch of the lower trunk arises the medial cord. All three posterior divisions converge instead into the posterior cord. Lateral, medial, and posterior cords are infraclavicular. The musculocutaneous nerve arises from the lateral cord. The radial nerve, after its origin from the posterior cord, passes deeply to the triceps brachii; the axillary nerve has the same origin too. The median nerve receives fibers from medial and lateral cords, running between the biceps and triceps. The ulnar nerve is a continuation of the medial cord. Initially posterior to the brachial artery, then it passes through the same plane of the median nerve. The brachial artery continues from the axillary artery and is the main arm artery, passing close to the median nerve and basilic vein. The venous drainage is guaranteed by a medial and a lateral vein, respectively, the basilic and the cephalic veins. If a growing tumor determines deep structural alterations, the typical anatomic landmarks can be completely lost.

Description of the technique

Anesthesia assessment

General anesthesia consists of propofol 1% (induction dosage, 2–3 mg/kg; during surgery, 0.3–0.5 mg/kg/h). If muscle relaxants are used during intubation, rocuronium bromide is administrated to permit IOM (intraoperative neurophysiological monitoring) and neuromuscular functions are then assessed by train-of-four tests [9]. Fluorescein (*Monico SPA*, *Italy*) is finally intravenously injected by the anesthesiologist, immediately upon completion of the induction. We use a dose of 1 mg/kg, lower than the dose for central nervous system tumors [1].

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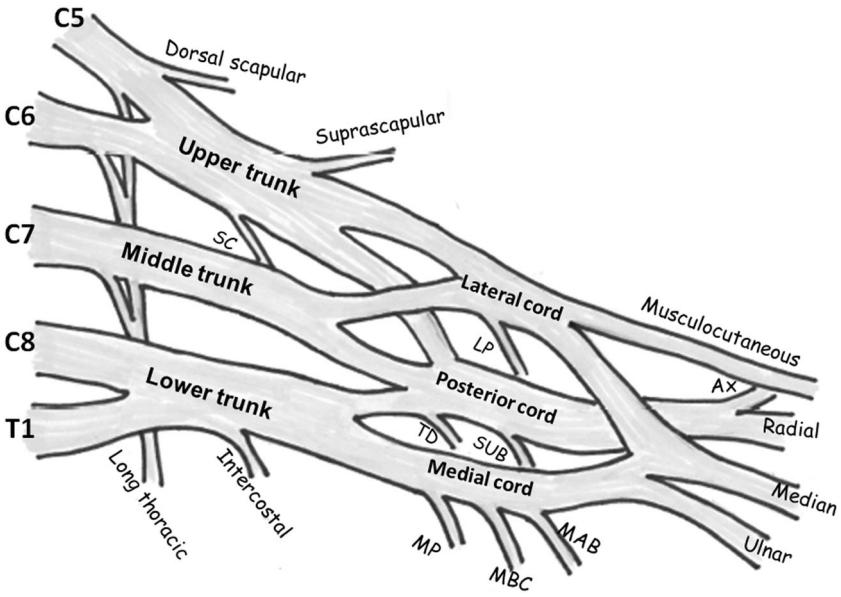

Fig. 1 Schematic representation of the brachial plexus with main trunks, cords, and main nerves of the arm (if not otherwise indicated, the names are referred to single nerves, while trunks and cords are clearly delineated). Ax, axillary nerve; LP, lateral pectoral nerve; MAB, medial antebrachial nerve; MBC, medial brachial cutaneous nerve; MP, medial pectoral nerve; TD, thoracodorsal nerve; SC, subclavius nerve; SUB, subscapular nerve

Positioning and skin incision

The patient is supine with the arm abducted. The head is in neutral position. A large area extending from supraclavear region down to the lower chest, and laterally including the shoulder and the limb, is prepped and draped (Fig. 2). The skin incision goes from the axilla to the border between arm and forearm.

