Orthopedic aspects of familial insensitivity to pain due to a novel nerve growth factor beta mutation

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Background  Congenital insensitivity to pain is a rare hereditary sensory neuropathy.

Patients  We present 6 patients from a family with a mutation in the nerve growth factor beta gene (NGFB).

Results  3 patients were homozygous with a mutilating arthropathy starting early in life, and 3 patients were presumably heterozygous with a milder course starting in adulthood. All patients had normal mental abilities. In addition to absence of deep pain, the patients had impaired temperature sensation, but no autonomic deficiency. Sural nerve biopsies showed a moderate loss of A-δ fibres and a severe reduction in C fibers. Clinically, the disorder most often affected the lower extremities, with an insidious progressive joint swelling or a painless fracture, but the spine could also be involved with gross and unstable spondylolisthesis. Fracture healing was uneventful, but the arthropathy was progressive, eventually resulting in gross deformity and instability. When treating patients with congenital disorders such as this one, it is important to consider the slowly progressive nature of the disorder, and the orthopedic operations should therefore be planned from a long-term standpoint. Arthrodesis, limb lengthening and spinal decompression or fusion are the only elective procedures that seem reasonable. To delay the development of neuropathic arthropathy, patient education is essential but difficult in the very young.

Interpretation  The different expression between homo- and heterozygous subjects and the central role of nerve growth factor make this disease an interesting model system for studies of disease mechanisms and the molecular background to pain.

Hereditary conditions affecting pain are not only interesting per se; they also provide a tool for the study of basic disease mechanisms. Moreover, well-characterized phenotypes are necessary for further genetic classification of hereditary neuropathies. Congenital insensitivity to pain is a group of rare hereditary sensory and autonomic neuropathies (HSAN). These patients lack deep pain and develop a plethora of bone and joint complications. Depending on mode of inheritance, neuropathology and clinical symptoms, they have been classified into 5 types (Dyck et al. 1983). We describe the orthopedic manifestations in a family with neuropathy probably best classified as HSAN type V, caused by a recently identified mutation in the nerve growth factor beta gene (Einarsdottir et al. 2004). This is interesting, as HSAN IV has also been associated with a nerve growth factor receptor mutation giving a different phenotype. Our patients were not mentally retarded, and had a different clinical presentation to that of most patients described in a recent review of the orthopedic manifestations of HSAN (Bar-On et al. 2002). In this paper, we describe the musculoskeletal phenotype of the nerve growth factor beta mutation.

Patients and methods

We studied the clinical presentation of congenital insensitivity to pain in a large family from Vittangi, a remote rural district in northern Sweden. The family originally came from southern Finland and moved to Sweden in the 16th century. As in
other isolated remote communities, consanguinity was common. Our study includes 6 patients, 3 with presentation of symptoms in childhood and 3 in adulthood. 4 patients were examined clinically, concentrating on the orthopedic manifestations and neurological disturbances. 2 patients were already dead and only clinical data were available. Routine hematological tests were taken to exclude other causes of polyneuropathy.

Nerve conduction, electromyography (EMG), sympathetic skin response (SSR), and quantitative sensory testing for vibration and temperature were performed. Nerve biopsies from the sural nerve were sampled from behind the lateral malleolus. The samples were examined by light and electron microscopy. Blood samples were taken for genetic analysis.

Results

The most severely affected patients were closely related to each other, with consanguineous parents (Figure 1). Symptoms appeared either in early childhood (3 homozygous children) or in adult life (3 presumably heterozygous subjects). The symptoms were more severe in the early cases, with painless fractures and joint destruction (Figures 2 and 3). 2 patients had problems with joint infections. One young boy developed a spinal deformity (Figure 4). Details of the 6 patients are shown in the Table.

Clinical examination of the 4 living patients revealed normal mental development, normal reflexes and no muscular atrophy or ataxia. They responded normally to touch, pressure and vibration. Sweating was normal and they had no signs of autonomic defects. All 4 had diminished sensation for deep pain and temperature modalities.
Biochemical profiles, nerve conduction velocities and EMG were essentially normal. Temperature threshold was increased in all 4 cases. Sym pathetic skin response was absent in 2 patients. Morphometric analysis of the nerve biopsies confirmed a moderate loss of thin myelinated fibers (A-δ) and a severe loss of unmyelinated fibers (C).

