

National Institute of Diabetes and Digestive and Kidney Diseases

**Charcot Neuroarthropathy Workshop
September 17 - 18, 2008**

**Bethesda Marriott
Bethesda, MD**

SUMMARY REPORT

WEDNESDAY, SEPTEMBER 17, 2008

SESSION I: INTRODUCTION AND BACKGROUND

Welcome

Judith Fradkin, M.D., Division Director, Diabetes, Endocrinology and Metabolism, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

Dr. Fradkin welcomed participants to the workshop and said that Dr. Griffin Rodgers, Director of NIDDK, sent his regards and thanks to all those who made this workshop possible. The workshop is important because it focuses on one of the highest concerns among people with diabetes—the possibility of losing a limb. Although Charcot Neuroarthropathy (CN) only affects approximately 1 percent of people with diabetes, this is 1 percent of 24 million individuals, which is significant.

Dr. Fradkin thanked the NIH's Office of Rare Diseases for co-sponsoring the meeting, and Dr. Teresa Jones, the head of the NIDDK Diabetes Complications Program. Dr. Fradkin thanked the organizers of the workshop, Dr. Andrew Boulton for taking on the responsibility of chairing the workshop, and Drs. William Jeffcoate and Jan Ulbrecht for participating in planning.

Diabetic Neuropathy and Foot Disease: A Major Medical, Economic, and Social Disaster with Potential for Prevention

Andrew J.M. Boulton, M.D., F.R.C.P., University of Manchester, United Kingdom (U.K.)

Dr. Boulton welcomed those in attendance and noted that CN as a disease falls between specialties. It is unusual to have representatives from many of these specialties—podiatrists, surgeons, physicians, and also researchers working on bone biology and calcium metabolism—in the same room at the same time, but that was the purpose in planning this workshop. One of the biggest challenges in CN research is finding enough patients at an individual research center to conduct in-depth studies. This meeting will address this issue and the need for future collaborations.

An overview of the history of CN indicates that Dr. Jean-Martin Charcot (1825-1893), a French physician/neurologist from the Pitié-Salpêtrière Hospital in Paris, receives credit for describing

the condition known as CN, which was named after Charcot at the suggestion of Sir James Paget. Charcot did recognize the contributions of those who came before him, such as Mitchell. Modern history of the effects of peripheral neuropathy comes from Dr. Paul Brand, a surgeon and missionary who worked in India on patients with leprosy and diabetes. Dr. Brand first described the damage to the peripheral nerves that caused disfigurement in extremities afflicted with leprosy. He described the gift of pain that is often lost in this neuropathy: “Pain – the gift that nobody wants” – until it is lost.

Diabetic peripheral neuropathy (DPN) is a phenomenon caused by the dying back of the long axons, particularly in the lower limbs. The clinical consequences of DPN are different among patients; some have burning sensations, paraesthesias, hyperaesthesiae, allodynia, and nocturnal-exacerbation, while others have insensitivity and are more at risk of foot ulceration. The United Kingdom Prospective Diabetes Study (UKPDS) showed that greater than 10 percent of people at the initial diagnosis of type 2 diabetes (T2D) have significant neuropathy that puts them in danger of foot problems. Most studies show that approximately 50 percent of older patients with T2D are at risk of insensitive foot ulcers. The MONICA/KORA Augsburg Survey also supports the prevalence of sympathetic diabetic neuropathy at approximately 30 percent; this prevalence is supported by many other studies from different continents and countries. A past study by Cavanagh of foot x-rays of randomly selected neuropathic patients reported that in those with a history of ulcers, 22 percent had traumatic fractures and 16 percent had Charcot changes, although most patients did not have an awareness of the fractures or obvious foot deformity. In a large, multi-center prospective study on neuropathy and foot ulcers in 1,035 people with diabetes reported by Abbott in 1998, the incidence of foot ulcers in those with neuropathy and no history of foot ulcers was 7.2 percent; foot ulcer risk increased by 5.6 percent per volt vibration perception threshold (VPT).

