MONOGRAPH
Mètode Science Studies Journal, 10 (2020): 213-220. University of Valencia.
DOI: 10.7203/metode.10.15032
ISSN: 2174-3487. eISSN: 2174-9221.
Submitted: 10/05/2019. Approved: 07/11/2019.

VESTIGES OF OUR FIRST STEPS

An evolutionary view of the supracondylar syndrome

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Understanding the evolution and function of structures in the past is key to understanding current biodiversity. This paper shows how an evolutionary perspective can help us to understand supracondylar syndrome. This pathology is caused by compression of the median nerve and/or the brachial artery in the arm and affects a significant percentage of the human population. We propose that this neuropathy is an atavism (the reappearance of an ancestral characteristic that had been lost along our evolutionary lineage) of the entepicondylar foramen: a channel present at the lower end of the humerus through which the brachial artery and the median nerve pass in some mammals. The origin of the foramen has been identified in the first tetrapods, and we propose that its original function could be linked to the evolutionary innovation of the cervical brachial plexus as well as the subsequent evolution of the entepicondylar foramen in amniotes –a group of terrestrial vertebrates that encompasses current reptiles and amphibians– and that it may be vestigial.

Keywords: supracondylar syndrome, entepicondylar foramen, first tetrapods, atavisms, vestigial organs.

INTRODUCTION TO THE SUPRACONDYLAR SYNDROME

Pain, a tingling sensation, numbness, and progressive weakness of the arm and hand are the common symptoms of a compressive neuropathy of the median nerve called supracondylar syndrome. Together with other neuropathies of the same type, supracondylar syndrome affects a percentage of the human population varying between 0.1 % and 2.7 % of adult individuals (see Opanova & Atkinson, 2014). This is a congenital syndrome and its main feature is compression of the median nerve and/or the brachial artery at the lower end of the humerus at the height of the elbow joint (Koo & Szabo, 2004).

The median nerve emerges from the cervical brachial plexus, a nerve network located at the base of the neck that connects the spinal cord with all the peripheral nerves in the arm. Along with the brachial artery, it runs through the anterior region of the arm, forearm, and hand and innervates the associated muscles (Figure 1). The brachial artery is a continuation of the axillary artery and is the main blood vessel of the arm. At the level of the elbow joint it divides into the radial and ulnar arteries which irrigate the entire middle and lower end of the upper limb (Figure 1). Treatment of this neuropathy usually entails surgical removal of the bone and its associated ligament.

> «The symptoms that characterise supracondylar syndrome are numbness, tingling, pain, and forearm and hand weakness»

THE SUPRACONDYLAR PROCESS AND STRUTHERS' LIGAMENT

Supracondylar syndrome is usually associated with the emergence of the supracondylar process, also known as the supracondyloid, supraepitrochlear, epicondylar, or epicondyloid process. This process consists of a spike-shaped bone spur arising from the mid-distal section of the humerus, that is, from the middle of the bone to the part closest to the elbow

(Opanova & Atkinson, 2014) (Figure 2, left drawing). This spur is normally between 4 and 8 centimetres from the medial epicondyle of the humerus (the region of the humerus closest to the body and at the height of the elbow joint) and projects by between 2 mm and 20 mm. It was first described in great apes by Tiedemann (1818) and later in humans by Otto (1839) and has a variable incidence depending on the human populations in question.

Normally, the process is associated with a fibrous ligament known as Struthers's ligament (Figure 2, left drawing) in honour of its discoverer, John Struthers (Struthers, 1848). This ligament inserts at the far end of the bone and runs to the medial epicondyle of the humerus and forms an arc through which the median nerve runs, usually accompanied by the brachial artery and sometimes also by the ulnar or radial artery. The presence of the median nerve and/or vessels in this supracondylar arch leads to their compression by Struthers's ligament.

«Treatment of this neuropathy usually entails surgical removal of the bone and its associated ligament»

Although supracondylar syndrome most often involves this type of compression, a wide range of elbow joint compressive neuropathies are possible because they ultimately depend on the median and ulnar nerve distribution and the degree of brachial artery entrapment. In any case, this compression type causes the characteristic symptoms of this syndrome, including numbness, tingling, pain, and forearm and hand weakness.

