Peripheral Arthropathy in Hereditary Sensory and Autonomic Neuropathy Types III and IV

David S. Feldman, MD, David E. Ruchelsman, MD,† Daniel B. Spencer, BS,* Joseph J. Straight, MD,* Mark E. Schweitzer, MD,‡ and Felicia B. Axelrod, MD§*

Background: To determine the features of the underlying destructive arthropathy in the peripheral joints of children with hereditary sensory and autonomic neuropathy (HSAN) type III and to compare and contrast this to the arthropathy noted in HSAN type IV, as both groups experience decreased pain perception.

Methods: From a database of 547 patients with HSAN type III and 32 patients with HSAN type IV, we performed a retrospective chart review and radiographic analysis of all patients who presented with joint swelling and deformity. Underlying joint pathology was classified as either osteonecrosis or Charcot arthropathy.

Results: In the HSAN type III population, 44 (8%; 22 males and 22 females) of the 547 patients had clinical evidence of arthropathy. In 42 patients, 48 joints demonstrated radiographic evidence of osteonecrosis; 45 (94%) of the 48 joints with osteonecrosis occurred in the lower extremity. In each case of osteonecrosis of the knee (n = 19), isolated involvement of the lateral distal femoral condyle was seen consisting of varying sizes of posterolateral osteochondral fragmentation. In the 32 patients comprising the HSAN type IV population, 18 (56%) were found to have radiographic findings consistent with Charcot arthropathy in a total of 30 affected joints. One patient demonstrated Charcot arthropathy of the spine and subsequent progressive spondylolisthesis. Nine patients (12 joints) also demonstrated osteomyelitis.

Conclusions: In patients with HSAN type III, osteonecrosis is the initial lesion preceding destructive arthropathy. Osteonecrosis and osteochondral fragmentation were always isolated at the lateral distal femoral condyle in the knee. This pathology may be amenable to surgical reconstruction and fixation to stabilize the knee and prevent further degeneration. Hereditary sensory and autonomic neuropathy type IV was most commonly associated with Charcot arthropathy or joint subluxation and dislocation. Late secondary changes at the articular surface may make radiographic distinction difficult. Charcot arthropathy affected both sides of the involved joint with evidence of collapse and fragmentation. With osteonecrosis, the articular process was found to be more focal.

Level of Evidence: Prognostic level II.

*Division of Pediatric Orthopaedic Surgery, †Department of Orthopaedic Surgery, and ‡Radiology Department, New York University Hospital for Joint Diseases, and §Dysautonomia Treatment and Evaluation Center, Department of Pediatrics, New York University Medical Center, New York, NY.

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Reprints: David S. Feldman, MD, Division of Pediatric Orthopaedic Surgery, NYU Hospital for Joint Diseases, 301 East 17th St, New York, NY 10003. E-mail: David.Feldman@med.nyu.edu.

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Disease states involving the central and peripheral nervous systems, such as diabetes mellitus, tabes dorsalis, syringomyelia, leprosy, and congenital insensitivity to pain syndrome, have been associated with Charcot arthropathy, a progressive painless deterioration of articular surfaces leading to joint destruction and deformity.[1] The congenital insensitivity to pain syndromes has been differentiated into the rare hereditary sensory and autonomic neuropathies (HSANs).[2–8] Both HSAN types III and IV are inherited as autosomal recessive disorders. Hereditary sensory and autonomic neuropathy type III remains the most common of this group of complex disorders affecting 27 of 100,000 live births;[9] HSAN type IV is the second most common HSAN, with only several hundred cases reported in the literature to date.

Hereditary sensory and autonomic neuropathy types III and IV have both been associated with the development of arthropathies.[2,6] Anatomic and physiological studies have demonstrated the underlying neuropathology responsible for the clinical manifestations seen in these 2 patient populations. Type III patients exhibit a marked decrease in the unmyelinated fibers controlling pain and temperature and only a slight decrease in myelinated fibers controlling proprioception.[10,11] Type IV patients demonstrate a marked decrease in both myelinated and unmyelinated fibers.[6]

Orthopaedic manifestations of HSAN type III, which has also been termed familial dysautonomia and Riley-Day syndrome,[12] include spinal deformity,[13–17] increased rates of fractures,[18–20] osteopenia and osteoporosis[9], foot deformities,[18,19] tibial torsion,[19] and osteochondritis.[18,20] In addition, peripheral arthropathy presenting with joint swelling and instability is seen.[18–21] The underlying radiographic features of the associated joint deformity are not well defined in the literature. In 1967, Brunt[22] originally reported the radiographic evidence of Charcot arthropathy as a cause of joint deformity in children with HSAN type III. Mitnick et al[21] noted a high incidence of osteonecrosis in clinically involved joints.