Intraoperative neurophysiological monitoring

Surgery is performed with continuous free running and stimulus-triggered EMG, to identify functioning nerves and to localize the safest entry point inside the tumor capsule. The supraspinatus, flexor carpi radialis and ulnaris, extensor carpi radialis, abductor digiti minimi, and opponens pollici muscles are tested during IOM. The stimulation is directly applied to tumoral structures. The stimulus has a square-wave shape, an amplitude of 0.01 milliseconds, a frequency of 1 Hz, and an increasing voltage from 0.1 to 2 mA. Also, F-waves from ulnar and median nerve are registered.

Surgery for plexiform neurofibromas

After dissection of subcutaneous planes, multiple plexiform tumors are observed. Neurofibromas usually present two or more entering and exiting fascicles, commonly larger than those seen in schwannomas; however, tumor removal proceed in the same manner. They have a capsule strictly adherent to the tumor masses [4]. Surgery is then totally performed with the surgical microscope (*Pentero microscope*, *Carl Zeiss Meditec*, *Germany*), equipped with the YELLOW560 filter, specifically designed for fluorescein visualization. Starting from the upper part of incision, after an adequate tumor exposure, to identify the nerves is the first objective: with the aid of direct stimulation, the capsule is tested to recognize fascicle-free zone, which is then superficially incised [6–8]. Since there, the fascicles directly entering into a true capsule are stimulated, to asses if functional or not. In the latter cases, they can be transected, preceding therefore with piecemeal resection.

Fluorescein visualization

Fluorescein accumulates in tumoral tissues through a damaged blood-nerve barrier. The intake inside a normal nerve is only slight, if compared to the tumors. At least 30 min are necessary before the first fluorescence visualization to permit an effective intratumoral fluorescein diffusion. During resection, the microscope can be switched by the surgeon alternatively from fluorescent to white-light illumination, to verify in real time the entity of resection, according to the different enhancement between tumor and normal nerves.

The YELLOW560 filter is activated to progressively separate all the nerves, only slight fluorescent, from the surrounding intensely fluorescent neurofibromas (Fig. 3). In the present illustrative case, following IOM and with careful dissection, the ulnar and the radial nerves have been isolated. Finally, the fluorescence filter allowed us to correctly identify also medial brachial cutaneous, ulnar, median, and radial nerves, along with basilic vein and brachial artery. The vessels showed a

