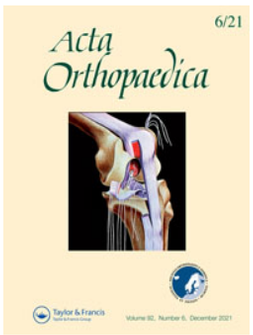

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Hypothesis

Anterior knee pain in the young patient—what causes the pain?

"Neural model"

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ABSTRACT Anterior knee pain in young patients is the commonest type of knee disorder in clinical practice. However, the pathogenesis of this condition is unknown. On the basis of our recent research, we suggest a "neural model". In our view, hyperinnervation in the lateral retinaculum, mainly nociceptive substance P-positive nerves induced by the release of neural growth factor, is involved in the pathogenesis of anterior knee pain. We hypothesize that periodic short episodes of ischemia may trigger neural proliferation.

A criticism of the patellofemoral malalignment theory

In the 1970's, anterior knee pain (AKP) was ascribed to the presence of patellofemoral malalignment (PFM) (Hughston 1968, Merchant et al. 1974, Merchant and Mercer 1974, Ficat et al. 1975, Insall 1979). We define PFM as an abnormality of patellar tracking consisting of lateral displacement or lateral tilt of the patella, or both, in extension, that reduces in flexion (Figure 1) (Insall 1979). For many years, the PFM theory was widely accepted as an explanation for the genesis of AKP. Currently, however, it is questioned by many and one reason is the poor relationship between symptoms and malalignment (Figures 2 and 3).

We believe that PFM is a necessary but not the sole cause of pain—i.e., it produces a "favorable environment" and neural damage is the "provoking factor" or "triggering factor" (Sanchis-Alfonso et al. 1998). Overload or overuse may be another "triggering factor". In our surgical experience, we have found that in patients with symptoms in both knees, when the more symptomatic knee is operated on, the symptoms in the contralateral less symptomatic knee, disappear or decrease in many cases, perhaps because we have reduced the load on this knee. However, some of the patients who have PFM may be asymptomatic because they have adequate dynamic control of patellar tracking during activities.

The great number of surgical techniques used to treat patients with AKP suggests a lack of understanding of the pathophysiology, which is another reason against the universal acceptance of the PFM theory. Our studies have centered on pathophysiology (Sanchis-Alfonso et al. 1998, 2001, Sanchis-Alfonso and Roselló-Sastre, 1998, 2000). It is well-known that pain in patients with PFM can not be ascribed to a single factor, but to several. The infrapatellar fat pad, subchondral bone, the quadriceps tendon, patellar ligament, synovium, the medial and lateral retinaculum all have a rich nerve supply and these structures, individually or in combination, may cause pain (Fulkerson 1983, Fulkerson et al. 1985, Wojtys et al. 1990, Dye et al. 1998, 1999, Witonski and Wagrowska-Danielewicz, 1999, Sanchis-Alfonso et al. 1999, Biedert and Sanchis-Alfonso 2002).

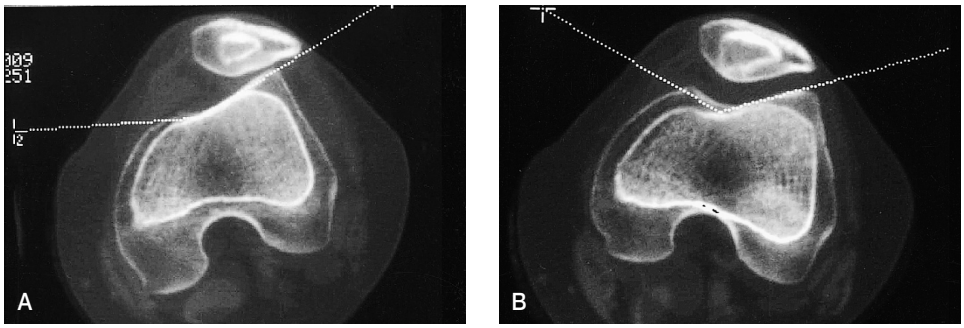


Figure 1. An 18-year-old woman, who was referred because of anterior knee pain and patellar instability of her left knee. She had recurrent hemarthroses and severe giving-way with falling to the ground during activities of daily living. CT shows the patella lateralized at 0°—PFM type 1—(A), and relocated in the femoral trochlea at 30° (B) (reproduced with permission from Sanchis-Alfonso et al. 1994).