Orthopaedic manifestations of HSAN type IV, also termed congenital insensitivity to pain with anhidrosis,[8] include fractures, joint dislocations, as well as Charcot arthropathy in the periphery and spine,[23–30] which may be complicated by superimposed osteomyelitis.

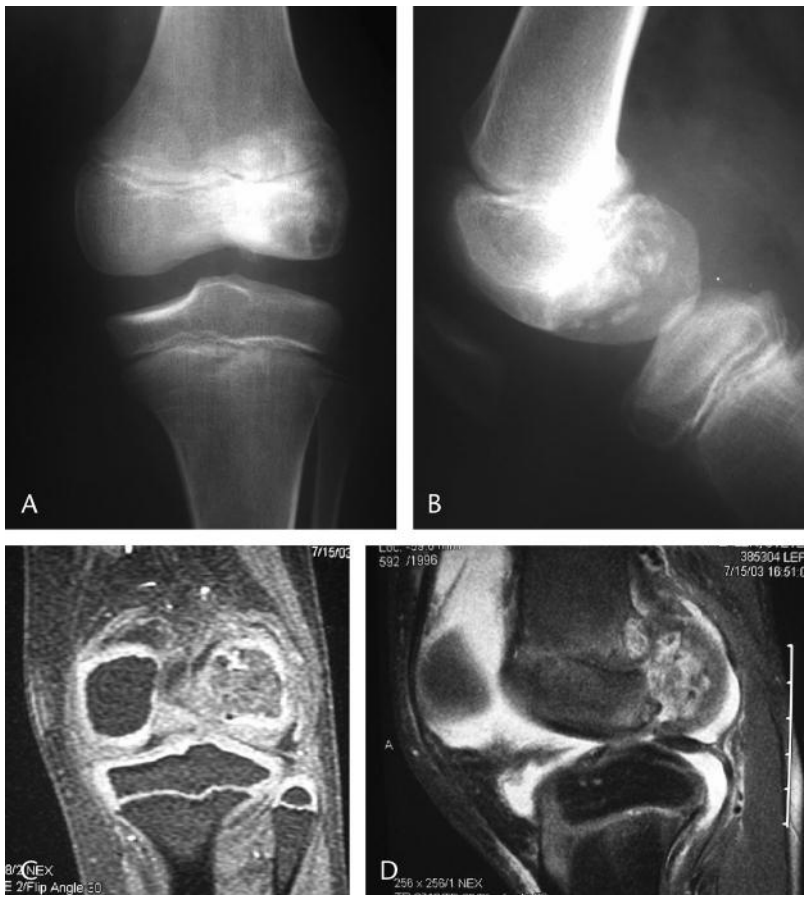

FIGURE 1. A–D, Radiographs and MRI of the knee in a patient with HSAN type III with osteonecrosis limited to the lateral femoral condyle.

The impact of peripheral arthropathy in both HSAN types is severe deformity and limitation of function. The purpose of this study was to determine the features of the underlying destructive arthropathy in the peripheral joints of children with HSAN type III and to compare and contrast this to the arthropathy noted in HSAN type IV. The study of these 2 disorders lends itself to an analysis of the radiographic and clinical features of the neuropathic arthropathies and potential treatment strategies.

METHODS

From a database at our medical center of 547 patients with HSAN type III and 32 patients with HSAN type IV, an institutional review board–approved retrospective review of patients who were referred to the first author (D.S.F.) for peripheral joint swelling and deformity was undertaken. The database is maintained by the Dysautonomia Treatment and Evaluation Center of the New York University Medical Center (director, senior author F.B.A.). This tertiary referral center is exclusively dedicated to the clinical care of children with and research for HSAN and other autonomic and sensory disorders. Our Division of Pediatric Orthopaedic Surgery works closely with the faculty of the Dysautonomia Treatment and Evaluation Center to provide care of the musculoskeletal manifestations of these rare disorders. Radiographic analysis of all clinically involved joints was performed by a senior pediatric orthopaedist to determine the etiology of the arthropathy.

