Orthopaedic Manifestations of Navajo Familial Neurogenic Arthropathy

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Background: Navajo Familial Neurogenic Arthropathy is a disease identified in Navajo children, primarily residing in Arizona, New Mexico, and Utah. To date, there are no reports in the orthopaedic literature regarding this disorder, particularly the clinical manifestations and treatment considerations.

Methods: We carried out a retrospective chart and radiographic review of 2 patients with Navajo familial neurogenic arthropathy. We present these 2 patients as representative of the orthopaedic manifestations of Navajo familial neurogenic arthropathy.

Results: Both patients have significant axial and appendicular bone abnormalities, Charcot-type arthopathy, heat intolerance and also anhidrosis. They have normal intelligence. Both patients underwent surgical interventions, with recurrent deformity and infection being the most common complications.

Conclusions: Navajo familial neurogenic arthropathy is a rare clinical entity, seen most commonly in the southwestern regions of the United States. Patients are found to have a myriad of orthopaedic abnormalities, and surgical intervention, while sometimes indicated, can be fraught with complications.

Level of Evidence: Level IV, case series.

Key Words: Navajo, neuropathy, arthropathy, hereditary, sensory, autonomic

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The Navajo people are the largest Native American tribe in North America. They are also referred to as Southern Athabaskan (together with the Apache) based on their dialect or language family. The Southern Athabaskan people reside primarily in Arizona, New Mexico, and Utah.[1,2]

Four distinct disorders have been identified that are unique to the Southern Athabaskan people: Navajo poikiloderma, brainstem dysgenesis, severe combined immunodeficiency, and Navajo Neuropathy.[1]

Navajo Neuropathy is an entity that has been described in the neurology literature since 1976.[3] Appenzeller was the first to categorize a subset of children of Navajo ancestry, described as having severe sensory loss, corneal ulcerations, acral mutilation, hypotonia, and areflexia, but have normal intelligence. Additional features linked to Navajo Neuropathy were identified in an epidemiologic study by Singleton in 1990.[2] These included liver disease and systemic infections. The mode of transmission is considered to be autosomal recessive. Children classically present with onset of symptoms in the early first decade of life, and the diagnosis is based on MRI (brain and spinal cord) findings, liver function studies, and also nerve conduction velocities and nerve biopsy.[2,4] Navajo Neuropathy has been theorized to be similar to hereditary sensory and autonomic neuropathy (HSN) type II, despite the clinical findings of hypotonia, metabolic disorder, and leukoencephalopathy not commonly seen in HSN II.[2]

Nearly 20 years later, Johnsen characterized the disorder of Navajo familial neurogenic arthropathy.[5] This neuropathy was also thought to be specific to the Navajo population, representing a distinct entity from Navajo Neuropathy. Clinical findings, EMG, nerve conduction, and nerve biopsy results were different from those seen in Navajo Neuropathy, however, the mode of inheritance was also considered to be autosomal recessive. Children were found to have painless fractures leading to Charcot arthopathy, and also autonomic dysfunction, particularly heat intolerance and anhidrosis. Onset is within the first or early second decade of life, with normal early development. Navajo familial neurogenic arthropathy is most closely categorized as HSN types IV or V (congenital insensitivity to pain with complete or partial anhidrosis, respectively), despite the lack of "severe hyperpyrexia, overt sensory loss, and mental retardation[5]" seen in HSN IV.

Although Navajo familial neurogenic arthropathy may be classified more broadly as a hereditary sensory autonomic neuropathy, there is little in the orthopedic literature regarding this specific disorder, its epidemiology, and treatment principles. We present the orthopaedic manifestations of Navajo familial neurogenic arthropathy as seen in 2 of our patients.

CASE 1

Our first patient is an 18-year-old male of Navajo descent. His early developmental history is normal, with no prior medical history or hospitalizations as a young child. At age 5 he fell out of a truck, and was referred to an orthopaedist for a persistent, nonpainful right knee effusion. An MRI revealed a nondisplaced distal femoral physeal fracture, which was treated with cast