THE ATAVISTIC NATURE OF THE ENTEPICONDYLAR FORAMEN

As he was writing the first chapter of *The origin of man and selection in relation to sex* (1871), Charles Darwin contacted Dr. Struthers because of the latter's interest in studying the causes of supracondylar syndrome and the variability of the supracondyloid process and its ligament. Darwin recognised it as a rudimentary organ homologous to the entepicondylar foramen –the channel present at the lower end of the humerus through which the brachial artery and the median nerve run (Figure 2, right drawing). This was referred to as the supracondyloid foramen at the time, and a common «origin» for it was subsequently demonstrated for humans and other mammals:

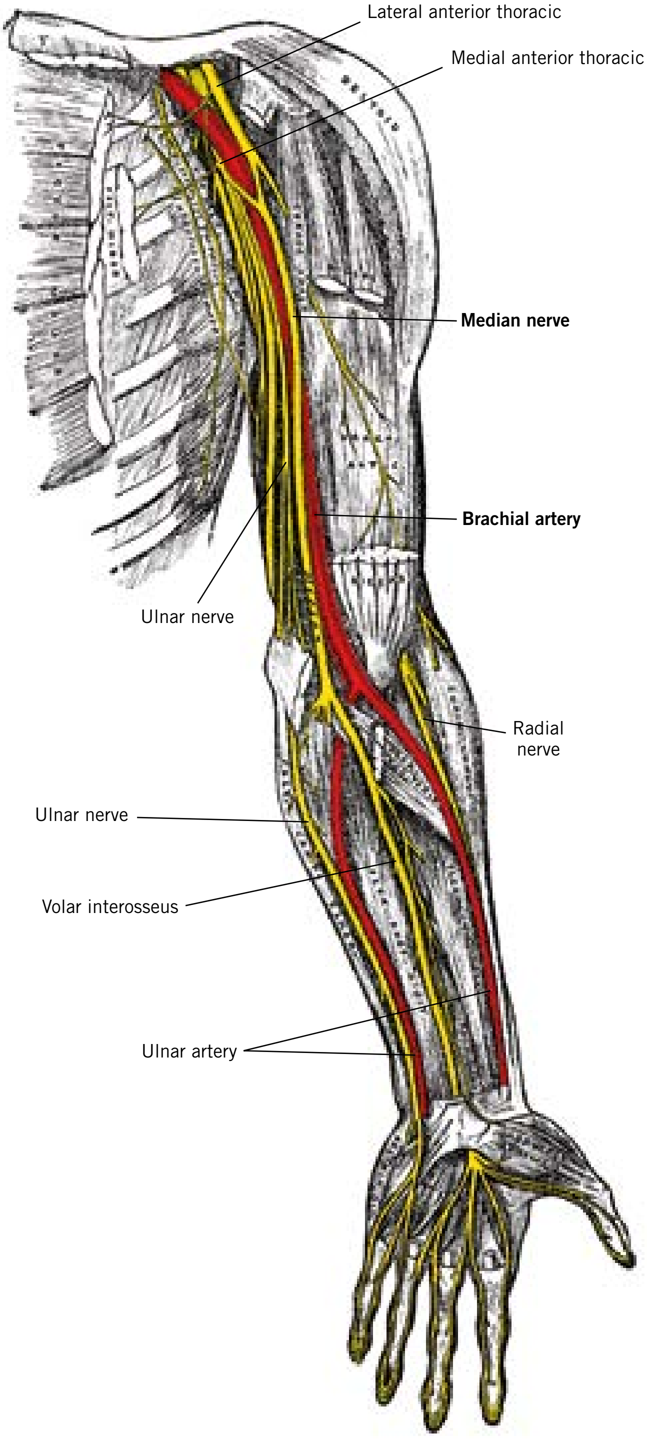

Figure 1. Layout of the main upper-limb peripheral nerves and blood vessels in *Homo sapiens*. The brachial artery and the median nerve are highlighted.

SOURCE: Modified from Gray, H., & Carter, H. V. (1918). *Anatomy of the human body*. Philadelphia: Lea and Febinger.

