CUSTOMER HAS REQUESTED:

Electronic Delivery (ELDEL)

docdel@ahsl.arizona.edu

Document Delivery/ILL
Arizona Health Sciences Library
520-626-6840
ahsill@ahsl.arizona.edu

Request #:215521

Friday, October 07, 2011

TN: 215521

Patron: Jones, Desiree

Call #: **W1 NE561 v.43 no.4-6 1993**
Location:

Pages: 1120-5

Journal Title: Neurology

Volume: 43
Issue: 6
Month/Year: 06 1993

Article Author: Johnsen SD, Johnson PC, Stein SR

Article Title: Familial sensory autonomic neuropathy with arthropathy in Navajo children.

Notes:

Paging History:

NOS LAC INC OTHER_____

Re-Page by --/--/--

Charge:

This is not a bill. Please do not pay from this slip.

Initials _____

Need by: 12/05/2011

CUSTOMER INFORMATION:

Desiree Jones (djones)
2550 West Ironwood Hill Drive
#833
Tucson, AZ 85745

College of Public Health

Method of Payment:

djones1@email.arizona.edu
520-429-2746
Fax:

8. Consensus statement. Report and recommendations of the San Antonio conference on diabetic neuropathy. Diabetes 1988;37:1000-1004.
9. Anderson DW, Mantel N. On epidemiologic surveys. Am J Epidemiol 1983;118:613-619.
10. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF. Sensory neuropathy in non-insulin–dependent diabetes mellitus. Am J Epidemiol 1990;131:633-643.
11. Mayne N. Neuropathy in diabetic and non-diabetic populations. Lancet 1965;2:1313-1316.
12. Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Neurology 1992;42:1823-1839.
13. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978;1:168-188.
14. Palumbo PJ, Elveback LR, Whisnant JP. Neurologic complications of diabetes mellitus: transient ischemic attack, stroke, and peripheral neuropathy. Adv Neurol 1978;19:593-599.
15. Lombardo A, Oliva G, Scornavacca G, et al. Diabetes in the elderly: remarks from an epidemiological study carried out in a town in south-eastern Sicily (Militello V.C.). Acta Diabetol Lat 1990;27:231-242.
16. Vaccaro O, Imperatore G, Ferrara A, Palombino R, Riccardi G. Epidemiology of diabetes mellitus in southern Italy: a case-finding method based on drug prescriptions. J Clin Epidemiol 1992;45:835-839.

Familial sensory autonomic neuropathy with arthropathy in Navajo children

Stanley D. Johnsen, MD; Peter C. Johnson, MD; and Stephen R. Stein, MD

Article abstract—Eight Navajo children had a neuropathy characterized by Charcot's joints and unrecognized fractures. Their reflexes were intact and they had normal strength. The sensory examinations in the group were variable. Many had no discernible sensory deficit. Others had subtle deficiency in deep pain sensation, temperature discrimination, and corneal sensitivity. Electromyography and nerve conduction velocities were normal in the seven studied; however, sural nerve biopsy revealed a marked reduction in small myelinated and unmyelinated nerve fibers. This sensory neuropathy, which we call "Navajo familial neurogenic arthropathy," differs from the acromutilating sensory neuropathy previously described by Appenzeller et al in Navajo children. It also differs clinically from a number of previously reported cases of hereditary sensory autonomic neuropathies in non-Navajos. The disorder in these eight children emphasizes the usefulness of pathologic investigation of the sural nerve in patients with Charcot's joints with minimal or no other neuropathic signs.

NEUROLOGY 1993;43:1120-1125

Appenzeller et al[1] described a sensorimotor neuropathy in the Navajo population characterized by acromutilation, corneal insensitivity, and scarring, weakness, and scoliosis. This complex condition with liver disease, encephalopathy, and myelopathy appeared to have autosomal recessive inheritance and was not present in nearby Native American tribes.[2] We describe another type of sensory neuropathy, distinct from the neuropathy described by Appenzeller et al, in Navajo children with prominent Charcot's joints and unrecognized fractures.

Clinical features of patients with Navajo neurogenic arthropathy. Eight Navajo children from three families all had similar clinical histories. All parents were normal and also had normal children. In one family, half-siblings were involved; however, the half-siblings had the same father, and their mothers were sisters. All parents denied consanguinity. The early development of all patients was normal. They all reported no significant problems until late in the first or early in the second decade of life. However, review of Indian Health Service records revealed that several had recurrent hospital admissions in infancy for unexplained high temperatures. All but one had painless fractures, primarily in weight-bearing joints. They also had severe progressive arthropathy, mostly in the knees and ankles, with prominent recurrent joint swelling. Several required joint fusion; over 35

From the Section of Child Neurology, Division of Neuropathology, Barrow Neurological Institute, Children's Health Center, and the Orthopedic Department, St. John's Hospital and Medical Center, Phoenix, AZ.