It is critical that patients with diabetes are screened for neuropathy because: the annual risk of foot ulceration is 5 to 7 percent in DPN cases (<1 percent in non-neuropathic patients); DPN is asymptomatic in up to 50 percent of cases; it is common in up to 50 percent of older T2D patients; most symptoms are treatable; it is associated with increased mortality; and secondary complications, such as erectile dysfunction, are seen in many patients and are treatable. Every 30 seconds a leg is lost to diabetes somewhere in the world, and 70 percent of all leg amputations happen to people with diabetes. Foot problems are the most common cause of admission to hospital for people with diabetes, and foot problems may account for 40 percent of healthcare resources in developing countries. In addition, the direct cost of an amputation is estimated to be \$30K to \$60K. Most amputations begin with a foot ulcer, and each year, 4 million people worldwide get a foot ulcer. CN does not make up a large proportion of these costs. One in every six people with diabetes will have a foot ulcer during their lifetime. The take-home message should be that up to 85 percent of amputations can be avoided.

Recent U.S. adjusted data for 2007 indicate that the economic impacts of diabetic foot ulcers and lower-extremity amputations are \$18.9 billion and \$11.7 billion, respectively; potential savings based on practical reductions could equal \$11 billion and \$6.5 billion annually. International trends in numbers of amputations from 1995 to 2007 indicate that significant decreases are occurring in the United Kingdom, Germany, Sweden, and the Netherlands. Trends in the United States show no major decreases.

An approach for reducing diabetic foot problems is the creation of a multidisciplinary team to oversee prevention and treatment. An 11-year prospective study of hospital admissions for diabetic foot problems in Ipswich, England, showed that a multidisciplinary team approach could reduce the number of major amputations (decreased by 62 percent) and total amputations (decreased by 70 percent). Although there are other contributory factors to account for these decreases, the study confirmed the possibility that this approach warrants further study.

An important study for early assessment and prevention of diabetic foot ulcers was conducted in Texas and was supported by the NIH. The control group received standard therapy (i.e., therapeutic shoes and insoles, foot specific education, and foot care for up to 10 weeks). Two intervention arms were established, one called Structured Examination Therapy (i.e., control therapy plus a mirror to inspect their feet and a log book to record findings of their examination), and the other called Temperature Therapy (i.e., control therapy plus a temperature monitoring device). Results indicated that patients in the Temperature Therapy arm saw a significant decrease in re-ulceration. Other studies also support the concept that temperature monitoring has advantages for people with diabetes at risk for foot ulceration. Technologies to encourage temperature measurement of the feet to prevent foot ulceration have been developed and are being used successfully in some medical facilities.

The Comprehensive Diabetic Foot Exam (CDFE) Task Force of the American Diabetes Association (ADA) met in Chicago earlier this year and produced a technical review recently published in *Diabetes Care*. The purpose of the meeting was to review studies published in the past 10 years to develop recommendations for the range of tests to use for screening for risk of foot ulcers in the diabetic population. An additional purpose was to address concerns from practitioners on the best test(s) to recommend. The review strongly suggested that risk factors include neuropathy, peripheral vascular disease, past history of foot ulceration, microvascular complications (especially nephropathy), poor glycemic control, cigarette smoking, foot deformity, and amputation. Various prospective studies have indicated the usefulness of screening tests for foot ulcers. For example, from the North West Diabetes Foot Care Study (NWDFCS), it was known that the absence of ankle reflexes, monofilament insensitivity, a Neuropathy Disability Score (NDS) score greater than 6, past ulcer history, and ulcer present at baseline were valid tests for predicting ulcers. The Seattle Diabetic Foot Study (SDFS) found that monofilaments were the only predictive assessment of DPN, but that HbA1C, impaired vision, monofilament insensitivity, past ulcer, and previous amputation were predictive of ulcers. These studies showed that screening techniques can be simple and cost effective, with no complicated or highly technical tests needed for identifying those with impending problems.