«Vestigial organs appear with a high frequency among adult individuals»

> In some of the lower Quadrumana, in the Lemuridae and Carnivora, as well as in many marsupials, there is a passage near the lower end of the humerus, called the supra-condyloid foramen, through which the great nerve of the fore limb and often the great artery pass. Now, in the humerus of man, there is generally a trace of this passage, which is sometimes fairly well developed, being formed by a depending hook-like process of bone, completed by a band of ligament. Dr. Struthers, who has closely attended to the subject, has now shown that this peculiarity is sometimes inherited, as it has occurred in a father, and in no less than four out of his seven children. When present, the great nerve invariably passes through it; and this clearly indicates that it is the homologue and rudiment of the supra-condyloid foramen of the lower animals. Prof. Turner estimates, as he informs me, that it occurs in about one per cent of recent skeletons. But if the occasional development of this structure in man is, as seems probable, due to reversion, it is a return to a very ancient state of things, because in the higher Quadrumana it is absent. (Darwin, 1871)

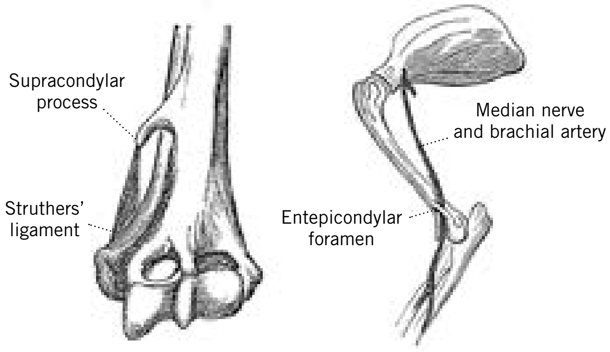

Figure 2. The left image shows supracondylar syndrome in a human humerus in which the supracondyloid process and Struthers' ligament can be observed. The image on the right shows the medial view of the anterior limb of a cat (*Felis catus*) with the median nerve and the brachial artery running through the entepicondylar foramen in the distal humerus.

SOURCE: Modified from Struthers, J. (1873). On hereditary supra-condyloid process in man. *The Lancet*, *101*(2581), 231–232.

«Charles Darwin said that the occasional appearance of the entepicondylar foramen in humans would be a reverion from an evolutionary point of view»

Although Otto (1839) was the first to recognise the supracondyloid process as a homologue of the entepicondylar foramen, as we can see, Charles Darwin had also identified the relationship between the two. He also said that the occasional appearance of this foramen or «passage» in the human being would be a reversion from an evolutionary point of view, because it would mean the reappearance of a characteristic which is absent in the group of primates that share the most direct predecessors with the hominins, but is found in their remote ancestors (mammals). On the contrary, vestigial organs (for instance, the vermiform appendix in humans, which does not have any adaptive value for digestive purposes) normally appear with high frequency among adult individuals and they usually entail a loss of the original functions. This occurs even if these were retained because they had acquired new functions – through selection – very different from those of the original organ (in the case of the appendix, the production of lymphatic tissue).

The possible causes of the appearance of atavistic structures are related to the quiescent presence of genetic information and the embryonic development processes necessary for their formation (Hall, 1984). Hence, atavisms show the importance of knowing the history of different groups of organisms in order to understand the origin of current diversity, because evolution cannot completely purge the alleles and/or processes responsible for generating structures which no longer perform a function, even if they had a function in the past. For example, hind limbs with skeletal elements typical of the legs of their terrestrial ancestors appear in cetaceans. Or horses which occasionally emerge with an extra hind-limb «toe' which was a characteristic of extinct species not so well adapted to prolonged fast-paced locomotion (Hall, 1984). Because of our underlying clinical interest, possible genotype development anomalies and their potential evolutionary meaning are best known in the human species. Examples include hypertrichosis, an abnormal growth – both in distribution and density – of hair on the torso and face, or the presence of the coccygeal process, also known as the vestigial tail (Hall, 1984).

Therefore, it seems possible that the appearance of the supracondyloid process in humans may also be atavistic and reminiscent of the entepicondylar foramen typical of tetrapods (vertebrates that have legs with fingers), and that it could be detrimental to individuals with this atavism. Thus, we can see the importance of understanding the evolution of this channel in humans and why it is imperative to understand why and when it appears. The answer to this question will allow us to learn from when in evolutionary history it has been present, in which taxon it first appeared, and what possible adaptive advantages (if any) the presence of this channel may have caused.