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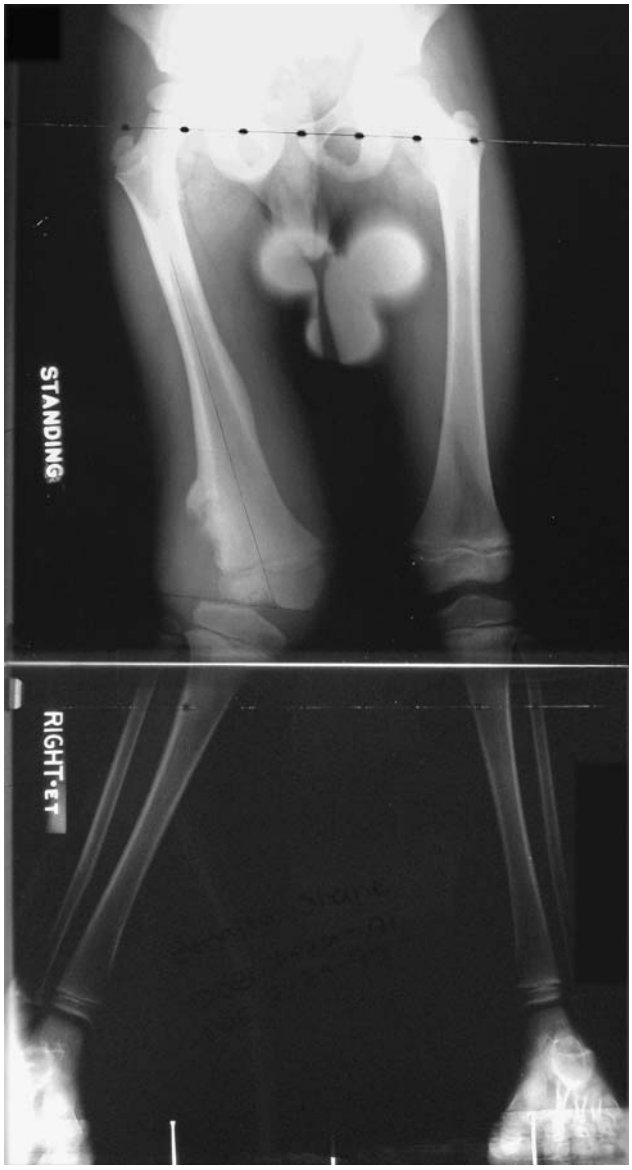

FIGURE 1. AP legs.

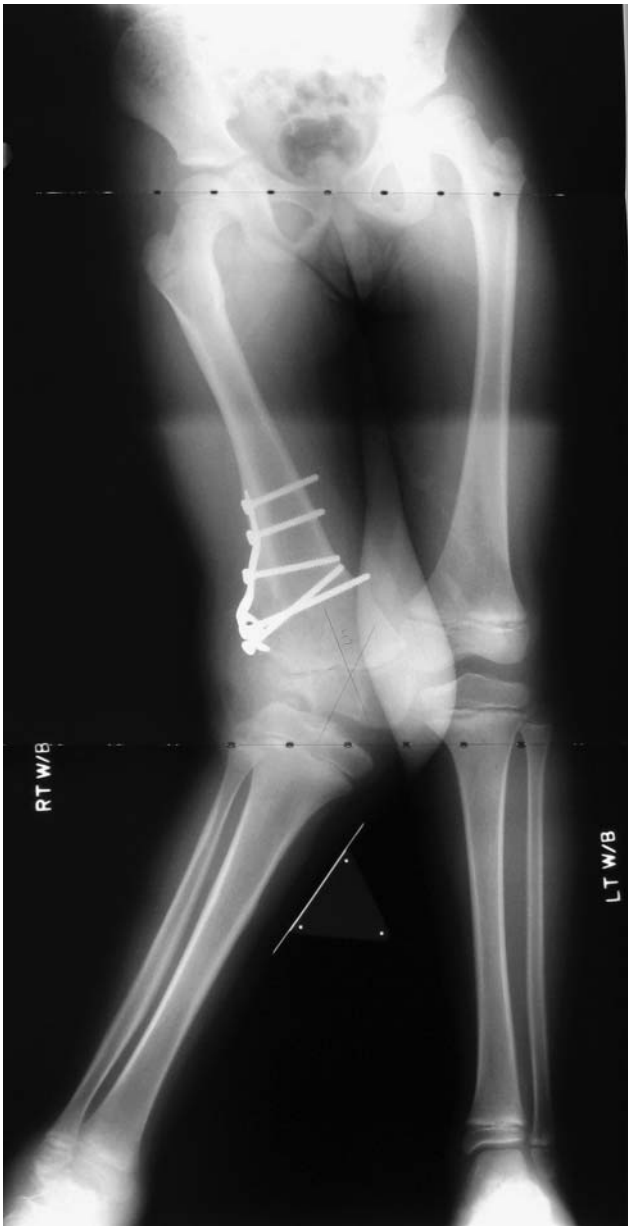

FIGURE 2. Eighteen months. s/p osteotomy: AP legs.

immobilization. At that time he was also referred to a neurologist given concern for other clinical findings of anhidrosis and an abnormal response to painful stimuli. Clinical referral notes have further indicated that there was no evidence of hypotonia, areflexia, or acral mutiliation. His sensory exam was reported to be normal to light touch, temperature, and proprioception. He had no findings of developmental delay or mental retardation.