Received July 1, 1987. Accepted for publication in final form October 15, 1992.

Address correspondence and reprint requests to Dr. Stanley D. Johnsen, Barrow Neurological Institute, Section of Child Neurology, 222 W. Thomas Rd., Phoenix, AZ 85013.

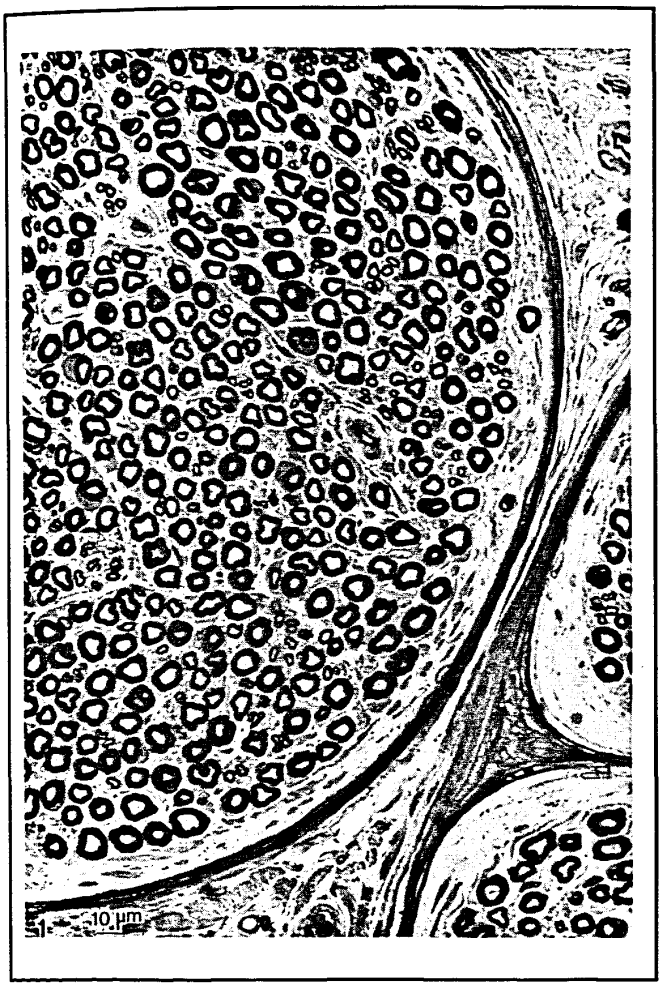

Figure 1. Sural nerve biopsy from patient 1. The number of small myelinated fibers are reduced as are the unmyelinated axons and associated Schwann cells, which, in this preparation, appear as light gray material separating myelinated fibers. Epon-embedded, 1-μm section, paraphenylenediamine stain.

orthopedic procedures were performed on the group. Three had only a foot deformity caused by painless fractures, one had a severe lumbar vertebral fracture, and another had elbow involvement. All had a history of heat intolerance and lack of sweating, but only one had hyperpyrexia during our evaluations. All children came from the Arizona portion of the Navajo reservation.

The neurologic examination of the patients revealed no motor weakness, coordination abnormalities, or alteration of tendon reflexes. Pupillary responses to light were diminished in two.

Sensory abnormalities were difficult to elicit in most of the patients. Only one patient clearly had markedly decreased response to deep pain and temperature discrimination, while others reported no alteration of response to light touch, pin prick, deep pain, position sense, and vibration sense. The patient with obvious sensory loss was the youngest, but had little clinical trouble. He was identified because of an involved sibling and unexplained fevers. The younger children were clearly inconsistent in reporting possible sensory deficit, and even the older teenagers also frequently gave varying responses. Two other patients persistently reported a decrease in response to Achilles tendon pressure, and three reported decrease in corneal sensitivity. The others reported no alteration of response to the sensory modalities noted above. Three teenagers were examined repeatedly, and minor alterations in sensation were eventually identified. The most consistent finding was a subtle but distinct deficiency in discriminating temperature differences on the extremities. Temperature differences below 3 °C could not be distinguished on the volar surface of the forearm, whereas three normal controls consistently distinguished 1.5 °C differences. No alteration of temperature sensation could be defined on the face. Review of the Indian Health Service records revealed that four of the patients had been evaluated by other neurologists and were stated to have normal sensory examinations, emphasizing at least the minimal nature of the sensory findings.