THE FIRST TETRAPODS AND THE ORIGIN OF THE ENTEPICONDYLAR FORAMEN

The first tetrapods, that is, the group of vertebrates that ventured onto the land surfaces characteristic of the terrestrial environment in the upper Devonian period (≈ 385–359 million years ago), evolved from sarcopterygian fish including coelacanths. This group of fish is characterised by its lobed and fleshy fins and skeletal elements resembling those of the extremities of the first tetrapods. Specifically, a group of these sarcopterygian fish (see *Tiktaalik roseae* in Figure 3) are considered a transitional form between fish and true tetrapods.

This group of extinct sarcopterygians had a set of foramens distributed along the humerus as well as a channel in a bony crest located on its ventral side. The median nerve and the brachial artery would have run through this crest to the forearm, thus representing the first outline of the entepicondylar foramen. This ventral nerve and blood vessel route from the shoulder to the forearm (Figure 4) is recognised as the ancestral condition for all tetrapods because it is still evident in later tetrapod forms such as *Acanthostega* (Figure 3).

However, in current amniotes – terrestrial vertebrates including current reptiles and amphibians – and in most tetrapods (see *Seymouria*, Figure 3) with an entepicondylar foramen, their brachial artery and median nerve do not run only along the ventral surface of the humerus but rather, change their path (Figure 4) from a more dorsal to a more ventral position (Landry, 1958). Two extinct tetrapods (*Mesanerpeton* and *Ossirarus*) have an intermediate layout in which the vessel and nerve run between the ventral and dorsal surfaces of the humerus (Smithson & Clack, 2018).

This change in the vessel and nerve path is because the distal region of the humerus (the furthest from the bone point of origin) experienced an anatomical reorganisation (specifically, a torsion) that led to the appearance of a distal end depression. In turn, this caused the nerve and vessel path to change from below the bone (through the ventral crest) in humeri without the ability for torsion, to run along the medial edge of the humerus (in *Mesanerpeton* and *Ossiarus*), and eventually change