A diagnosis of Navajo familial neurogenic arthropathy was made by the neurologist, based on his clinical picture, normal NCV, and a normal brain MRI. A sural nerve biopsy was also performed later in his clinical course, confirming the diagnosis.

In follow-up for his fracture care, the patient was seen to develop a progressive valgus deformity of his right knee (Fig. 1). A distal femoral varus producing osteotomy was carried out, however ultimately the deformity recurred along with findings consistent with Charcot arthropathy (Fig. 2). Distal medial femoral hemiepiphysiodesis was then used to further aid in correcting his malalignment. His postoperative course was complicated by a deep wound infection and life-threatening sepsis. Multiple surgical debridements and a prolonged ICU hospitalization were required for management.

At present, this patient is a household ambulator. He uses a wheelchair for any activity outside the home. He reported no complaints at his most recent clinic appointment, despite deformities of his spine, knee, ankle, and feet (Figs. 3–7). Treatment presently consists of close observation, limitation of activity, and protective orthoses as needed.

CASE 2

This is a 13-year-old male of Navajo descent, raised on the Navajo reservation in Arizona. He was the product of a full-term pregnancy without perinatal complications. His birth and developmental history were uncomplicated, having achieved

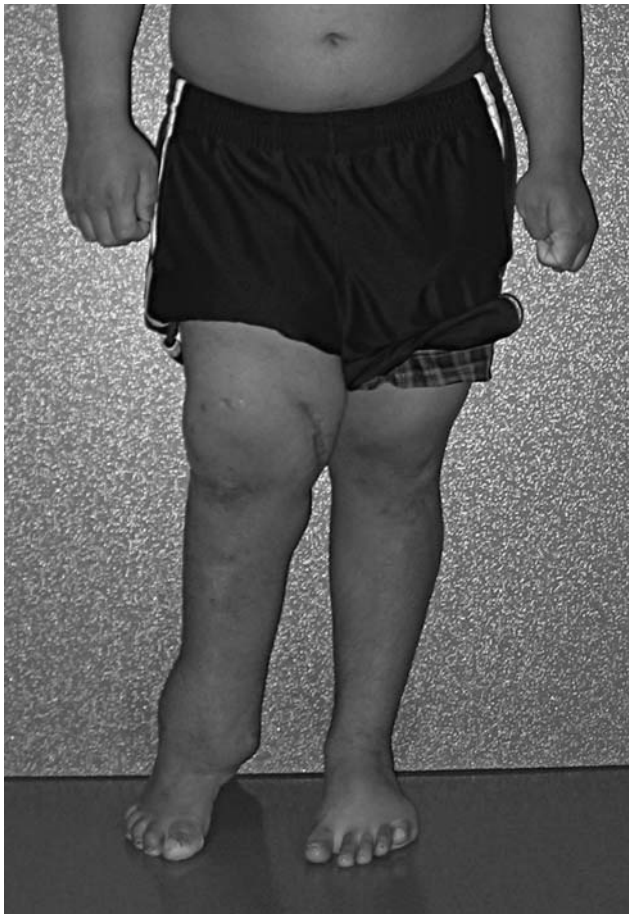

FIGURE 3. Clinical photograph.

developmental milestones as expected. At age 4, his family sought medical attention given his symptoms of heat intolerance and anhidrosis. Neurologic evaluation was undertaken, further identifying an abnormal response to deep painful stimuli, but with an otherwise normal sensory exam. The patient was thought to be of normal intelligence, and had no history of liver disease, systemic infection, corneal scarring, or acral mutilation. There was no family history of other affected members. This clinical picture ultimately led to a diagnosis of Navajo familial neurogenic arthropathy.

Two years later this patient was found to have developed a deformity of his left knee. Physical examination revealed significant genu valgum and a large, asymptomatic knee effusion. Radiographs and MRI identified considerable joint destruction, consistent with Charcot arthropathy (Fig. 8). Distal medial femoral hemiepiphysiodesis was used to correct his malalignment (Fig. 9). A wound infection complicated his early postoperative course, which resolved with oral antibiotics. Despite this surgical intervention, his left knee deformity worsened, with increasing valgus and articular destruction. Deformity and Charcot changes have also been established in his right ankle, right elbow, and spinal column (Figs. 10–12). Further surgical management has been circumvented, particularly given his propensity for progression of deformity and a potentially heightened risk for infection.