Recommendations from the CDFE for screening in the community include the following:

History and general exam

- Peripheral vascular disease
- Past foot ulceration or amputation
- Renal status
- Footwear assessment
- Dermatological assessment
- Foot deformity

Neuropathy Assessment

- 10 gram monofilaments tested at four sites (MTH 1, 3, and 5 and hallux plantar), and one other of the following: 128 Hz tuning fork vibration—hallux; pinprick sensation—dorsal hallux; ankle reflexes; and VPT—biothesiometer/VPT meter

Vascular Assessment

- Foot pulse assessment—dichotomous. If any pulse is absent or Hx of PVD, then test for the ankle brachial index if possible.

Risk and Followup

- Risk Category (RC) 0: annual review
- RC 1 (LOPS ± Deformity): 3 to 6 monthly
- RC 2 (PAD ± LOPS): 2 to 3 monthly and consider vascular referral
- RC 3 (ph ulcer or amputation): every 1-2 months by specialist

Charcot Neuroarthropathy: Historical Aspects

Lee J. Sanders, D.P.M., Lebanon VA Medical Center, Lebanon, PA

Historic concepts of CN help us to better understand the pathogenesis and natural history of this rare disease. Several historical accounts of the history of this condition credit William Musgrave with the earliest description of arthritis with venereal (gonorrheal rheumatism) and non-venereal disease; however, Musgrave did not provide an incident description of neurogenic arthropathy “Charcot’s joint disease” of the foot and ankle. Contemporary analysis of Musgrave’s 1703 *De Arthritide Symptomata (Hist.4 Ex Colica Paralyticus, Arthriticus, Inunctione trucidatus)* reveals that what has been cited as a clear description of arthritis in paralyzed limbs is actually a case of paraplegic joints caused by a toxic motor neuropathy secondary to lead poisoning (Colica Pictonum). It should be understood that paraplegic joints are not the same as Charcot joints. The reader is referred to Sydney Eichenholtz’s 1966 monograph on Charcot joints and his observations of paraplegic joints.

In 1831, J.K. Mitchell published a manuscript describing the spinal origin of rheumatism and suggested a relationship between tuberculosis of the spine and arthropathy of the foot and ankle. In 1864, Mitchell’s son, Silas Weir Mitchell, described alterations in the “nutrition” of joints related to nerve injuries sustained by Union soldiers during the American Civil War. He observed cases of spinal injury in which rheumatic symptoms occurred. S.W. Mitchell concluded that “the indisputable fact [is] that there are rheumatisms depending for existence on neural changes.”

Jean-Martin Charcot’s earliest observations of the tabetic arthropathies were published in 1868. In this paper Charcot cites the writings of J.K and S.W. Mitchell, and depicts the unique clinical manifestations of the tabetic arthropathies and their symptoms. He describes his observations of a sudden and unexpected arthropathy, which often began without apparent cause and was frequently preceded by lancinating pains in the limbs. He observed the sudden onset of generalized swelling of the limbs in the absence of trauma to the knee, hip, and shoulder. He described sensory, motor, and trophic disorders similar to those seen today in patients with diabetes. Charcot presented his findings in 1881 at the 7th International Medical Congress in

London, one of the most prestigious meetings in the history of medical science. His contribution to the Congress consisted of a demonstration and lecture on multiple joint diseases resulting from locomotor ataxia. During his presentation he displayed the wax model of a 60-year-old woman with arthropathic affections of locomotor ataxy, together with the complete skeleton and photographs of different stages of the disease. Interestingly, Charcot did not describe or mention neurogenic arthropathy of the foot and ankle. Sir James Paget, President of the Congress, was so impressed by Charcot's presentation that he reported in the proceedings of the meeting that Charcot's description was of a distinct pathological entity that should carry the name of "Charcot's disease."