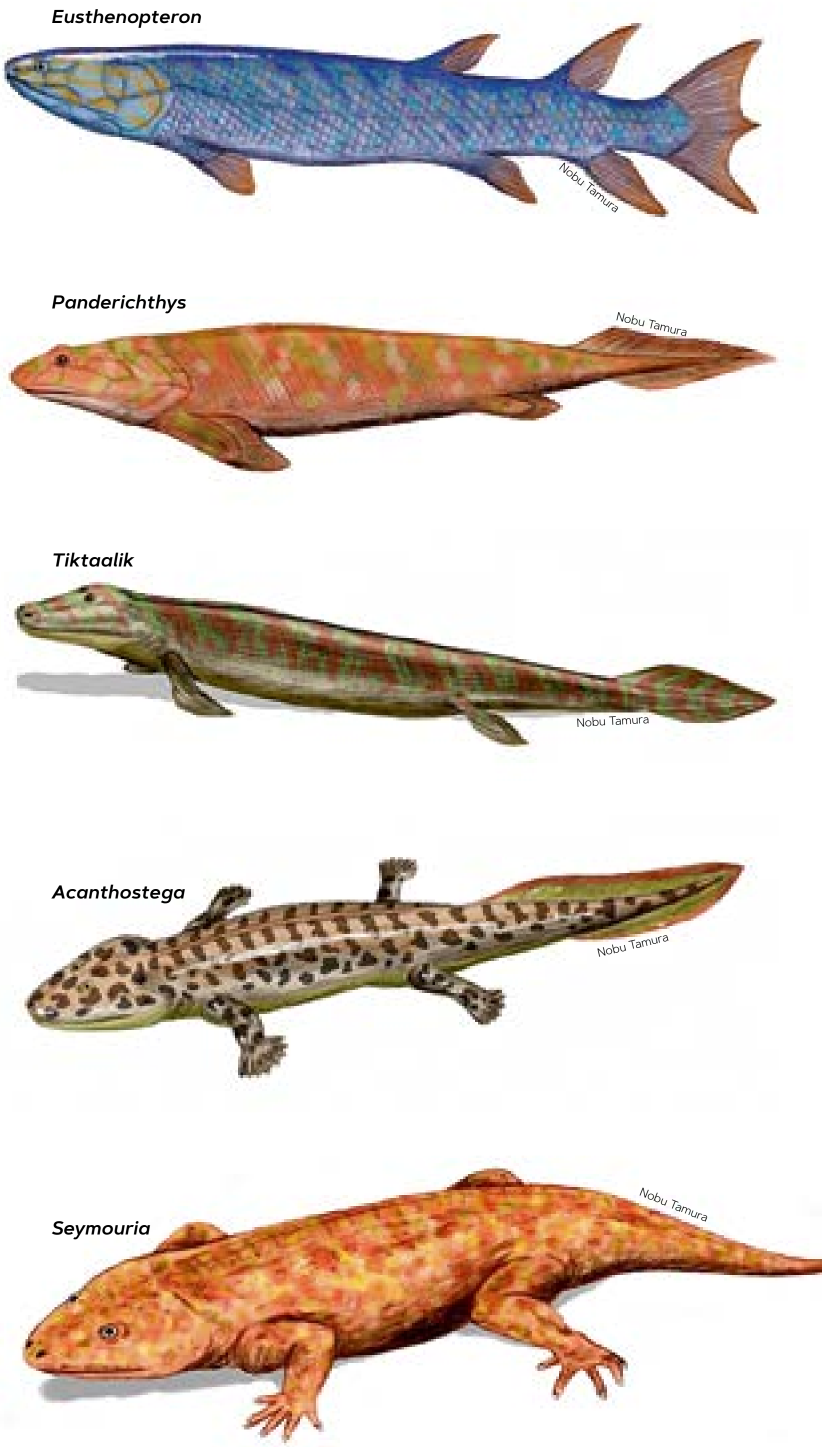

Figure 3. Reconstructions of some extinct species which are relevant in the study of the absence or presence of the entepicondylar foramen. From top to bottom, the sarcopterygian fish species 1) *Eusthenopteron*, 2) *Panderichthys*, 3) *Tiktaalik*, from which later tetrapods evolved such as 4) *Acanthostega*, and 5) *Seymouria*. These latter two species presented evolutionary novelties such as the reorganisation of the axial skeleton that led to the acquisition of a well-defined cervical region in *Acanthostega* or a more stylised humerus in *Seymouria*.

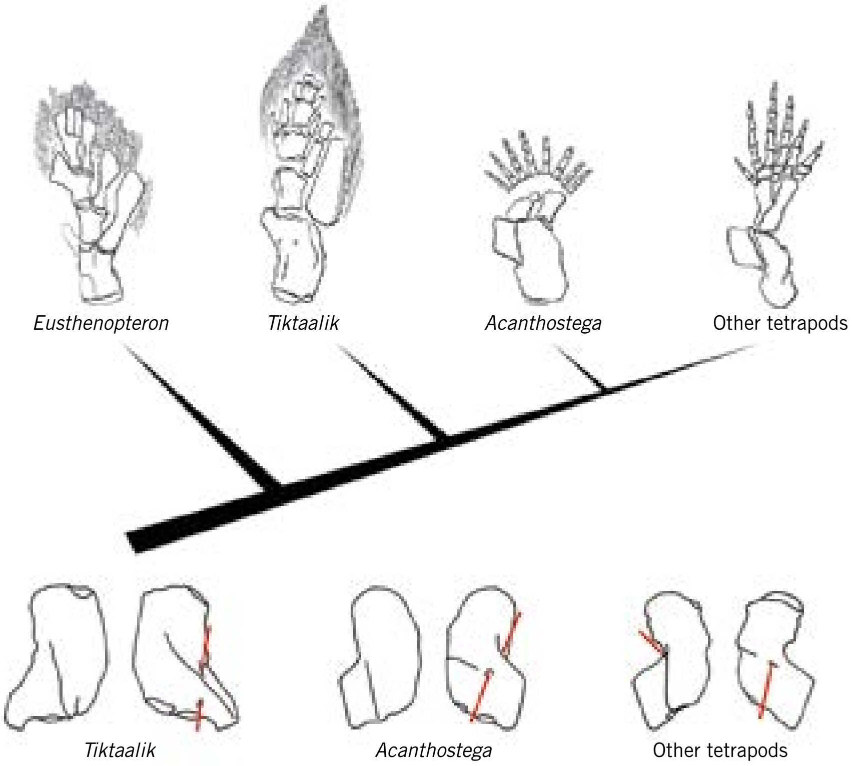

Figure 4. Origin of the entepicondylar foramen and humeral torsion in basal tetrapods. The top image shows a cladogram of some basal tetrapods and tetrapodomorphic fish, showing their pectoral fins. The bottom image shows a dorsal (left) and ventral (right) view of the humerus for the indicated taxa, showing the entepicondylar (foramen) channel with the path (in red) followed by the median nerve and brachial artery.