The functional status and activity level of this patient have declined over the past several years. He takes few steps or crawls while at home; a wheelchair is his primary mode of ambulation. His orthopaedic interventions have remained conservative and nonsurgical. He was provided with a new lower extremity orthosis and wheelchair modifications at his last clinic visit.

DISCUSSION

The hereditary sensory and autonomic neuropathies constitute a group of inherited neuropathies that have

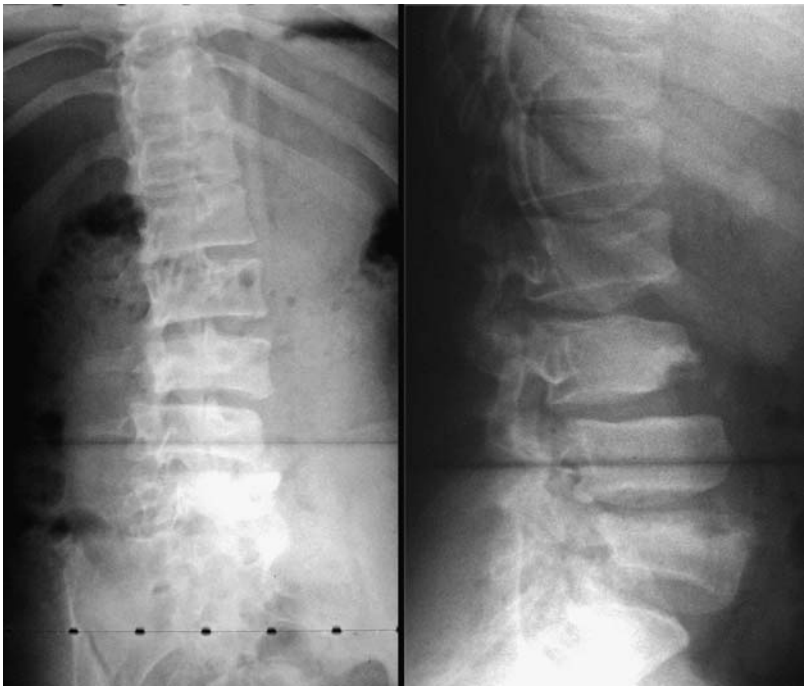

FIGURE 4. PA/Lat spine.

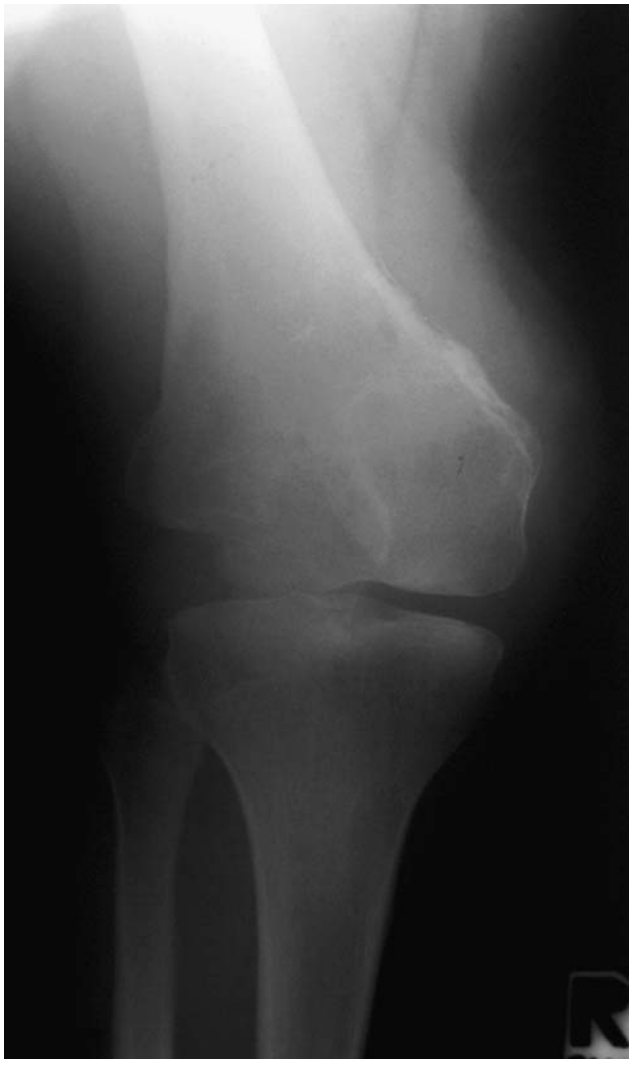

FIGURE 5. AP right knee.