EMG, motor nerve conduction velocities, and sensory latencies were normal in the seven patients studied. For example, the range of the peroneal nerve conduction velocities was 45 to 50 m/sec compared with our normal range of 40 to 65 m/sec. The sensory latencies were also normal from both the sural and the median nerves. Sural nerve biopsies performed on four patients from three families were abnormal.

Illustrative cases. Patient 1. This 14-year-old boy presented with a prominent deformity of the dorsum of the right foot that caused problems with fitting shoes. His response to Achilles tendon pressure was diminished; no other sensory deficit was elicited. The skin on the palmar surface of the hands was obviously thickened. The neurologic examination was otherwise normal.

On sural nerve biopsy, the endoneurial area was reduced by one-half, but routine and special stains of paraffin sections appeared normal. In 1-μm–thick, plastic-embedded sections, the number of small myelinated fibers was markedly reduced (figure 1). Total myelinated fiber density was 8,240 fibers/mm^2 (figure 2), slightly below our laboratory normal density of 12,000 fibers/mm^2 and below published norms.[3-6] Small myelinated axons (<7 μm in diameter) comprised only 47% of the total, compared with our normal of 65%. Teased nerve fibers revealed no abnormalities. Immunofluorescent microscopy revealed trace IgA, 2+ diffuse IgG, 2+ subperineurial IgM, 1+ C3 which was subperineurial and endoneurial, and 3+ endoneurial and perineurial albumin. Many electron microscopic fields showed virtually no unmyelinated nerve fiber profiles or denervated Schwann cell processes (figure 3), suggesting the fibers had never developed. There were only 4,318 unmyelinated nerve fibers/mm^2, which is sharply reduced from published normal ranges of 30,000 to 60,000 fibers/mm^2.[3,4,7] The distribution was unimodal and the peak occurred at 1 μm, which was in the normal range (figure 4).[6] Two other patients showed an identical profile.

Six months later, he fell off a bull while competitively riding. While he had no pain initially, he subsequently developed pain in his legs and back. Spinal x-rays revealed severe destruction of the fourth and fifth lum-

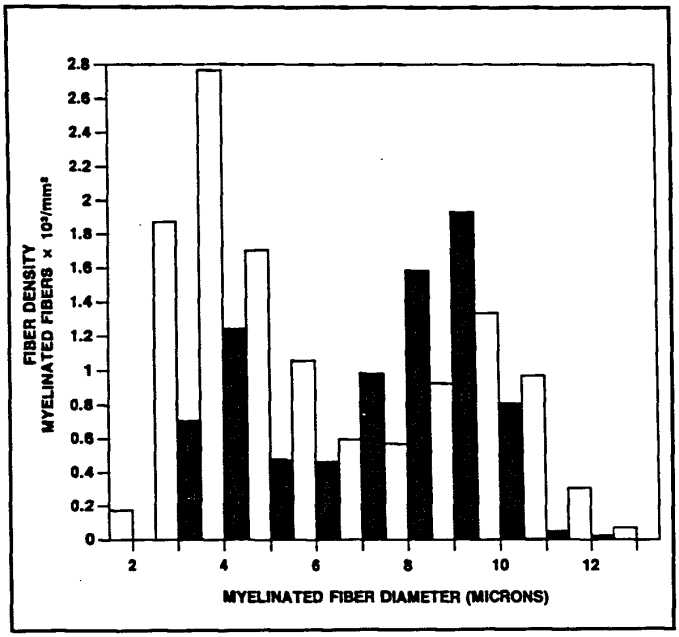

Figure 2. Size distribution of myelinated fibers in sural nerve. The histogram shows that for patient 1 there is a reduced number of small myelinated fibers when compared with a normal control. (□) Normal density = 12,000/mm² (66% < 7 μm); (■) patient (M.C.) density = 8,240/mm² (47% < 7 μm). The numbers given compare mean total density. The parenthetical numbers give the percentage of the total density of myelinated fibers under 7 μm, comparing a control with the patient.