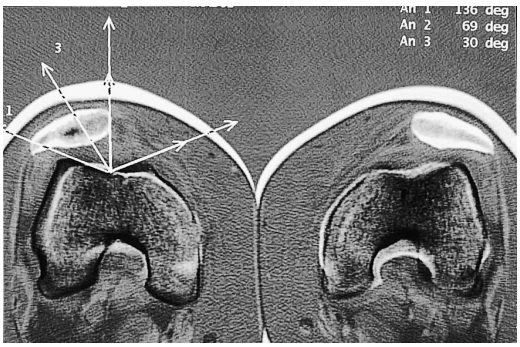


Figure 2. CT at 0° of knee flexion in a patient with AKP in the right knee, while the left knee was asymptomatic. However, in both knees, the PFM is symmetric (reproduced with permission from Sanchis-Alfonso 2003).

"Neural model" in the genesis of anterŠr knee pain in patients with PFM

In previous papers (Sanchis-Alfonso et al. 1998, 2001, Sanchis-Alfonso and Roselló-Sastre 1998, 2000), we described the histological changes in the lateral retinaculum of patients with painful PFM. The findings in our studies strongly support the view that in some patients with PFM, pain develops in the lateral retinaculum. However, this does not preclude the possibility of pain developing in other anatomical structures.

In the lateral retinaculum of patients with painful PFM, we found nerve ingrowth, consisting of myelinated and unmyelinated nerve fibers with a

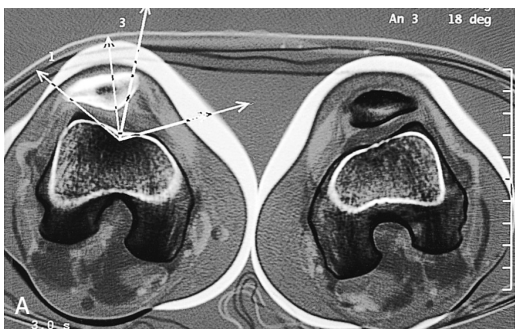
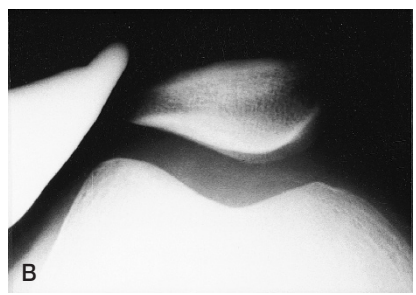
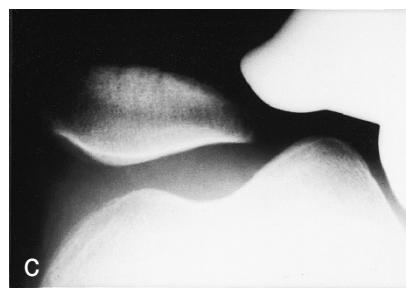


Figure 3. (A) CT at 0° in a patient with severe AKP in the left knee. This knee, which was operated on with an Insall's realignment 2 years ago, caused severe symptoms despite correct patellofemoral congruence. The right knee was asymptomatic despite the presence of PFM. In this case, an axial stress radiograph of the left knee (C) showed an iatrogenic medial subluxation of the patella. Note the axial stress radiograph of the right knee (B). We therefore conclude that malalignment, even of significant degree, may remain dormant throughout an individual's life, whereas in other cases it is associated with symptoms (reproduced with permission from Sanchis-Alfonso 2003).





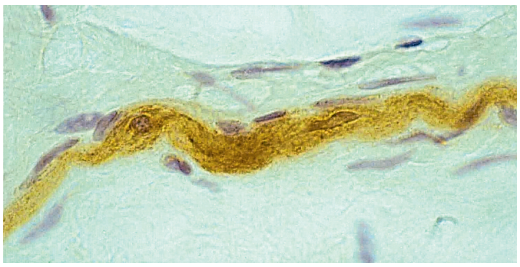


Figure 4. Substance P (SP) is seen as a granular pattern in nerve fibers. (hematoxylin counterstained, original magnification ×1000) (reproduced with permission from Sanchis-Alfonso and Roselló-Sastre 2000).