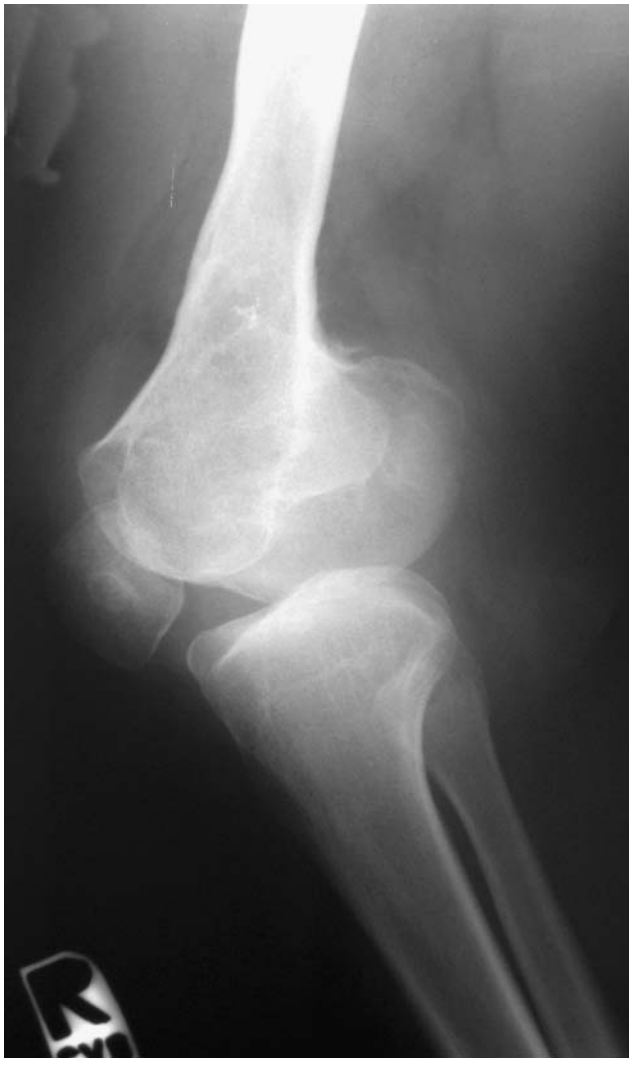

FIGURE 6. Lateral right knee.

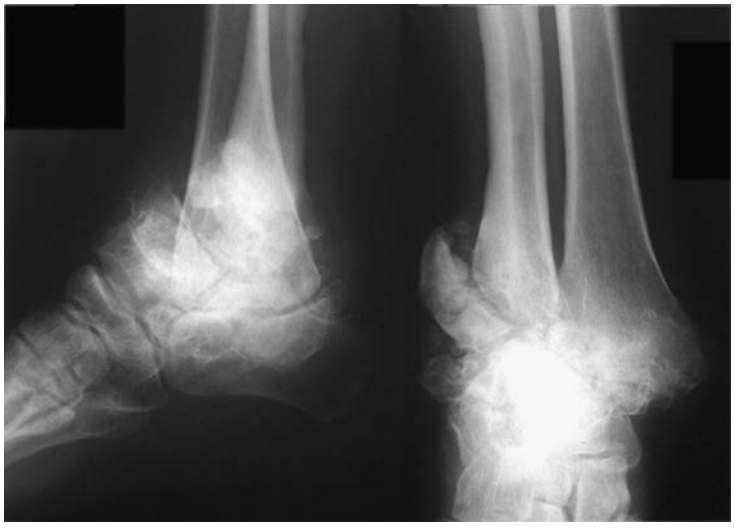

FIGURE 7. AP/Lat right ankle.