SOURCE: Modified from Smithson & Clack (2018).

to run through the humerus itself via entepicondylar channel dorsoventral pathway (Figure 4). Therefore, the distal-end depression of the humerus is associated with the perfection of locomotion in the terrestrial environment which led to an increase in stride length (Smithson & Clack, 2018).

«The first tetrapods had to transform not only their locomotor apparatus, but also their respiratory and auditory systems»

It is even more interesting to try to explain why even more recent tetrapods in the Carboniferous period (≈ 359–299 million years ago) all the foramens present in sarcopterygians (for example, *Eusthenopteron*, Figure 3) disappeared, except for the entepicondylar foramen (Clack, 2012). During the transformation in basal tetrapods from an «L» shaped humerus, typical of *Acanthostega* and *Icthyostega*, to the more stylised humerus present in later tetrapods, such as *Seymouria* (Figure 3), blood vessels stopped running through bone channels to free themselves by running through soft tissue. This would have meant greater irrigation because the blood flow would no longer have been limited by the bone space within the channels, and would thus allow the increased development of the appendicular musculature required for more active terrestrial locomotion.

Therefore, we can deduce that the entepicondylar foramen appeared in the first tetrapods as a channel that allowed the median nerve and the brachial artery to pass through the ventral crest of the humerus. Later on, in the more derived forms present in the Carboniferous period, this channel changed its orientation requiring the nerve and vessel path to also change from ventral-only to a dorsoventral route. This path change happened in response to the improved locomotion necessary in the new terrestrial environment. However, it is important to underline the fact that the median nerve arises from the brachial plexus, and that its appearance in parallel to the cervical region probably occurred as an evolutionary innovation among tetrapods.

AN EVOLUTIONARY INNOVATION IN TETRAPODS

Although the transformation of fins into legs was key to the conquest of the terrestrial environment by vertebrates, the first tetrapods not only had to transform their locomotor apparatus, but they also had to change their respiratory and auditory systems in order to cope with the physical and functional challenges that their new environment entailed. This led to the radical transformation of the skeleton of a group of sarcopterygians (see *Panderichthys* in Figure 3), as had previously happened with the loss of the caudal fin or the appearance of the shoulder girdle. The latter resulted from the disappearance of a series of bones and the separation of others that would go on to become part of the shoulder girdle of the first tetrapods such as *Acanthostega* (Figure 3). This reorganisation of the axial skeleton required the acquisition of a well-defined cervical region.

Recently it has been proposed that the appearance of the brachial plexus was an evolutionary innovation in tetrapods (Hirasawa & Kuratani, 2018), which was most likely associated with the appearance of this well-defined cervical region. In elasmobranch fish – such as sharks and rays – the pectoral fin muscles are innervated directly by branches of the spinal nerves. These nerves are poorly developed (Figure 5, above) although they may present anastomosis (the loose union of nerves). In both actinopterygian fish – trout, salmon, etc. – and in non-tetrapod sarcopterygians, the muscles of the pectoral fins are innervated by nerves that form plexuses (Figure 5, middle). However, the muscles of the anterior limbs of tetrapods are innervated by, at most, seven nerves. In tetrapods, the brachial plexus typically consists of a set of spinal nerves around the cervicothoracic boundary of the axial system and most of the limb muscles are innervated by nerve fibres comprising two or more plexus roots (Hirasawa & Kuratani, 2018). This structure is exclusive to tetrapods, suggesting that the brachial plexus was an evolutionary novelty of the clade.