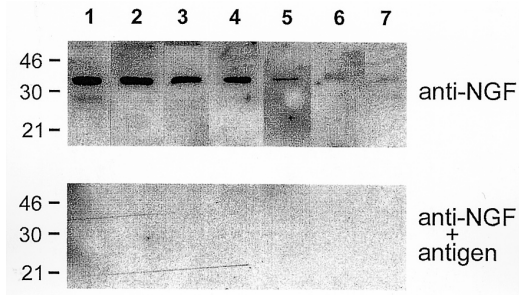


Figure 5. Immunoblot detection of NGF, showing a thick band located at the level of the NGF precursor in the pain group (cases 1 to 4) and absence or a very thin band in the group of patients with instability as their main symptom (cases 5–7). The numbers at the left indicate molecular mass in kD.

predominant nociceptive component—i.e., substance P-immunoreactive nerves (Figure 4) (Sanchis-Alfonso and Roselló-Sastre 2000). Substance P is the main nociceptive neurotransmitter. This fact is not new. Indeed, hyperinnervation has been implicated in the pathophysiology of pain in other orthopedic conditions, such as chronic back pain and jumper's knee (Coppes et al. 1997, Freemont et al. 1997, Sanchis-Alfonso et al. 1999).

We have shown that such hyperinnervation is associated with the release of neural growth factor (NGF), a polypeptide that stimulates axonogenesis (Sanchis-Alfonso and Roselló-Sastre 2000, Sanchis-Alfonso et al. 2001) (Figure 5). NGF has two biologically active precursors: one of about 34 kD of molecular weight, and the other of 27 kD (Dicou et al. 1997). We found the 34 kD precursor in the lateral retinaculum of patients with painful PFM, which means that the nerve fibers of the lateral retinaculum must still be in a proliferative phase (Sanchis-Alfonso et al. 2001).

This nerve ingrowth was mostly located in and around the vessels (Sanchis-Alfonso et al. 1998) (Figure 6). This fact is not new either. Indeed, vascular innervation has been implicated in the pathophysiology of pain in other orthopedic conditions, such as osteoid osteoma (Hasegawa et al. 1993), and the lumbar facet syndrome (Grönblad et al. 1991). Thus, we have seen S-100 positive fibers in the adventitia and the muscular layer of medium and small arteries (Figure 6) in the lateral retinaculum of patients with painful PFM. S-100 protein is a good marker when studying nerves, because it can identify Schwann cells that accompany the axons in the myelinated nerves. It is well-known that myelinated fibers lose their myelin sheath before entering the muscular arterial wall, but this was not so in our patients. Since we used S-100 for immunostaining of only the myelinated fibers, and the myelin sheath is said to be lost before

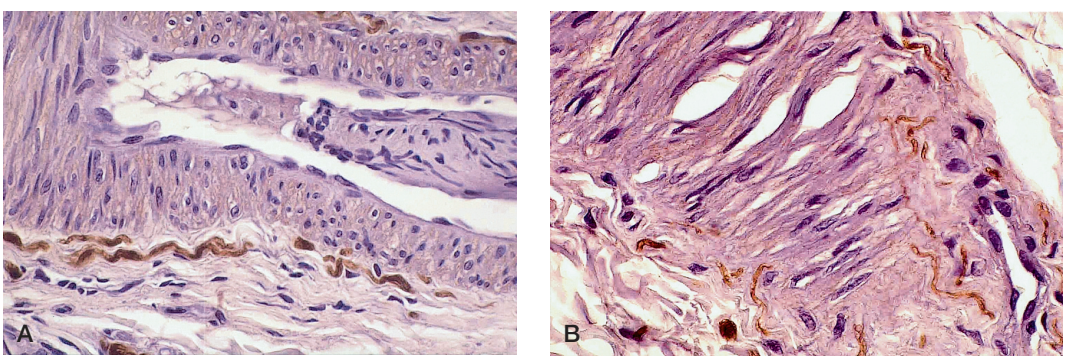


Figure 6. An unusual finding is present in our cases: a rich vascular innervation consisting of tiny myelinated fibers that, enter the outer muscular layer from the arterial adventitia, and form a necklace. Transverse (A) and tangential sections (B) (S-100 protein, Magnification ×400) (reproduced with permission from Sanchis-Alfonso et al. 1998).