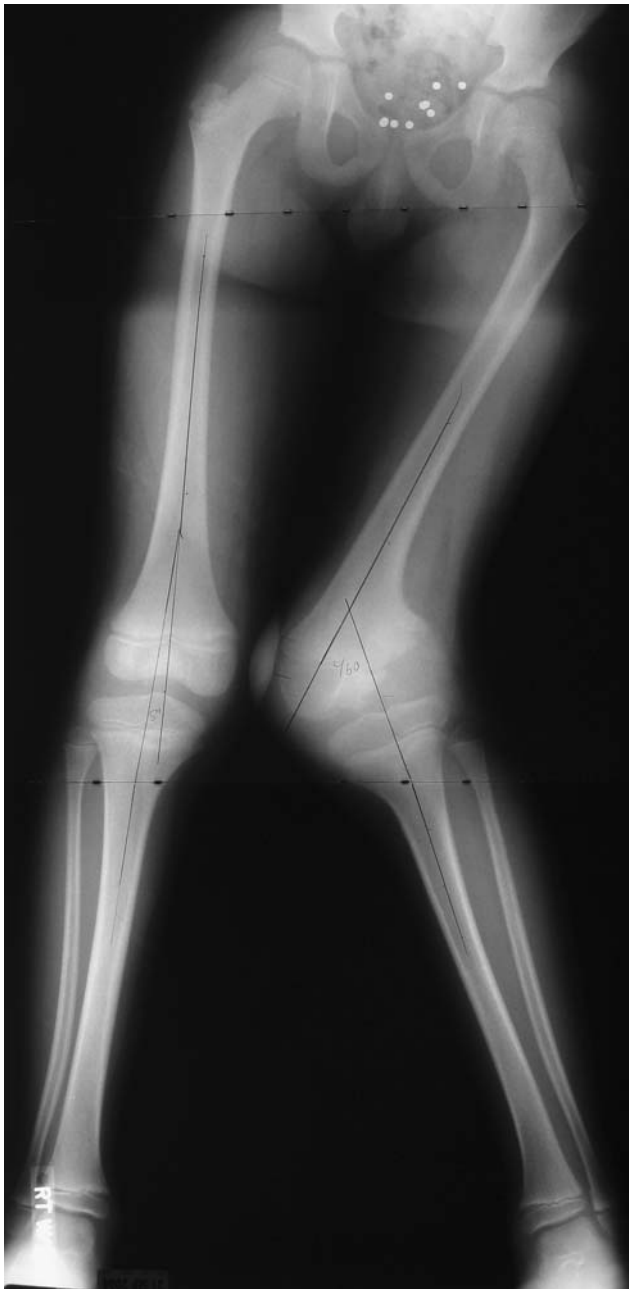

FIGURE 8. AP legs.

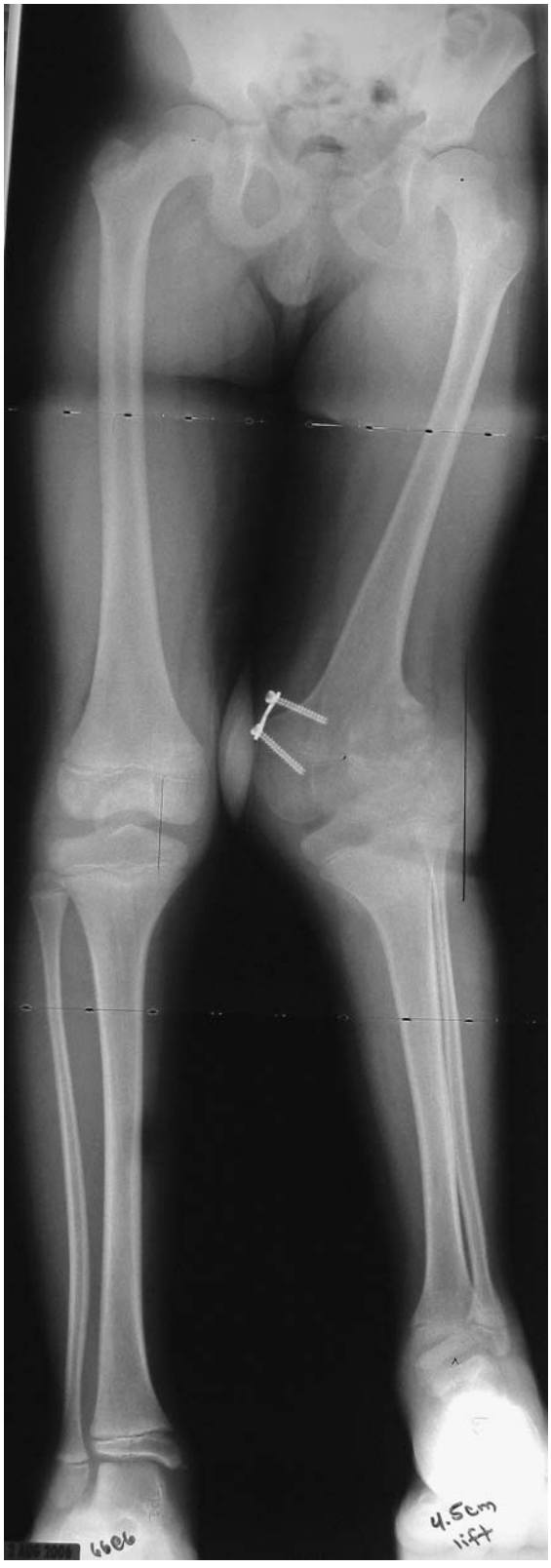

FIGURE 9. AP legs.