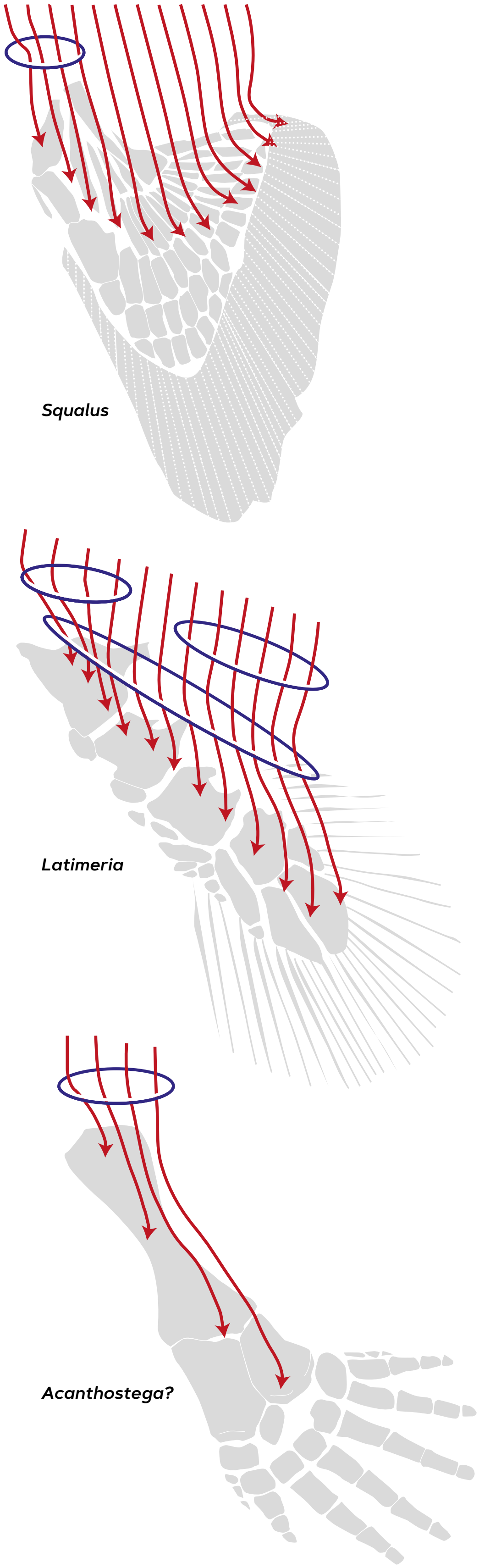

Figure 5. Origin of the brachial plexus as an evolutionary innovation in tetrapods. The image at the top shows the pectoral fin of an elasmobranch fish, showing the nerves (red arrows) and some anastomosis –the loose union of nerves– (circled). In the centre, pectoral fin of a lobed-fin sarcopterygian fish with extensive anastomosis. The image at the bottom shows the innervation pattern of a basal tetrapod (here hypothetically representing *Acanthostega*) which shows the appearance of the brachial plexus and its distal and proximal branching (see text for more detail).

SOURCE: Modified from Hirasawa & Kuratani (2018).

Fürbringer (1888) proposed that most of the muscles of the proximal ends of tetrapod limbs (near the bone insertion point) are innervated by the anterior root (preaxial) nerves of the brachial plexus, while most of the distal-end muscles are innervated by the posterior root (postaxial) nerves. He also noted that the appendage width had considerably narrowed as the first tetrapods appeared. Thus, Fürbringer concluded that the limb nerves had become rearranged during the evolution of the first tetrapods and that this originated in the innervation pattern in the brachial plexus changing from an antero-posterior (front to back) to a proximal-distal (top to bottom) one. This is consistent with the hypothesis that the main axis of the skeletal elements had changed during the during the fin-to-limb transition (Shubin & Alberch, 1986).

Although this change in innervation pattern from the antero-posterior axis to a proximal-distal has not yet been explicitly mentioned, it must be related to the migration of the median nerve path from a ventral position to a dorsal-ventral one (Figure 4) because the lower end of the humerus dropped as terrestrial locomotion efficiency improved. Likewise, this main axis of the limb and innervation change would also explain the conservation of the entepicondylar foramen only in the humerus and not in the remaining bone elements present in sarcopterygians.

«Atavisms show the importance of knowing the history of the different groups of organisms to understand the origin of current diversity»

In summary, it is relatively clear that the entepicondylar foramen appeared in tetrapodomorphic sarcopterygian fish with a ventral orientation and later this became more evident in *Acantosthega* and subsequent Carboniferous tetrapod forms. In the latter it emerged as a structure associated with the appearance of the cervical brachial plexus with a dorsoventral orientation as a consequence of a drop of the lower end of the humerus. This can be interpreted as an adaptation to improve terrestrial locomotion efficiency by increasing stride length, which would require greater innervation.