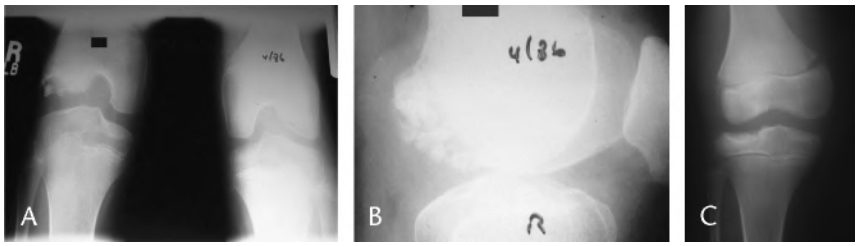

FIGURE 2. A and B, Appearance of osteonecrosis with posterolateral fragmentation in HSAN type III knee. C, Early Charcot arthropathy in HSAN type IV knee.

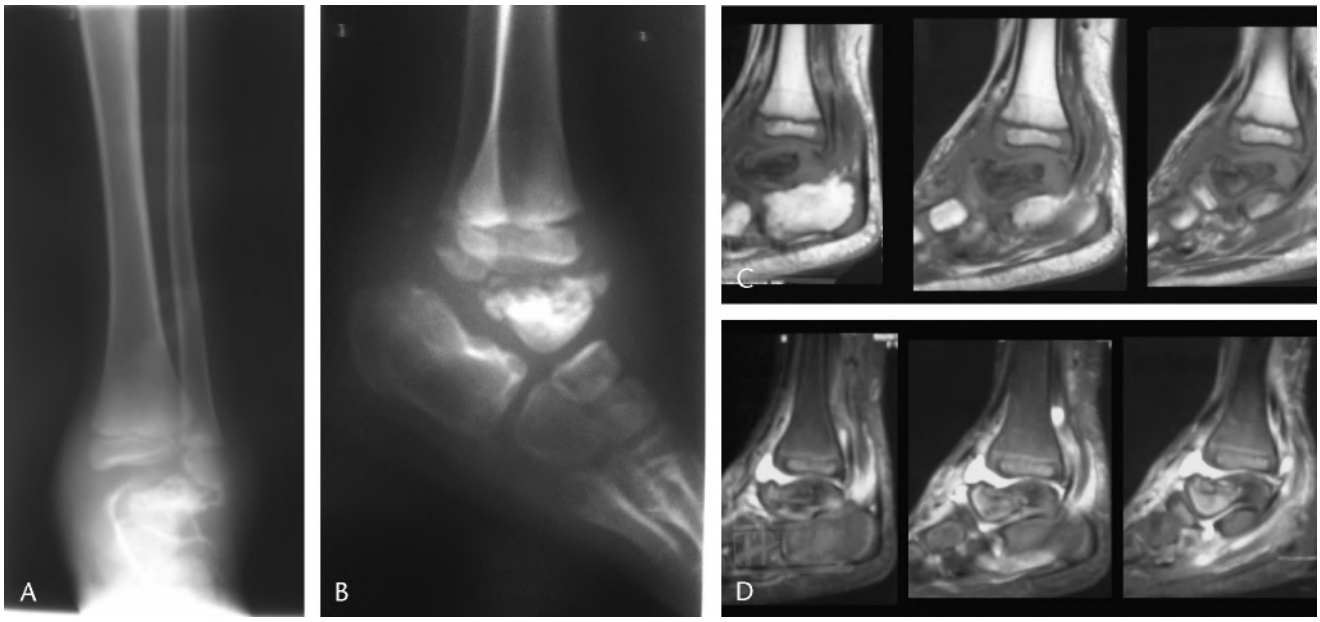

FIGURE 3. A and B, Osteonecrosis of the talus in a patient with HSAN type III. Radiographs reveal fragmentation, collapse, and sclerosis of the talus; the tibial plafond is intact. C and D, T1-weighted MRI image shows complete marrow replacement.