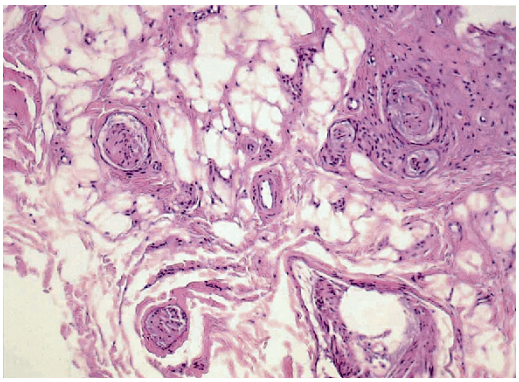


Figure 7. Nerve fibers mimicking amputation neuroma (Hematoxylin-eosin, magnification ×100) (reproduced with permission from Sanchis-Alfonso et al. 1998).

the nerve enters the muscular arterial wall, we were surprised to find S-100-positive fibers in the muscular layer of medium and small arteries. This would indicate an increase in vascular innervation. As Byers suggested in 1968, pain can be generated and transmitted by vascular pressure-sensitive autonomic nerves.

Chronic lateral subluxation of the patella may cause adaptive shortening of the lateral retinaculum (Fulkerson 1983). During flexion of the knee, the patella migrates medially into the femoral trochlea (Sanchis-Alfonso et al. 1994). This produces recurrent stretching on the shortened lateral retinaculum that may cause secondary changes in the nerve, such as neuromas (Figure 7) and neural myxoid degeneration (Fulkerson 1983, Fulkerson et al. 1985). As for neuromas, we found a clear relationship between neuromas and pain; as regards neural myxoid degeneration, we detected no relationship between it and pain (Sanchis-Alfonso et al. 1998).

We believe that hypoxia may play a role in the genesis of AKP in certain patients. It has been reported that hypoxia of the peripheral nervous system can trigger synthesis by neurons (Calzà et al. 2001) or other cells (Lee et al. 1996, Abe et al. 1997, Woolf et al. 1997) of vascular endothelial growth factor (VEGF) and NGF. VEGF acts as a hypoxia-inducible angiogenic factor that causes hypervascularization (Shweiki et al. 1992, Minchenko et al. 1994, Liu et al. 1995, Jackson et al. 1997, Berse et al. 1999, Hayashi et al. 1999, Richard et al. 1999, Steinbrech et al. 1999, Marti et al. 2000). In a preliminary study, we found that patients with painful PFM had, VEGF (Figure 8) in stromal fibroblasts, vessel walls, endothelial cells and large nerve fibers, in equal amounts in axons and in perineurum (Sanchis-Alfonso 2003). Moreover, we also noted an increase in the number of vessels in the lateral retinaculum of patients with painful PFM and a still greater increase in the group with severe pain, than in the groups with moderate or slight pain (unpublished observations). NGF stimulates neural sprouting and hastens neural proliferation in vessel walls (Isaacson and Crutcher 1995, Kawaja 1998). This is just like the pattern of hyperinnervation that is seen in the lateral retinaculum of patients with painful PFM (Sanchis-Alfonso et al. 1998). Finally, we found histological changes associated with ischemia, such as arterial vessels with obliterated lumina and thick muscular walls, infarcted foci of the connective tissue, fibroblasts showing autophagic intracy-