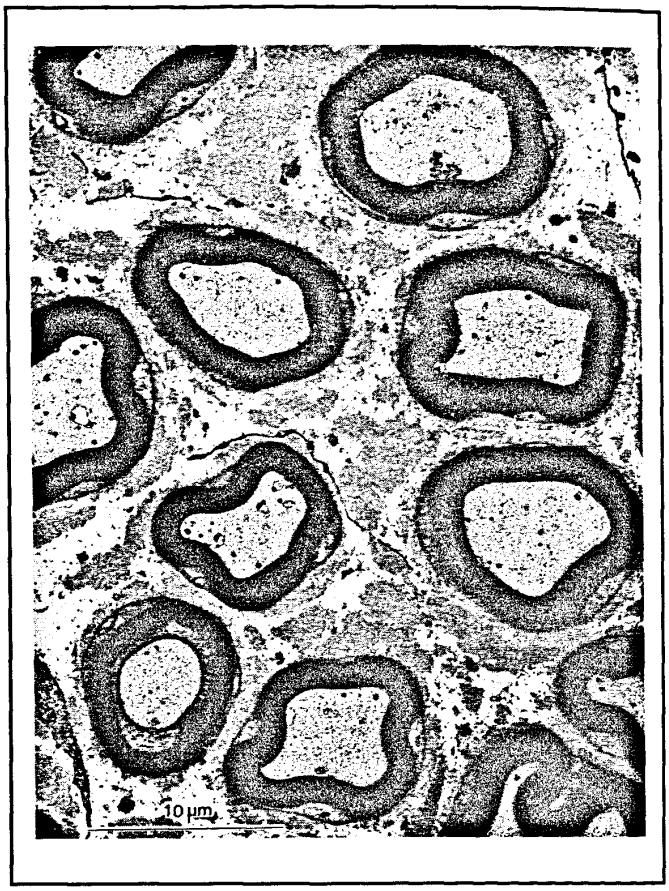

Figure 3. Electron micrograph of sural nerve biopsy from patient 1 reveals the absence of small myelinated fibers, unmyelinated fibers, and denervated Schwann cell processes between the myelinated fibers. The large myelinated fibers and axons appear normal.

bar vertebrae. A myelogram revealed a complete block at the same level. Persistent painful back problems have subsequently developed.

Patient 2. He was examined at age 20. He had a history of severe destruction of his right knee and ankle, both requiring fusion. The neurologic examination, including a detailed sensory examination, was normal; however, the patient was poorly cooperative for some aspects of the examination. He died in a drowning accident thought to relate to a seizure. No autopsy was performed. Prior to death, a sural nerve biopsy had been done.

Unlike the previous case, the size of myelinated fibers varied in some, but not all, nerve fascicles (figure 5). Otherwise, fascicles were identical to those described above. By electron microscopy, axonal sprouts were readily identified, and there were redundant Schwann cell processes and stacks of empty Schwann cell processes, indicative of fiber degeneration. Unmyelinated nerve fiber density was 6,195 fibers/mm²; the peak was again around 1 μm (figure 6).

Discussion. Although often ignored in reviews of hereditary sensory autonomic neuropathy, the acromutilating sensory neuropathy described by Appenzeller et al[1] is well known to neurologists and orthopedic surgeons who work with the Navajo population. This Navajo neuropathy (NN) is characterized by delayed childhood development secondary to a slowly progressive neuromuscular weakness with atrophy and corneal ulceration with scarring. Biting the hands early in life may lead to infection, deformity, or self-induced digital amputation. Weakness, atrophy, areflexia, absence of corneal reflex, corneal opacities, and diminution of epicritic and gnostic sensations are present, although expression may be variable and mild. MRI,[8] EMG, motor nerve conduction velocities, and sensory latencies are usually abnormal.

In contrast, our patients had early normal development with no serious problems in their first decade. In their second decade, however, they developed painless fractures of the feet or injuries to the knees with intermittent joint suppuration followed by severe progressive arthropathy. Parents reported that the children did not sweat and did not tolerate heat, buy only one had concurrent intermittent hyperpyrexia. However, hospital records revealed others with early life hospitalizations for unexplained hyperpyrexia. They had bony deformities and thickened skin of the palmar surfaces, but deep tendon reflexes and strength were normal unless altered by a bony deformity. The sensory examinations were variable in the group. No sensory abnormality could be identified in some of the patients. In one, clear loss of deep pain and temperature sensation was noted. In others, there were equivocal findings of depressed response to Achilles tendon pressure, corneal sensation in two patients, pupillary response in two patients, and