To verify the underlying cause of joint pathology, a senior faculty member of our institution's Division of Musculoskeletal Radiology was asked to review 26 randomly selected sets of radiographs of patients (13 from each cohort) while being blinded both to the hypothesis of the study and to the underlying diagnoses of the patients. Radiographic criteria for osteonecrosis were focal subchondral crescents, isolated condylar fragmentation, and the absence of kissing lesions. Criteria for neuropathic arthropathy were kissing articular irregularities and destruction with or without joint debris.

RESULTS

Forty-four (8%; 22 males and 22 females, 50 joints) of the 547 patients with HSAN type III had clinical evidence of peripheral joint involvement. In 42 patients, 48 joints demonstrated radiographic evidence of osteonecrosis, with 3 patients having more than 1 joint involved. The average age at the time of diagnosis of joint osteonecrosis was 15.2 years (range, 3–44 years). Forty-five (94%) of the 48 joints with osteonecrosis occurred in the lower extremity. Of the 48 involved joints, osteonecrosis was demonstrated 19 times (40%) in the knee (2 patients demonstrated bilateral osteonecrosis of the knee) and 13 times in the hip (27%). Two adult patients (2 joints) demonstrated evidence of secondary osteoarthritis. Osteonecrosis was seen in 5 patients in the tarsal navicular (10%), 5 in the first metatarsal head (10%), and 3 in the talus (6%). In the upper extremity, osteonecrosis was demonstrated once each (2%) in the proximal humerus, capitellum, and the first metacarpal head.

In each case of osteonecrosis of the knee, isolated involvement of the lateral distal femoral condyle was seen (Fig. 1). A typical radiographic appearance of the lateral distal

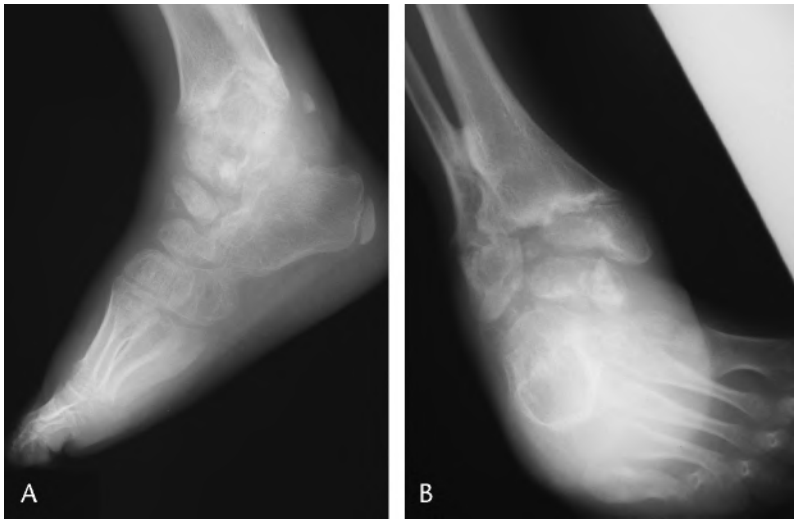

FIGURE 4. A and B, Charcot arthropathy of the ankle in a patient with HSAN type IV.