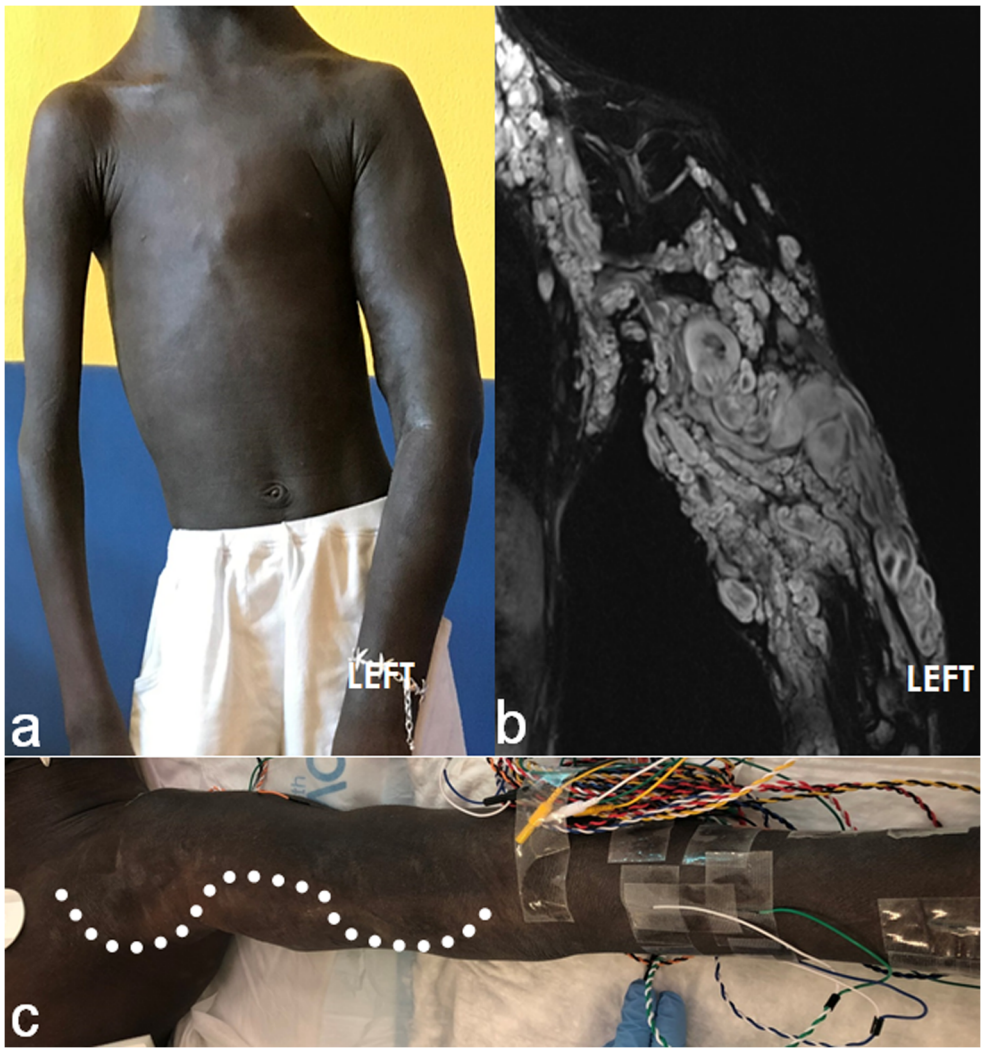

Fig. 2 Preoperative patient's pic (**a**) and coronal MRI (**b**) showing large and deforming plexiform neurofibromas with multiple components affecting the entire upper left arm. The normal anatomy and distribution of brachial plexus and its derived nerve are not well-recognizable at MRI. In **c**, the surgical position: the patient is supine with the arm abducted. The head was in neutral position. A large area from the clavicle to the lower chest, and laterally including the shoulder and the involved limb, is prepped and draped. The curvilinear skin incision (*dotted line*) allows to achieve access both to the median and the radial nerves. In this phase, all needles for IOM are placed

fluorescence intensity that was intermediate between the normal nerve and the tumor, due to intravascular diffusion of the dye (Fig. 4). The last IOM control with direct stimulation assessed integrity of ulnar, median, and radial nerves.

Indications

Indications are patients harboring large and deforming plexiform neurofibromas [2, 4], with residual or intact peripheral

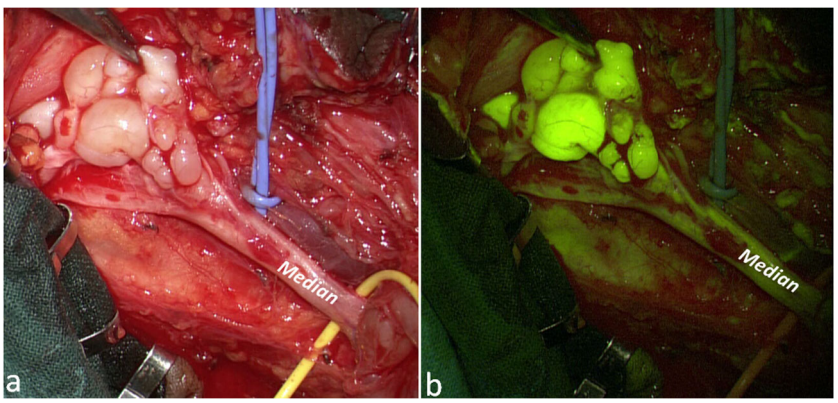

Fig. 3 While proceeding with resection, the median nerve was identified, and the neurofibroma invading the nerve was clearly visible (**a**). Under YELLOW560 filter, the tumor showed intense fluorescence (**b**) if compared with the moderate fluorescein uptake of the nerve. Following IOM and fluorescein findings, the median nerve was completely exposed. The basilic vein is separated with a blue vasoloop