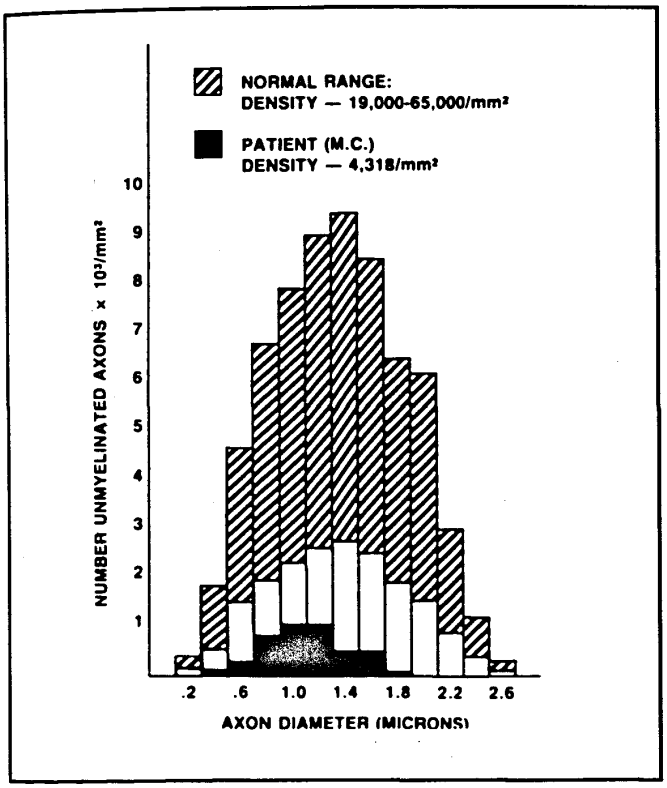

Figure 4. Size distribution of unmyelinated axons in sural nerve. The histogram demonstrates a sharp reduction in the density of unmyelinated axons, with only a few small axons remaining for patient 1 when compared with a normal control. Cross-hatched bars indicate normal range, the black bars indicate the patient's fiber density, and the clear area shows the separation of the patient's density from the normal range.

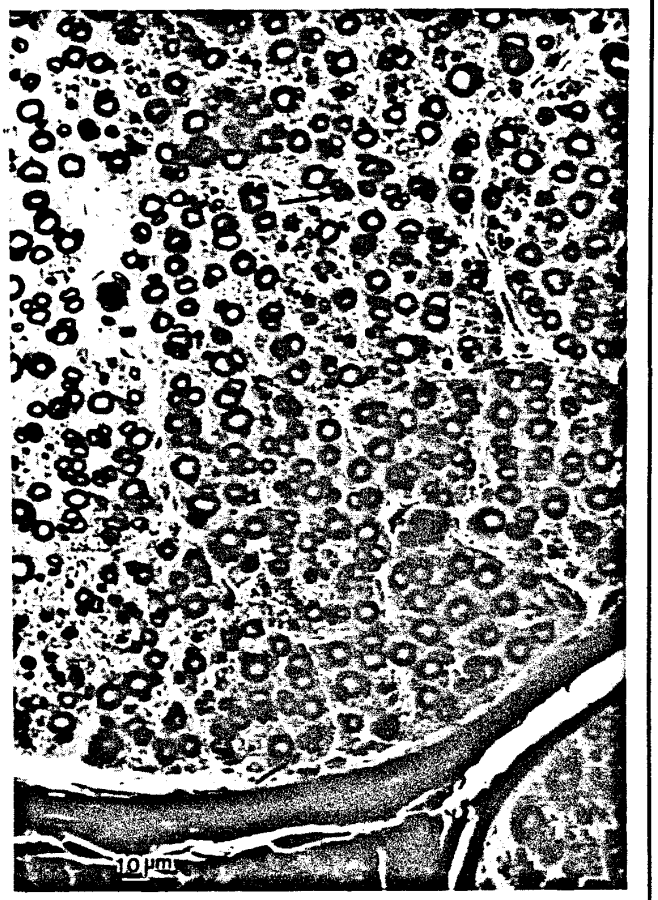

Figure 5. Sural nerve biopsy from patient 2 shows for some fascicles a wider range of myelinated fiber sizes than was present in the other three patients. Smaller fibers are often found in axonal sprouts (arrows). Epon-embedded, 1-μm section, paraphenylenediamine stain.

minor deficiencies in discriminating temperature differences in the three so studied. There was no correlation between the severity of the joint involvement and the sensory examination. The patient with the most obvious sensory deficit had only hyperpyrexia. EMG, motor nerve conduction velocities, and sensory latencies in the seven patients so studied were normal. Because the symptoms and findings differ markedly from NN, the disorder is unique and we have come to refer to it as "Navajo familial neurogenic arthropathy" (NFNA), emphasizing the major clinical manifestation (table).