It is important to note a case presentation at the 7th International Medical Congress by a lesser-known English surgeon, Herbert W. Page, which described bilateral arthropathy of the foot and ankle in a case of *tabes dorsalis*. Page did not hesitate to associate the bone and joint changes that he observed in this patient with the group of tabetic arthropathies described by J.-M. Charcot. It is now recognized that Page was the first person to describe "the Charcot foot." To support this view, it should be noted that the first publications of Page's description of foot deformity associated with *tabes dorsalis* appear in the *Transactions of the 7th International Medical Congress*, the *British Medical Journal* (August 13, 1881), and the *Transactions of the Clinical Society of London* in April 1883. In the *Transactions of the Clinical Society of London* (1882-1883), Page recorded the earliest description of a rocker-bottom foot deformity associated with a tabetic arthropathy. The first published case series of the tabetic foot, "pied tabétique," by Charcot and Féré, did not appear until November 1883 in *Archives de Neurologie*. In the introduction to their paper, the authors contend that theirs is the first published description of the tabetic foot. "Described for the first time, by one of us, the bone and joint conditions of the ataxic are well recognized today, at least their general features, when located on the long bones of the limbs and their large joints.... Similar changes corresponding to the short bones and small joints of the foot have not yet been the subject of published observations." Charcot and Féré presented five observations of tabetic patients with locomotor ataxia, lancinating pains, and foot deformities. Observation II was the incident case presented by Herbert W. Page at the 7th International Medical Congress in 1881. In fact, the case is presented, word-for-word, from Page's presentation at the Congress. Charcot and Féré introduced the term *pied tabétique* to describe the extensive bone and joint destruction of the foot and ankle observed in patients with *tabes dorsalis*.

The association between Charcot's joint disease of the foot and ankle and diabetes mellitus was established for the first time in 1936, by William Reily Jordan. The similarity of Jordan's case to that produced by syphilis, in the absence of serologic confirmation, led him to believe that this condition was "a diabetic process of a neurologic trophic nature." The importance of the diabetic form of neuropathic osteoarthropathy was established in 1955, in a report by Donald Miller and William Lichtman. They noted that "whereas tabes of syphilitic origin was formerly the usual cause of these painless deformities of the feet with complicating soft tissue infections, ulcers and osteomyelitis, the diabetic neuropathic foot is now showing the higher incidence."

Therapy for Charcot's joint disease in the 19th century included: bedrest, firm bandage support, plaster casts, physical therapy, and off-loading the foot. During the 20th century, protection of the limb, early splinting and bracing, stabilization and alignment by conservative or operative

means, off-loading the foot, and external skeletal fixation have been promoted. Yet, in the first decade of the 21st century there is still an incomplete understanding of the pathogenesis and management of the diabetic Charcot foot. Recognition of this condition, especially in its earliest stage, remains problematic, with many cases going undiagnosed or misdiagnosed. Medical management remains the standard of care for most patients. Long-term surgical outcomes, including functional evaluations and quality-of-life studies comparing alternative methods of treatment, are lacking.

Of pressing need in this field is standardized nomenclature for the Charcot foot. Current nomenclature is often confusing, and there is a lack of consensus on uniform terminology for non-infective bone and joint disease in the neuropathic diabetic foot. Numerous medical eponyms as well as other terms and their variations exist in the literature to describe this condition. Some of these terms include Charcot's joint disease, the Charcot foot (*pied Charcot*), Charcot's osteoarthropathy, Charcot's neuroarthropathy, and diabetic neuropathic osteoarthropathy.

Given the history of this disease, in deference to J.-M. Charcot, the condition should rightfully be called Charcot's arthropathy or Charcot's neuropathic osteoarthropathy, crediting Charcot with his descriptions of a group of tabetic arthropathies; however, the incident description of neurogenic arthropathy of the foot and ankle should properly be credited to Herbert W. Page.