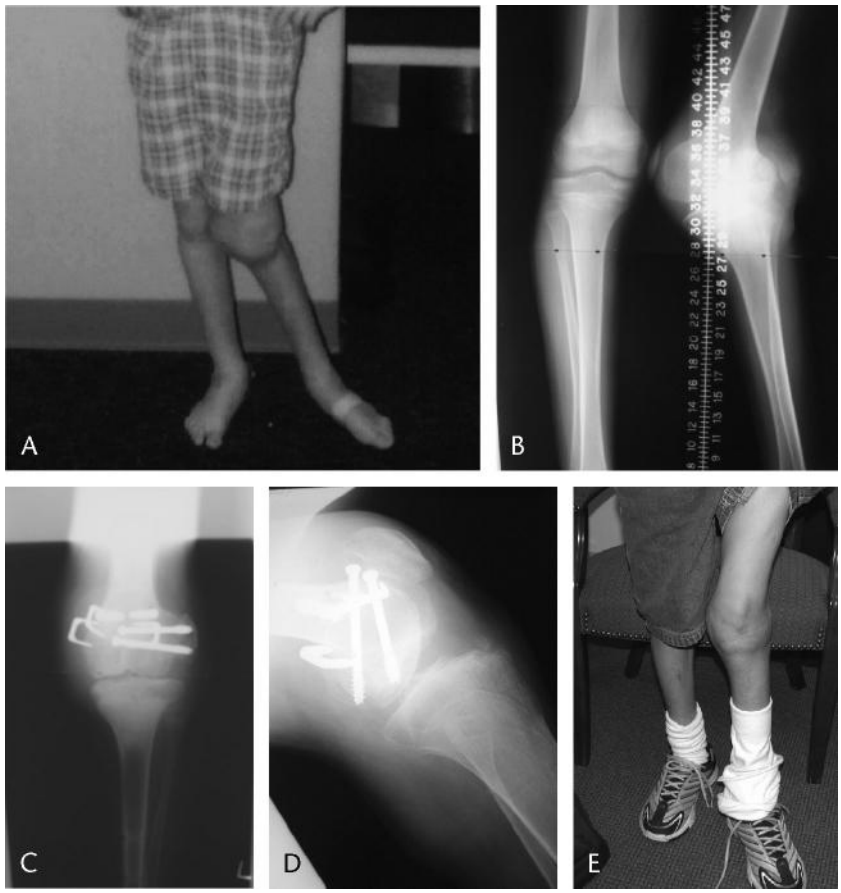

FIGURE 5. Preoperative clinical photograph (A) and radiograph (B) of valgus deformity with rotatory subluxation of the left knee in a patient with HSAN type III. Postoperative anteroposterior (C) and lateral (D) radiographs and clinical appearance (E) at latest follow-up after complex knee reconstruction and fixation of the osteonecrotic fragment.

femoral condyle was appreciated in each case. This consisted of varying sizes of typically isolated posterolateral fragmentation. Radiographs exhibited features including osteoporosis, subchondral lucency, and occasional sclerosis. In 4 cases, the fragment was displaced, and progressive posterolateral subluxation and instability occurred, presenting as marked valgus deformity and joint instability. In this large series of HSAN type III, there was no radiographic evidence of Charcot arthropathy.

Eighteen (56%; 30 joints) of the 32 patients comprising the HSAN type IV population had clinical evidence of joint involvement. The radiographic findings were consistent with Charcot arthropathy in all 30 affected joints. Eight of these patients had more than 1 peripheral joint involved. Of the 30 involved joints, Charcot arthropathy was seen 9 times in the knee (30%) and 7 times in the foot (23%). Charcot arthropathy of the ankle, hip, and elbow was seen in 4 patients each (13%), in the hand in 1 patient (3%), and in the spine in 1 patient (3%). Destructive changes at the knee consistent with Charcot arthropathy (Fig. 2C) were seen in the HSAN type IV patients, a pathology not seen in the HSAN type III cohort. Two patients with HSAN type IV were noted to have similar osteonecrosis of the knee as seen in the HSAN type III patients, that is, lateral condylar osteonecrosis with fragmentation (Figs. 1 and 2A, B). Hip dislocation was seen in 2 patients and subluxation in another. Radiographic evidence of osteomyelitis was seen in 12 joints in 9 patients (5 fingers, 3 tibias, 2 toes, 1 ankle, and 1 foot). Four patients exhibited features of both osteomyelitis and Charcot arthropathy.

Of the 26 sets of radiographs shown to the senior musculoskeletal radiologist in a blinded fashion, osteonecrosis and Charcot arthropathy were differentiated in 25 (96%) of the 26 cases. In all 13 cases of HSAN type IV, the radiographic diagnosis of Charcot arthropathy was made. In 12 of the 13 cases of HSAN type III, the diagnosis was osteonecrosis. For the one remaining patient with HSAN type III, an initial radiographic diagnosis of Charcot arthropathy was made and later amended to osteonecrosis (when shown early presenting radiographs). Late secondary changes at the articular surface made radiographic distinction difficult in this case. Charcot arthropathy affected both sides of the involved joint with evidence of collapse and fragmentation. With osteonecrosis, the articular process was found to be focal and disproportionately mild. The radiographic distinction between osteonecrosis and Charcot arthropathy is emphasized in the 2 cohorts presented. Osteonecrosis of the talus in a patient with HSAN type III was