The difference associated with nerve biopsies further supports the distinction between NN and NFNA. In NN there is a marked diminution of all myelinated as well as unmyelinated fibers, with evidence of degeneration and regeneration.[1] In contrast, large myelinated fibers were normal and small myelinated and unmyelinated fibers were markedly diminished in our patients (figure 1). The sural nerve in patient 2 showed, in addition, evidence of axonal loss and regeneration, perhaps secondary to proximal fascicular injury due to bony deformities (figure 5). Immunofluorescent studies reveal increased endoneurial plasma proteins consistent with a leak in the blood-nerve barrier similar to the pattern in hereditary sensory motor neuropathy type I.[9] The overall histologic picture suggests a congenital defect.

Table. Comparison of Navajo neuropathies

	NN	NFNA
Corneal insensitivity	Present	Absent
Corneal scarring	Present	Absent
Acromutilation	Present	Absent
Hands	Mutilated	Thick skin
Weakness	Present	Absent
Reflexes	Absent	Present
Nerve conduction	Slowed	Normal
EMG	Variable	Normal
Scoliosis	Develops	Absent
Progression	Weakness	Orthopedic
Hypohidrosis	Absent	Present
Nerve biopsy	Loss of all fibers	Decrease in small myelinated and unmyelinated fibers

The presence of two distinct sensory neuropathies in relatively large numbers in the small

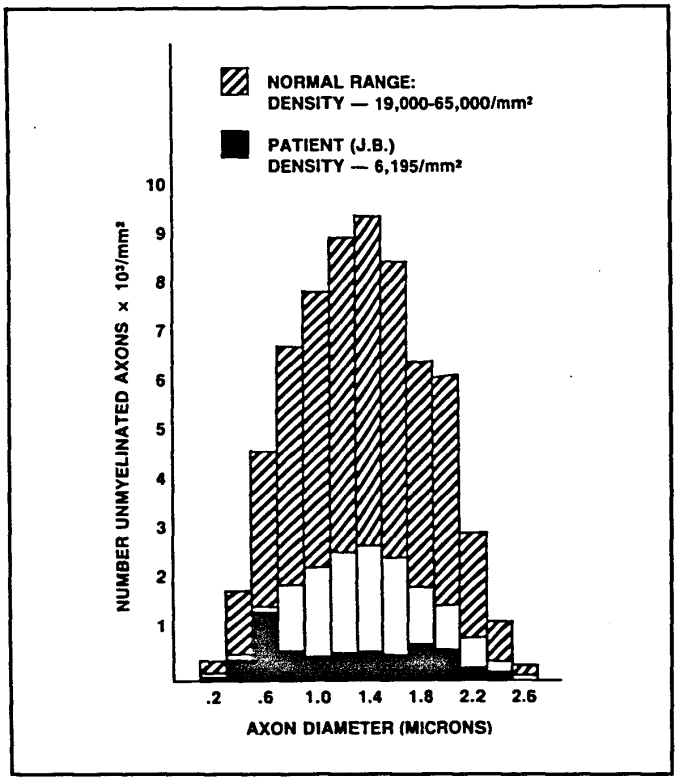

Figure 6. Size distribution of unmyelinated axons in sural nerve. Histogram for patient 2 has basically the same pattern as seen in figures 2 and 4, but with slightly more fibers. Cross-hatched bars indicate normal range, the black bars indicate the patient's fiber density, and the clear area shows the separation of the patient's density from the normal range.

Navajo population (about 200,000) is unusual. Neither neuropathy has been identified in the Navajos' Athapaskan relatives (the Apaches) or in neighboring tribes of different ancestry.[2] Inheritance is presumably autosomal recessive for both NN and NFNA. We could not identify consanguinity.

It was felt that further investigation of the autonomic sudomotor disturbance and the palmar hyperkeratosis is indicated but has been thwarted by patient and parental resistance.