Discussion

On the issue of the etiology of Charcot's arthropathy, it was noted that there were two prevailing theories, promoted by the French (Charcot) and Germans (Volkman and Virchow), regarding the pathogenesis of the disease. Charcot's concept of a nutritive trophic regulation of the bones and joints, mediated by the spinal cord, became the basis of the French theory for the etiology of arthropathy seen in ataxic patients. Charcot believed that the bone and joint changes seen in patients with *tabes dorsalis* were related to a lesion of the spinal cord or the peripheral nerves and that these arthropathies were often seen prior to the development of locomotor ataxia. The German neurotraumatic theory espoused that the joint changes in affected individuals were nothing more than a traumatic arthritis caused by the manner of locomotion peculiar to these individuals. Contemporary thinking supports a neurovascular theory for the etiology of neuropathic osteoarthropathy.

The Diabetic Charcot Foot: Definition, Classification, and Staging

Robert Frykberg, D.P.M., M.P.H., Carl T. Hayden VA Medical Center, Phoenix, AZ

George Kozak defined CN in the following manner: "Neuropathic arthropathy is a relatively painless, progressive, and degenerative process affecting single or multiple joints due to underlying neurologic deficits." Trauma generally initiates this process. CN is a rare disease (less than 1 percent of the population), but is a significant complication of diabetes. The true incidence is not really known, but values from past prospective studies have ranged from 0.15 to 29 percent; this disparity is seen because of the disparity in the types of patients studied. It clearly is higher in people with diabetic peripheral neuropathy but is rare in the general diabetic population. Many diseases have the potential to cause Charcot neuroarthropathy, including

diabetes, *tabes dorsalis*, leprosy, syringomyelia, alcoholism, peripheral nerve injuries, congenital insensitivity to pain, Lyme disease, and HIV.

The history of CN was described earlier. A fairly well-defined list of clinical features of acute CN has been described and is as follows:

- Vascular—bounding pulses, edema, erythema, local warmth
- Neuropathic—diminished or absent: pain, vibration, light touch, deep tendon reflexes, proprioception. Some pain is frequently present.
- Skeletal—Rocker bottom deformity, crepitus, hypermobility
- Cutaneous—ulcers, anhidrosis, callus

Etiological theories of diabetic osteoarthropathy included the Neurovascular Theory of the French and the Neurotraumatic Theory of the Germans. Most current researchers have settled on a combined theory as described by Edelman (1987) that is known as the Combined Theory because it includes aspects of the neurovascular and neurotraumatic etiologies.

All diabetic neuropathic bone disease is not necessarily Charcot arthropathy. Not every neuropathic fracture or dislocation results in arthropathy. There are patterns of diabetic osteopathy, described by Newman in 1981, which include osteoporosis, new bone formation, bone loss, osteoarthropathy, pathological fracture, and spontaneous dislocation. Although not all fractures lead to CN, it has been suggested that all should be treated as if they may.

Various classification schemas have been developed for CN. Eichenholtz (1966) was one of the first, but there have been many others who have proposed classification schemes, although none of them have been validated for outcomes. The Eichenholtz classification is comprised of three stages based on pathological findings. The stages are as follows:

Stage 1: Stage of Development (Acute stage) characterized by joint debris, fragmentation, capsular distension, subluxation, and dislocation.

Stage 2: Stage of Coalescence characterized by absorption, coalescing large fragments, and sclerosis.

Stage 3: Stage of Reconstruction characterized by bone ends rounded, decreased sclerosis, and attempted restoration of joint architecture

In 1990, Shibata recommended a fourth stage, stage 0, be added to the Eichenholtz classification. Stage 0 is characterized by swelling, local warmth, and clinical instability due to ligamentous injury/occult trauma; radiographic changes are absent or minimal. MRI has been recommended as the most sensitive imaging modality to detect the bone marrow edema characteristically present during this prodromal stage.

Clinical stages based on the classification schema include Acute (stages 0 and 1) and Chronic (stages 2 and 3). The Chronic stages begin when inflammation begins diminishing and healing begins.