Using a model of recessive inheritance for the 3 severe cases, we identified an 8.3-Mb region on chromosome 1p11.2-p13.2 shared by the affected individuals in the family. We found a mutation in the coding region of the nerve growth factor.
beta (NGFB) gene specific for the disease haplotype. Our analysis revealed a common haplotype for which all severely affected individuals were homozygous. This disease haplotype has also been seen in unaffected or mildly affected individuals, but only in heterozygous form (Einarsdottir et al. 2004).

Discussion

The previously used term “congenital indifference to pain” is somewhat misleading, since the HSAN disease does not seem to be a disturbed perception or reaction to pain, but rather due to a congenital peripheral nerve dystrophy (Dyck et al. 1983, Landrieu et al. 1990). The presence of peripheral neuropathy has become a criterion for diagnosis of congenital insensitivity to pain, distinguishing it from congenital indifference to pain (Dyck et al. 1983). The latter term is now reserved for conditions with a defect in the affective-motivational components of pain perception, but with normal peripheral sensory responses (Nagasako et al. 2003). The relatively few known cases of congenital insensitivity to pain and the wide variety of the clinical manifestations—as well as the course of the disease—have led to several classification systems, of which the HSAN I-V system is commonly used (Dyck et al. 1983). Most previously reported patients with congenital insensitivity to pain have been severely affected by their disease, with mental retardation and self-mutilation. Our patients have a different clinical presentation. Although pain perception is essential for survival, it is obviously possible to live a long and active life with the milder form of this disease, and the functional prognosis for the younger patients has improved with supportive treatment. In the mild form of the disease appearing in adulthood, often one of the distal joints was first affected with symptomatic instability. It is also interesting to note that these presumably heterozygous patients had a clinical presentation that resembled primary generalized osteoarthritis, and would probably have been considered as such if they had occurred as isolated cases. This illustrates the importance of neuromuscular mechanisms in the pathogenesis of osteoarthritis (Hurley 2003).

Bar-On et al. (2002) classified congenital insensitivity to pain of all types into 3 groups according to the musculoskeletal problems. We did not find this classification to be clinically helpful in our patients. In general, it seems that our cases had a less destructive course, although fractures with avascular necrosis and growth disturbances were also common in our patients with childhood onset. Two other differences were that our patients had onset of symptoms at different times and that all our patients were mentally normal. We could not classify patients with presentation in adulthood according to the Bar-On scheme. Furthermore, we found a spinal deformity with impeding paresis while Bar-On’s patients had no spinal problems. After the first lumbar fusion, our patient developed a spondylolisthesis also above the earlier operated level, and a second fusion was performed with good result. This emphasizes the importance of a close follow-up of the patients with neurogenic spinal instability.
In general, the treatment was demanding with many surgical failures. Without sensory feedback, the young patients were poorly motivated to wear a brace that only restricted their activity, without any functional benefits as long as the extremity was stable. Thus, one essential but difficult issue is patient education. One of the young patient’s party tricks was to jump down on her kneecaps because she—and her friends—enjoyed the funny sound when the patellae hit the floor. The child has to learn what normally causes pain, and avoidance of such destructive activities should be encouraged and rewarded. A personal assistant or a targeted education program may delay the progression of joint disease until the patient adheres to ordinances.

Surgery for these young patients requires planning, because of the progressive and lifelong nature of the disease. Deformity and instability are the main problems. Arthrodesis, corrective osteotomy and limb lengthening are the most commonly indicated operations (Ueharan et al. 2001). It is essential to perform the procedure at an appropriate age because of the risk of growth disturbances, particularly since our patients were strikingly shorter than their healthy relatives—perhaps due to the multiple injuries to the physes. The treatment of patients at adult age consists mainly of different kinds of orthosis, since the patient’s main problems are the deformity and not pain.

Author contributions
JM did the field work and data collection and prepared a preliminary manuscript. GT, GS and OS analyzed data and participated in the writing.

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