Classifying NFNA relative to other hereditary sensory autonomic neuropathies (HSAN) is difficult. The World Federation of Neurology classification of hereditary and congenital neuropathies lists seven subtypes of HSAN.[10] Two of these subtypes are relevant to the NFNA patients. Ouvrier and McLeod[11] maintain the nomenclature of Dyck[12] and call these two subtypes HSAN IV and HSAN V. The patients of Swanson et al[13,14] and others are classified as type IV. Swanson et al described a family of three boys who were mentally retarded, insensitive to pain and temperature, with anhidrosis, severe temperature instability, thickened palmar skin, and Charcot's joints. Others[15-17] have reported similar patients. Chatrian et al[18] reported a follow-up of the original patients on the progressive nature of the arthropathy. In all cases, EMG and motor nerve conduction velocities studies were normal.[14,18] A sural nerve study of an HSAN IV patient[19] demonstrated that unmyelinated fibers were virtually absent and small myelinated fibers were decreased. There was no ultrastructural evidence of axonal degeneration or regeneration. This biopsy is essentially identical to three of our present patients and differs slightly from patient 2, who also exhibited axonal regeneration. Thus, while NFNA patients lack all of the clinical features of HSAN IV patients, their biopsies are the same. Both groups have severe progressive arthropathy and thickened palmar skin, while NFNA patients lack the severe hyperpyrexia, overt sensory loss, and mental retardation.

Low et al[20] reported a girl with recurrent ulceration of her extremities and degenerative arthropathy of the ankles that began in her first year of life. Her motor development was normal, as was her physical examination, except for the loss of pain perception in the lower extremities and forearms and delayed temperature discrimination in the feet. EMG and motor nerve conduction velocities were normal. Nerve biopsy revealed a decrease in the number of small myelinated fibers and a normal density of unmyelinated fibers (32,000/mm²). Ouvrier and McLeod believe this to be the only distinct case of HSAN type V.[11] Donaghy et al[21] reported a consanguineous Kashmiri family with clinical and biopsy findings similar to HSAN V but with the addition of prominent neurotrophic keratitis. Dyck et al[12] reported three patients with many clinical similarities. These patients had a deficiency of small myelinated fibers and, to a variable degree, unmyelinated fibers. Dyck et al grouped their patients with Low's into HSAN V. NFNA has a marked reduction of unmyelinated nerve fibers, in contrast to the patients with HSAN V. The early symptomatology, skin ulcerations, and obviously abnormal sensory examination in the HSAN V patients also contrast with NFNA.

Dyck et al[22] reported several families who had neurogenic arthropathy and recurring fractures with "subclinical hereditary sensory neuropathy." Others[23,24] had previously described similar patients. Although these patients had no overt neurologic symptoms or signs, computer-assisted sensory examination of the tibial periosteum showed depressed responses. Motor nerve conduction velocities were slightly slow in 17%, sensory latencies were prolonged in 30%, and sensory amplitudes were depressed in 40%. Biopsy findings varied: segmental remyelination was present in a few but there were no abnormalities of unmyelinated fibers in those patients studied. While this apparently heterogeneous group of patients resembles ours clinically with the paucity of sensory findings, the electrophysiologic testing and pathology are quite different.

In summary, patients with NFNA pathologically resemble those with HSAN IV with a decrease in both small myelinated and unmyelinated fibers on sural nerve biopsy. The patients with NFNA are less prominent in their sensory, autonomic, and

mental symptomatology, while they both have severe arthropathy. They differ clinically and pathologically from the HSAN V patients. The patients of Dyck et al[22] with subclinical sensory neuropathy bear a superficial clinical resemblance, but the group lacks distinct pathology for accurate comparison.

NFNA patients emphasize the clinical need for studying the sural nerve pathologically where a subclinical sensory neuropathy is suspected. In this circumstance, neither the clinical examination, EMG, motor nerve conduction velocities, nor sensory latencies suggested neuropathy. The bone deformities with unrecognized fractures were the earliest sign. Although severe neurogenic arthropathy was defined in these patients, no clinical or electrical evidence for a neuropathy existed before biopsy. While a painless damaged joint might compel consideration of a neuropathy, pain can be an early, prominent, and misleading symptom in neurogenic arthropathy. In one series[25] of Charcot's joints, 10 of 15 patients experienced pain as an early symptom, albeit less than expected in relation to the clinical findings. Thus, any unexplained destructive joint disease with juxta-articular or intra-articular fractures, with or without suppuration or pain, should be considered as possibly neurogenic in origin. The causes of neurogenic arthropathy are legion.[26] The studies of these patients, along with those of Dyck et al[22] serve to emphasize the importance of a subclinical sensory neuropathy in the differential diagnosis. The pathogenesis of the severe destructive arthropathy in this and other sensory autonomic neuropathies is speculative. The severe progressive nature of the bone destruction in some of our patients suggested a fundamental disturbance in vascular autonomic regulation. Further elucidation of these mechanisms may prove of value in clinical management.