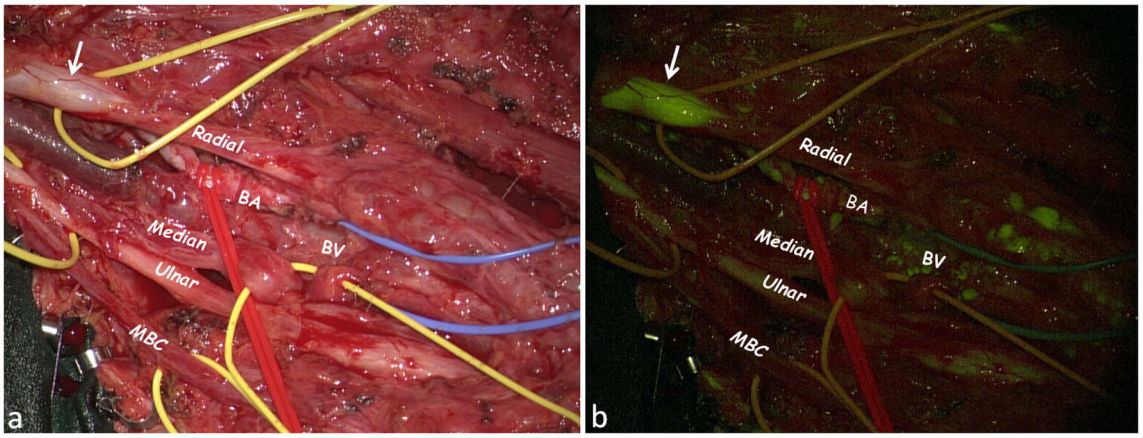

Fig. 4 The medial brachial cutaneous (*MBC*), median, and ulnar nerves were isolated while the neurofibromatous component enveloping them were removed. The portion of neurofibroma (*arrow*) infiltrating the radial nerve presented an intense fluorescein enhancement, respect to the normal nerve. The basilic vein (BV) wrapped by a blue vasoloop and the brachial artery (BA) with a red vasoloop showed a fluorescence pattern different from the nerves and the remaining tumor tissues

nerves function. The aim of surgery is to reduce pain, to improve functionality of the involved limb (if possible), and sometimes also to correct esthetical impairments. Even if considered benign, PN carry the risk of malignant transformation and should present a high recurrence rate [2, 5, 10].

Limitations

No specific limitations: this technique can be applied to all patients harboring PN. Patients should be informed that, in case of tumor remnants, a closer radiological follow-up is necessary. However, if pathological examination proves malignancy, the patient will be returned to surgery in a timely fashion for definitive surgery, even if often wide resection to clean margins is not accomplished without nerves or vessels sacrifice with severe neurological deficits.

How to avoid complications

Continue registration of nerve potential is mandatory to avoid nerve damages. The important vessels of this region can be identified with ioUS and flow evaluation techniques as color Doppler.

Specific perioperative considerations

To prevent local pain/discomfort and hypersensitivity secondary to edema and scar formation, patients must undergo specific physiotherapy treatments as soon as possible. Arterial blood pressure, heart rate, blood oxygen saturation, temperature and skin color, and creatinine levels are monitored pre- and post-operatively to evaluate potential fluorescein side effects. Yellow urination is a transitory not-harmful event usually lasting some hours.

Specific information to give to the patient about surgery and potential risks

The complications can be related to nerves and vascular damages, with the possible onset of new functional deficits. Fluorescein has a very high safety profile and related adverse events are anecdotal [3].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The patient and next of kin have consented to the submission of this "How I Do It" to the journal.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Key points

(1) Be sure that patients know the very low risks related to fluorescein injection.

(2) Correctly place the needles for EMG

(3) Strong collaboration with neurophysiologists for IOM to avoid irreversible nerve damages.

(4) Before the first YELLOW560 visualization, wait at least 30' after fluorescein administration

(5) Recognize intact nerves before the piecemeal resection.

(6) Intraoperative ultrasounds and color Doppler can identify major vessels

(7) Neurofibromas, also the subcutaneous components, appear intensely fluorescent if compared with normal nerves

(8) The vessels show intermediate fluorescence, due to fluorescein intravascular diffusion.

(9) Following fluorescence, the resection rate can be greatly increased: its limits are established by IOM. The main goal is to avoid neurological impairment

(10) A close neuroradiological and clinical follow-up is necessary in case of large remnants