identified by fragmentation, collapse, and sclerosis of the talus, with relative sparing of tibial plafond and tibiotalar articulation (Figs. 3A, B). Magnetic resonance imaging (MRI) served as a helpful diagnostic adjunct and in this case revealed complete marrow replacement (Figs. 3C, D). Similarly, when osteonecrosis occurred at the knee (Figs. 1 and 2), fragmentation of the lateral femoral condyle was evident. Underlying osteonecrosis was supported by the MRI finding of serpentine areas of low signal consistent with necrosis and marrow replacement. The articular surface of the tibia was spared early on. In contrast, Charcot arthropathy of the ankle (tibiotalar joint) in a patient with HSAN type IV consisted of fragmentation, irregularity, and disorganization of both the talus and distal tibia (ie, both sides of the joint were affected) (Fig. 4).

DISCUSSION

Hereditary sensory and autonomic neuropathy type III is an autosomal recessive multisystem disorder with protean clinical manifestations as a result of dysfunction of the sensory and autonomic nervous systems.[31] Neuropathologic analyses[10,11] have revealed a slight reduction in the number of small-diameter myelinated fibers (proprioception) and a marked diminution of the unmyelinated neurons (pain and temperature) of the peripheral nervous system, the number of cell bodies in the spinal cord intermediolateral gray cell column, and sensory and autonomic ganglia.

These anatomic abnormalities provide an explanation of the impairments in the sensory modalities seen in these patients. With marked impairment of pain and temperature sensation, patients fail to complain after significant injuries. They also often sit in positions that create joint stress. As a result, diagnosis and treatment of associated joint and long bone trauma may be delayed despite underlying pathology. This may account for the presence of focal lateral femoral condyle osteonecrosis, which was associated with children who had a history of repetitive falling on the knees in the W position (ie, thighs abducted on the floor with knees held flexed, creating knee valgus stress). In this group of patients with less impairment to proprioception, we did not find progressive joint subluxation and disorganization, which are the hallmarks of Charcot arthropathy.

Hereditary sensory and autonomic neuropathy type IV, which also follows an autosomal recessive inheritance pattern,[32] is associated with both severe loss of small myelinated and unmyelinated fibers. Impairment of temperature regulation, hyperactivity, and developmental delay are clinical hallmarks.[6] Orthopaedic manifestations of HSAN type IV include fractures and joint dislocations, as well as Charcot joints in the periphery and spine.[25,26,28–30,33–41]

In the HSAN type IV cohort, we noted a true Charcot arthropathy, which began with joint instability, and then progressive joint disorganization and destruction followed, a pathology not seen in the HSAN type III patients. In 2 cases, HSAN type IV patients also demonstrated similar changes indicative of osteonecrosis as seen in HSAN type III. The literature and our findings support that Charcot arthropathy is responsible for most joint deformities seen in patients with HSAN type IV.[6,24,26,34–36,38,42–45] This is consistent with the underlying neurological pathology seen in HSAN type IV, that is, severe diminution of the small myelinated fibers (proprioception).

In a large series of patients with HSAN type III, both osteonecrosis[18,20,21] and Charcot arthropathy[19,22,24] have been cited as the defining radiographic feature in clinically swollen and unstable peripheral joints. Although most common in adult patients with diabetes mellitus, tabes dorsalis, and chronic alcoholism,[27,46] Charcot arthropathy in 2 children with HSAN type III was originally reported by Brunt in 1967.[22] Laplaza et al[19] reported Charcot arthropathy in 20 patients (11%) of the 182 HSAN type III patients they reviewed. Bar-On et al,[18] in a review of 136 HSAN type III patients, found only 2 patients (3 joints) with evidence of Charcot arthropathy, as well as 1 patient with Perthes disease. In a retrospective review of 180 patients, Mitnick et al[21] reported 9 patients with evidence of osteonecrosis in unstable deformed joints and estimated the incidence of osteonecrosis in this population to be 5%. Ten of the 11 joints with osteonecrosis were weight-bearing joints of the lower extremity, most often the knee (n = 6) and hip (n = 3). In a review of 65 patients with HSAN type III, Yoslow et al[20] did not find any evidence of Charcot arthropathy, although they reported osteochondritis, including Perthes disease, in almost 8% of these patients.