References

1. Appenzeller O, Kornfeld M, Snyder R. Acromutilating, paralyzing neuropathy with corneal ulceration in Navajo children. Arch Neurol 1976;33:733-738.
2. Singelton R, Helgerson SD, Snyder RD, et al. Neuropathy in Navajo children: clinical and epidemiologic features. Neurology 1990;40:363-367.
3. Ferriere G, Denef J-F, Rodriguez J, Guzzetta F. Morphometric studies of normal sural nerves in children. Muscle Nerve 1985;8:697-704.
4. Jacobs JM, Love S. Qualitative and quantitative morphology of human sural nerve at different ages. Brain 1985;108:897-924.
5. Gutrecht JA, Dyck PJ. Quantitative teased fiber and histologic studies of human sural nerve during postnatal development. J Comp Neurol 1970;138:117-130.
6. Johnson PC. Peripheral nerve. In: Davis RL, Robertson DM, eds. Textbook of neuropathology, 2nd ed. Baltimore: Williams & Wilkins, 1991:1004-1087.
7. Ochoa J, Mair WG. The normal sural nerve in man. I. Ultrastructure and numbers of fibers and cells. Acta Neuropathol (Berl) 1969;13:197-216.
8. Williams KD, Drayer BP, Johnsen SD, Johnson PC. MR imaging of leukoencephalopathy associated with Navajo neuropathy. AJNR Am J Neuroradiol 1990;11:400-402.
9. Graham AR, Johnson PC. Direct immunofluorescent findings in peripheral nerve from patients with diabetic neuropathy. Ann Neurol 1985;17:450-454.
10. deJong JMBV. The World Federation of Neurology classification of hereditary and congenital neuropathies. In: deJong JMBV, ed. Handbook of clinical neurology, vol 60. Hereditary neuropathies and spinocerebellar atrophies. New York: Elsevier Science Publishers, 1991:1-4.
11. Ouvrier RA, McLeod JG. Hereditary sensory neuropathy. In: deJong JMBV, ed. Handbook of clinical neurology, vol 60. Hereditary neuropathies and spinocerebellar atrophies. New York: Elsevier Science Publishers, 1991:5-20.
12. Dyck PJ, Mellinger JF, Reagan TJ, et al. Not indifference to pain but varieties of hereditary sensory and autonomic neuropathy. Brain 1983;106:373-390.
13. Swanson AG. Congenital insensitivity to pain with anhidrosis. Arch Neurol 1963;8:299-306.
14. Swanson AG, Buchan GC, Alvord EC. Anatomic changes in congenital insensitivity to pain. Arch Neurol 1965;12:12-18.
15. Brown JW, Podosin R. A syndrome of the neural crest. Arch Neurol 1966;15:294-301.
16. Pinsky L, DiGeorge AM. Congenital familial sensory neuropathy with anhidrosis. J Pediatr 1966;68:1-13.
17. Rafel E, Alberca R, Bautista J, Navarrete M, Lazo J. Congenital insensitivity to pain with anhidrosis. Muscle Nerve 1980;3:216-220.
18. Chatrian GE, Farrell DF, Canfield RC, Lettich E. Congenital insensitivity to noxious stimuli. Arch Neurol 1975;32:141-145.
19. Goebel HH, Veit S, Dyck PJ. Confirmation of virtual unmyelinated fiber absence in hereditary sensory neuropathy type IV. J Neuropathol Exp Neurol 1980;39:670-674.
20. Low PA, Burke WJ, McLeod JG. Congenital sensory neuropathy with selective loss of small myelinated fibers. Ann Neurol 1978;3:179-182.
21. Donaghy M, Hakin RN, Bamford JM, et al. Hereditary sensory neuropathy with neurotrophic keratitis. Brain 1987;110:561-583.
22. Dyck JD, Stevens JC, O'Brien PC, et al. Neurogenic arthropathy and recurring fractures with subclinical inherited neuropathy. Neurology 1983;33:357-367.
23. Eichenholz S. Charcot joints. Springfield, IL: Charles C. Thomas, 1966.
24. Hodgson RJ, Pugh DG, Young HH. Roentgenologic aspect of certain lesions of bone: neurotrophic or infectious? Radiology 1948;50:65-71.
25. Demuynck M, Hoogmartens M. The neuropathic joint. Acta Orthop Belg 1984;50:645-657.
26. Greider TD. Orthopedic aspects of congenital insensitivity to pain. Clin Orthop 1983;172:177-185.