There have been many classification systems that focused on patterns of bone deterioration in the ankle and foot associated with CN. In 1966, Harris and Brand described a pattern of tarsal disintegration in leprosy that is determined by posture and mechanical stress, which often is initiated by unrecognized trauma. The pattern includes deterioration in the posterior pillar (type 1), central body of the talus (type 2), anterior pillar-medial arch (type 3), anterior pillar-lateral arch (type 4), and the cuneiform-metatarsal base (type 5). In 1991, Sanders and Frykberg proposed a 5-step classification for patterns of bone destruction. These were designated as Type I for the forefoot (MTP, metatarsal, and phalanges); Type II for the midfoot (LisFranc's and intercuneiform); Type III for the tarsal bones (Chopart's and naviculo-cuneiform joints); Type IV for the ankle and subtalar joints; and Type V for the calcaneus (calcaneal insufficiency avulsion fractures). Brodsky in 1992 and 1993 suggested an anatomic classification of the mid- and rear-foot comprised of Type I for the midfoot (tarsometatarsal and/or naviculo-cuneiform joints); Type II for the hindfoot (midtarsal (T-C and C-C) and subtalar joints); Type IIIA for the ankle joint; and Type IIIB for calcaneal avulsion fracture. There are other subtypes and stages proposed by other authors, such as Schon (1988) and Rogers (2008), but these are not used widely.

In summary, several systems are available for classification or staging of Charcot foot, including pathophysiologic, anatomic, radiographic, and clinical, although none have been validated as predictive of outcome or treatment. Early diagnosis remains the best strategy to prevent further deformity. The most commonly used classification is that developed by Eichenholtz, because it is the easiest to use and best facilitates management by making diagnosis early during the acute phase or in Stage 0 as defined by Shibata.

Discussion

The two overriding needs in CN research are to develop an internationally agreed upon classification system for CN and a definition. The classification system needs to be simple and based on radiographic and clinical changes. It may be premature to develop a classification unless a definition of CN is developed first, which impedes understanding what the classification system should include. For example, the current classification systems include disease processes (injuries, fractures, joint disturbances) that do not necessarily progress to CN, but rely more on descriptions of a series of processes, and overlapping processes, which render a clinical picture. Diagnosis depends on pattern recognition that may rely on experiences and preconceptions, which is not good enough to diagnose a disease. It is clear that all fractures do not lead to CN, which is part of the problem, because fracture is included in the classification.

The difficulty in diagnosis may be illustrated by the physician who sees a patient who has a hot foot and a fracture; this is a relatively clear case of Charcot foot. The problem is that without a definition, this is difficult to diagnose. Another patient may come in with an end-stage x-ray but does not have an awareness of when they received the fracture, although it is likely the patient ignored some of the Charcot signs, such as the swelling and temperature increase. It is unclear how to handle these types of clinical situations within any classification or definition schema. There was discussion on whether the Shibata "Stage 0" is actually already included in the Eichenholtz classification.

Charcot made his descriptions based on clinical signs and not radiographic evidence. Because there is a great discrepancy between the eventual outcome of similar fractures, or disruption of tissue, it is likely that the definition and classification should be made inclusive by putting all forms of disruption of tissue in a neuropathic foot in the Charcot category, because they all should be treated the same. However, by using such a broad definition of CN (sensitivity), we will be accepting a number of “false positives” that will not typically develop into fully manifested Charcot changes (i.e., simple neuropathic fractures of metatarsals that go on to normal healing). The important point is to raise the clinical index of suspicion for this disorder to effect earlier diagnosis, treatment, and limitation of deformity.

Epidemiology of Charcot Neuroarthropathy

David Margolis, M.D., Ph.D., University of Pennsylvania, Philadelphia, PA

It is difficult to conduct a high-quality epidemiologic study of Charcot foot. The studies in the literature report on the incidence and prevalence of the condition. Incidence is the number of new onsets of a disease in a specified *at risk* population in a measured period of time, and is often measured as a rate. *At risk* means that an individual can develop a Charcot foot (i.e., they have feet), not that they are more likely to develop the disorder, which might be better described as a population of interest. Prevalence is a measure of the instances of a disease within a measured population within a given period of time, often reported as within a lifetime, during a period of time, or at a point in time. In a steady-state population, the point prevalence of a disease and the incidence of a disease are closely related based on the average duration of the disease. Both incidence and prevalence are dependent on a clear definition and diagnosis of the disease, which is problematic in conducting an epidemiologic study for CN.