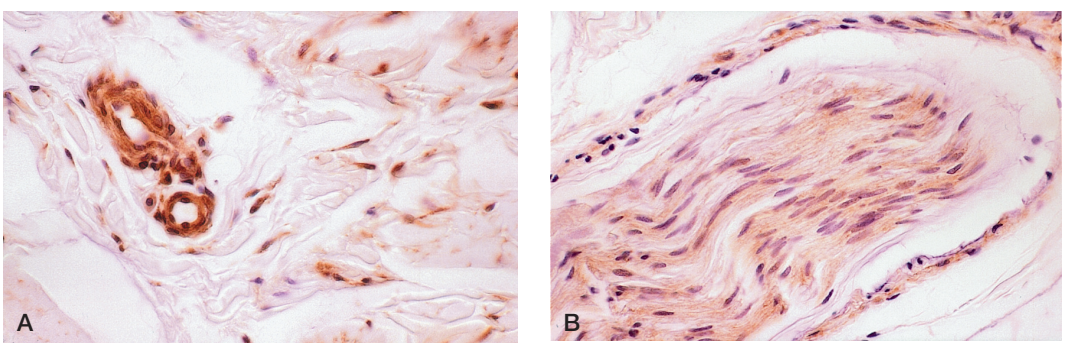


Figure 8. (A) The vascular endothelial growth factor (VEGF) is present in small vessels (wall and endothelium) and perivascular fibroblasts. (B) Some cases have VEGF expression even in the perineural shift and inside the axons. (VEGF, hematoxylin counterstained, magnification ×400) (reproduced with permission from Sanchis-Alfonso 2003).

toplasmic vacuoles, neoangiogenesis, and changes in nerves, such as neural sprouting (Richardson and DeGirolami 1995, Society for Ultrastructural Pathology 1995, Kraushaar and Nirschl 1999, Sanchis-Alfonso 2003).

Our histological findings (Sanchis-Alfonso et al. 1998, Sanchis-Alfonso and Roselló-Sastre 2000) accord with those of Messner et al. (1999) in experimentally-induced Achilles tendinosis. The results of this study lend credence to the validity of our histological observations. The histological evaluation of tendinosis showed hyperinnervation, hypervascularization and an increase in immunoreactivity for substance P. It should be kept in mind that Achilles tendinosis is due to repetitive overloading of the Achilles tendon—i.e., microtraumas—and is related to the duration and intensity of various activities, a mechanism similar to symptomatic PFM.

In conclusion, we suggest that brief episodes of tissular ischemia, perhaps due to vascular torsion (Sanchis-Alfonso et al. 2001), and secondary to medial traction on a retracted lateral retinaculum from PFM, may trigger the release of NGF and VEGF. When NGF is present in the tissues, it induces hyperinnervation, attraction of mastocytes, and the release of substance P by free nerve endings (Malcangio et al. 1997, Sanchis-Alfonso and Roselló-Sastre 2000). Substance P stimulates mastocytes, which can liberate nonneurogenic pain mediators, such as histamine (Grönblad et al. 1991). Mastocytes can also release NGF (Nilsson et al. 1997). Substance P increases the release of prostaglandin E2, which stimulates nociceptors (Ahmed et al. 1998). Substance P and prostaglandin E also induce bone resorption, which can explain the osteoporosis found in some cases of AKP (Sherman and Chole 1995). Finally, substance P and VEGF stimulate endothelial cell proliferation and migration, which are essential for the development of a new vascular network that may promote tissue repair—for example, healing of microtears in the lateral retinaculum, but indirectly maintain the vicious cycle (Ashton et al. 1994). Obviously, further studies, now being pursued, are needed to support the ischemia hypothesis.

Future directŠns

If the "neural model" of AKP proves to have some validity, it would lead in many cases to therapeutic recommendations to alleviate pain more effectively and safely than the attempts to correct "malalignment". Thus, a pharmaceutical approach, such as drug inhibitors of the synthesis and release of substance P, such as capsaicin, or substance P receptor antagonists, or drug inhibitors of angiogenesis—e.g., the newer cyclooxygenase-2 (COX-2) inhibitor anti-inflammatory drugs—could be of special interest in the treatment of pain in these patients. Finally, if we can show that regional anoxia plays a key role in the genesis of pain, topical peripheral vasorelaxant drugs (for preventing vasospasm) could also be of particular interest in the treatment of pain in these patients.

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No competing interests declared.

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