Congenital insensitivity to pain is the cause of both osteonecrosis and Charcot arthropathy, and they present with similar clinical features, including joint swelling, deformity, and instability. Radiographic evaluation is essential to distinguish the underlying pathology and thus the treatment.[47–49] However, differentiating osteonecrosis from Charcot arthropathy on radiographs may be difficult (Figs. 5A–C). For example, upon review of the radiographs in a child with HSAN type III with bilateral knee involvement, Mitnick et al[21] concluded that there was bilateral knee osteonecrosis and not Charcot arthropathy as had been previously diagnosed. As noted in our review, late secondary changes at the articular surfaces make the distinction challenging. Radiographic findings indicating osteonecrosis range from diffuse osteoporosis and subchondral lucency to sclerosis with bone collapse. Radiographic features of Charcot arthropathy include joint effusion, subluxation, sclerosis, and microfractures, whereas osteophytes may develop as the periarticular ligaments become more lax with progression of the deformity.[47] Because osteonecrosis and osteochondritis may also be seen in advanced Charcot joints, correct radiographic diagnosis becomes even more challenging. Magnetic resonance imaging may be diagnostic when early osteonecrosis is clinically suspected, as plain films may initially be unremarkable.

We report radiographic evidence of osteonecrosis in 48 joints in 42 HSAN type III patients. In the largest series of patients with HSAN type III presented in the literature, we could not document any cases of Charcot arthropathy in type III patients presenting with joint swelling, instability, and deformity. Although we used the same database as that of Laplaza et al,[19] our definition of Charcot arthropathy was different. They have indicated that the absence of detectable pain plays a role in the clinical course of the osteonecrosis, particularly in the knee; however, this does not make the diagnosis

one of Charcot arthropathy. Charcot arthropathy is thought to have both a vascular and mechanical stage.[50] Often, joint destruction is preceded by intense hyperemia and may have bone resorption.[50–52] Charcot arthropathy does not have a uniform progression of joint destruction; it, by definition, has a disorganized appearance and progression.[50,51,53,54] This differs greatly from the joint pathology seen in HSAN type III.

In HSAN type III, we conclude that destructive arthropathy at the lateral distal femoral condyle and other joints is secondary to an initial focal osteonecrosis. The etiology of osteonecrosis in HSAN type III may be multifactorial. Decreased autonomic innervation of the arteriole wall[10,11] may lead to vascular spasm and ischemia. In addition, impaired perception of pain makes these patients susceptible to repetitive trauma and thus osteonecrosis. Histopathologic analyses of specimens from the joints of patients with HSAN types III and IV may help elucidate the underlying pathophysiology.

Treatment of the osteonecrosis seen in the lateral femoral condyle of these patients is amenable to reconstruction and fixation before widespread articular degeneration (Figs. 5A–E). Treatment for Charcot arthropathy depends on the stage of involvement, the particular joint, and the magnitude of deformity present. Patients with HSAN type IV require vigilant monitoring and education to prevent joint destruction. This includes seating instruction. We recommend that children with HSAN types III and IV avoid sitting on the floor because of joint positioning. Charcot arthropathy in HSAN type IV patients may be amenable to surgical correction to correct or prevent malalignment and dislocation.

The incidence of osteonecrosis in HSAN type III is higher than previously reported in the literature and most often occurs at the lateral distal femoral condyle of the knee. In our series, the reported incidences of osteonecrosis and Charcot arthropathy in HSAN types III and IV, respectively, represent the underlying radiographic features of clinically evident arthropathy in these 2 patient populations. Our results may represent an underestimation of the true frequency of radiographic osseous abnormalities in the peripheral joints of children with these rare disorders of sensory dysfunction. This limitation reflects the paucity of clinical symptoms as clinically asymptomatic joints were not imaged, as well as the retrospective nature of this study. Furthermore, as musculoskeletal manifestations may be delayed because of the underlying sensory neuropathy, an accurate assessment of the time course between the first appearance of these radiographic findings and clinical manifestations of joint swelling, deformity, and instability remains unavailable.

We conclude that there are 2 types of "neuropathic joints" seen in these disease states. One is primarily osteonecrosis, and the other is classic Charcot arthropathy with joint subluxation. The differentiation of these types is critical for evaluation and treatment. Further study is needed to determine if this distinction will aid the treatment of neuropathic arthropathy for other diagnoses as well.

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