been well described in the orthopaedic literature. These disorders present with a variable degree of motor, sensory, and/or autonomic dysfunction, resulting in a myriad of orthopaedic manifestations.[6]

Navajo Neuropathy and Navajo familial neurogenic arthropathy have both been associated with the hereditary sensory and autonomic neuropathies. Navajo Neuropathy has a pattern of nerve fiber loss that is most similar to HSN II (congenital sensory neuropathy). Although the demyelination pattern is similar, Navajo Neuropathy also has characteristic features of hypotonia,

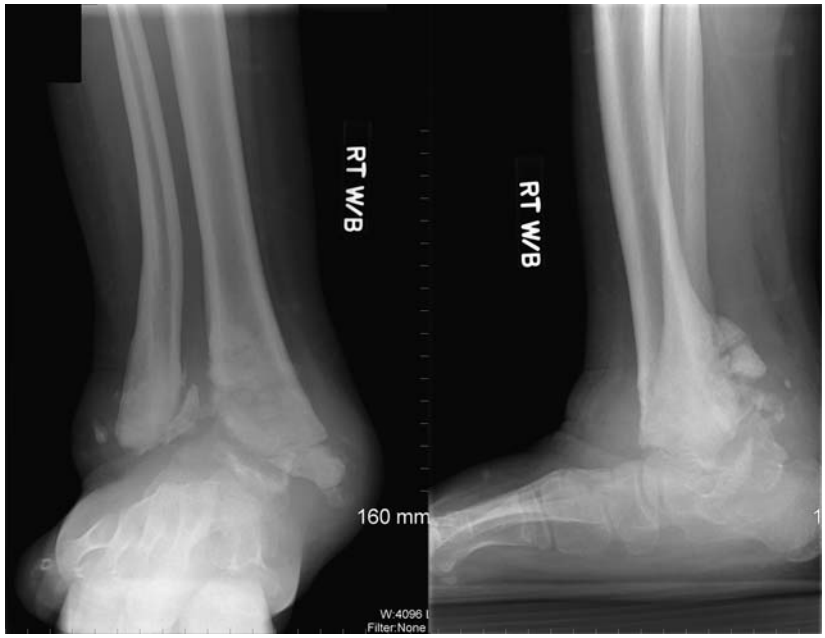

FIGURE 10. Standing AP/Lat right ankle.

metabolic disturbances, and leukoencephalopathy, which are not classically found in patients with HSN II.

Navajo familial neurogenic arthropathy has been most closely related to HSN type IV, and to a lesser degree HSN V. The sural nerve biopsies evaluated in both Navajo familial neurogenic arthopathy and HSN IV have decreased numbers of small myelinated fibers, and unmyelinated axons are found to be absent.[5] Despite having similar neuropathology, patients with Navajo familial neurogenic arthropathy do not have the other

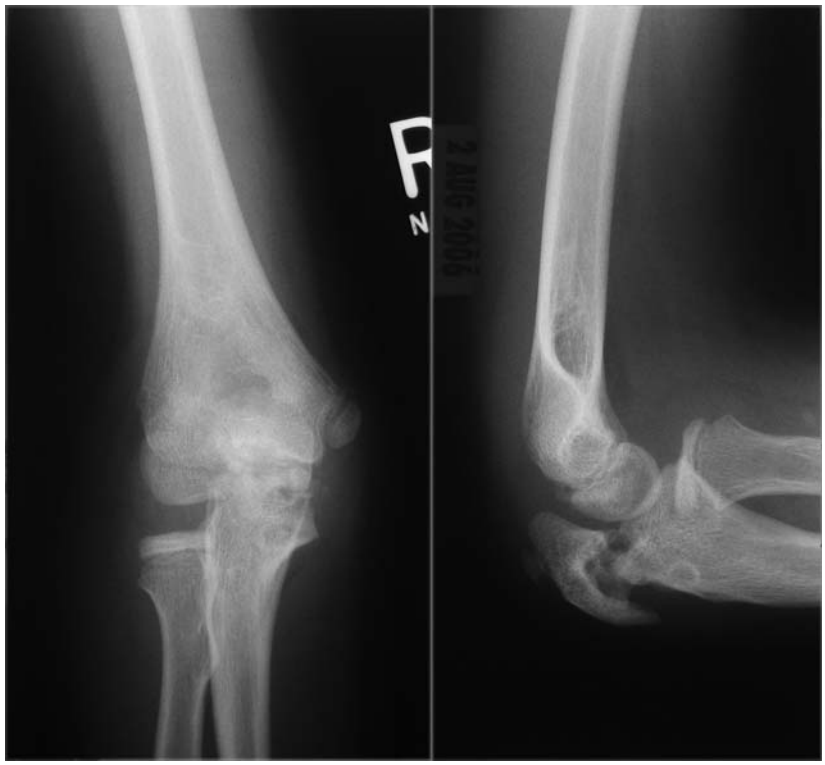

FIGURE 11. AP/Lateral right elbow.