HYPOTHESIS ON THE EVOLUTION OF THE ENTEPICONDYLAR FORAMEN IN AMNIOTES

Different hypotheses (based on functional or merely constructive arguments) have been proposed to explain the subsequent evolution of the entepicondylar foramen in amniotes and their presence or absence, especially in mammals. However, none of these explain the pattern of appearance and disappearance of this foramen observed in different groups of current and extinct organisms.

Some of these hypotheses propose that it has a function in protecting a) the brachial artery while it contracts during flexion and extension movements (Ruge, 1884), b) the artery and nerve against blows or external pressures (Tiedemann, 1818), or c) the brachial artery and the median nerve during forearm flexion (Huntington, 1918). However, there is considerable disagreement among specialists in this field and other authors have rejected all of these theories (see Landry, 1958; Ruge, 1884). Other hypotheses propose purely constructional roles for the presence or absence of the foramen; for instance the presence of the foramen would be favoured in humeri with wider distal-end bases and its absence favoured in humeri with narrower bases (Meckel, 1825). Similarly, the increased pronator teres muscle insertion area in humans would explain the absence of the foramen in our species (Ruge, 1884). However, these hypotheses have also been rejected by some (Stromer, 1902).

To date the most accepted hypothesis to explain the presence or absence of the foramen is that of Landry (1958) who proposed that the entepicondylar foramen would serve to prevent the nerve from dropping from the armpit through the elbow joint. The armpit is deep in quadrupeds and encloses most of the humerus, and so the skin on the elbow does not hold the nerve in place. While the radial and ulnar nerves pass behind the humerus before entering the forearm, the median nerve extensively branches and so is the only filiform structure of the arm that must be retained at the level of the elbow joint.

Landry (1958) hypothesised that mammals such as ungulates which are adapted for running, lost the entepicondylar foramen not because the supine function (allowing upward forearm palmar rotation) disappeared, but because the humeral abduction function (allowing the humerus to move away from the body) was lost. Paradoxically, anthropoid primates (including human beings) seem to have lost the entepicondylar foramen precisely because of their great capacity to abduct their arms. To account for this, Landry (1958) proposed that the skin over the elbow joint has adjusted to slow the fall of the median nerve.

However, although Landry's hypothesis (1958) may explain the consistent absence of the foramen in all the representatives of the same order, it does not explain why it varies in other orders in the same family or genus. Apparently, the presence of the entepicondylar foramen is ancestral in mammals because it is also present in non-mammalian synapsids, Mesozoic mammals, and monotremes, also extending to different groups of reptiles such as notosaurs and some lepidosaurs.

«Some vestigial organs may eventually disappear because of pernicious effects associated with the organ or structure»

CONCLUSION

The evolution of the entepicondylar foramen in amniotes remains an enigma that is far from resolved because of its apparently random pattern of appearance and disappearance in the tree of life. This could indicate that it is actually a vestigial organ related to the acquisition of the first dactyl limbs by tetrapods at the end of the Devonian and early Carboniferous periods. These limbs required innervation by a main nerve which was achieved by median nerve innervation after the brachial plexus innovation and the first appearance of a well-defined cervical region. The functional demands of this new mode of locomotion led to reorganisation of the humerus (a torsion), causing the median nerve and brachial artery to change to a dorsal-ventral position, facilitated by the presence of the entepicondylar foramen.

Explanations for the functionality of the entepicondylar foramen proposed for more than a century by different authors, from Home (1814) to Landry (1958), are doubtful because we lack clear evidence for an unequivocal pattern for its presence or absence. Randomness in the appearance or disappearance of a feature at different taxonomic scales – from order to genus – along with the loss of its ancestral function, are features which define vestigial organs. Some vestigial organs acquire new functions different to their original ones but others may eventually disappear because of pernicious effects associated with the organ or structure – the ultimate metabolic cost of producing a useless or potentially detrimental feature. The compressive neuropathy of the median nerve and blood vessels generated by supracondylar syndrome could perhaps have such an effect and would therefore become target for natural selection to discard.

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