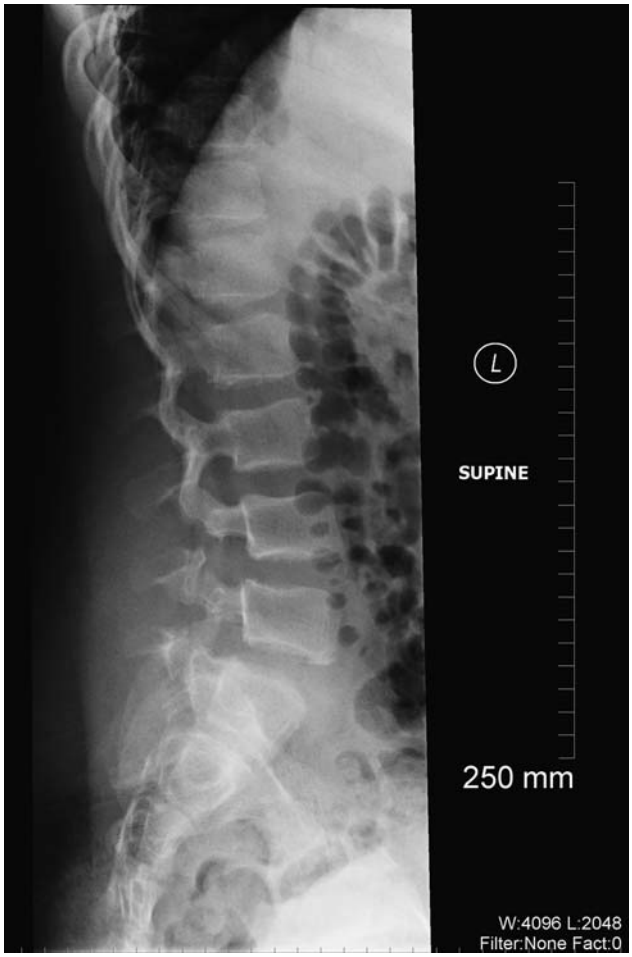

FIGURE 12. Lateral spine.

characteristic findings linked to HSN IV, namely mental retardation, hyperpyrexia, self-mutilatory behavior, and more global sensory loss.[7–9] Furthermore, genetic studies regarding HSN IV have identified a mutation in the tyrosine kinase A receptor gene (TRKA), which is "involved in the development and function of nociceptive and sympathetic sensory neurons.[6]" Thus far we have not been able to identify any literature associating the TRKA gene with the diagnosis of Navajo familial neurogenic arthropathy.

Regardless of how Navajo familial neurogenic arthropathy might be more broadly classified, our goal was to highlight some of the orthopaedic manifestations and treatment principles linked to a disorder seen specifically in the Navajo population. Both patients had normal early development and normal intelligence. They displayed autonomic dysfunction consisting of anhidrosis and heat intolerance. Both were found to have an abnormal response to deep painful stimuli, ultimately resulting in bony deformity with Charcot arthropathy, but had an otherwise normal sensory exam to light touch, vibration, proprioception, and temperature. Neither were found to have any other affected family members, or evidence of immune compromise.

Our patients displayed a variety of orthopaedic anomalies, including limb malalignment, Charcot arthropathy with destruction of both upper and lower extremity joints, and structural spine abnormalities resulting in coronal and/or sagittal plane deformity. Dr Johnsen, in a Personal Communication in 2008, highlighted that the most common orthopaedic procedures carried out in this patient population included fusions and osteotomies. He also reported a relatively high failure rate, with some patients ultimately requiring an amputation. Families must be aware of the nature and extent of this disorder, and have realistic expectations for treatments. Recurrence of deformity is a significant risk in these patients, and a bone or joint infection can be devastating.

We are unaware of any effect on life expectancy in these patients. We therefore recommend frequent orthopaedic evaluation, optimizing the patient's functional status in light of their deformities. The use of weight relieving orthoses, avoidance of repetitive trauma, and the use of assistive devices (ie, wheelchair) for ambulation should be emphasized to help maintain function in patients with Navajo familial neurogenic arthropathy.

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