For a hypothetical epidemiologic study for CN, there must be a well-defined population to study that can be successfully followed over years; a well-defined diagnosis that can be easily applied reliably by all physicians; the money, interest, and time to conduct and maintain the study; and well-defined questions to answer. There appears to be some problem in meeting all of these criteria for CN.

There are few epidemiological studies of Charcot foot. A recent study by Frykberg and Belczyk (2008) reported the incidence of Charcot between 0.1 and 29.0 percent. The disparate numbers were the result of reviewing studies that had different definitions of the disease and surveyed different populations. Studies reporting the prevalence of CN found it to be between 0.08 and 13 percent. Because individuals with CN tend to live for more than 1 year after diagnosis, the results reported in this review of studies (incidence rates often greater than the prevalence rates) should make CN researchers very wary of the accuracy and meaning of these incidence and prevalence rates. Risk factors or health attributes thought to be associated with CN described in published studies have include age greater than 50 years, obesity, length of duration of diabetes, osteoporosis, and history of transplant surgery. Gender was neutral as a risk factor.

A thoughtful study by Lavery et al. is a fine example of the challenges in designing and conducting an epidemiologic study for CN. The study was on 1,666 patients followed for 2 years in a San Antonio, TX, disease management program. Many outcomes and health attributes were studied and well defined. Charcot neuroarthropathy was defined as lower-extremity fracture or dislocation in the presence of sensory neuropathy with loss of protective sensation.

This was likely not a primary endpoint of the study. Exams were conducted yearly with well-trained examiners. The incidence of CN was approximately 0.1 percent. Issues that may influence the validity of this result include that the goal of the study was really to determine the rate of foot abnormalities over time in a population of individuals referred into a diabetes care program; follow up was at least yearly but based on clinical concerns could be more frequent; the definition of CN may not be universally accepted; and treatment instituted by this care center may have influence the rate of onset of CN.

An approach to studying the epidemiology of CN could be to use existing datasets. An example is The Health Information Network (THIN), a network of physicians in the United Kingdom (England and Wales) who use a common computerized medical record system. Data are similar to the General Practice Research Database (GPRD). Physicians conduct a mandatory set of almost yearly examinations on those with diabetes. These databases currently contain 4.78 million subjects and 300 practices. A recent manuscript by Margolis et al. using THIN data from 2002 to 2006 on the association between foot ulcer and lower extremity amputation and chronic renal insufficiency found that the prevalence was approximately 0.1 percent, similar to the prevalence shown in other studies. As an example of a CN study using this database, data exist from 125,933 individuals with about 300,000 person-years of follow up. Using a set of diagnostic codes, the prevalence of CN is 2.1 percent in people with a diabetic foot ulcer and 0.05 percent in those without a foot ulcer. This population-based assessment of CN is within the lower bounds of the previously discussed review. However, it is unlikely that the study was an accurate assessment of the prevalence of Charcot's arthropathy because there likely were problems with reporting, a low predictive value of diagnostic codes for a disease like CN that is not well defined. However, assuming that the underlying cause of reporting bias is not differential, ratios of point estimates used more advanced analyses may be reasonable.

A review of CN in diabetes mellitus by Rajbhandari (2002) concluded that the true prevalence of CN in patients with diabetes mellitus was not known. Furthermore, they stated that it is likely that many cases are undiagnosed due to the lack of recognition of the typical acute presentation and the often asymptomatic nature of the condition. In addition, there are no agreed-upon clinical or radiological diagnostic criteria for CN; it is likely that cases are misdiagnosed or missed.

In conclusion, there are few good studies that can be used to determine the incidence or prevalence of CN in people with diabetes. The quality of many of the studies may be a concern, and there are a variety of definitions for the outcome(s) of interest. Unless a common definition of CN is devised, it may be too soon to conduct high-quality epidemiology studies. Currently, most available studies are not population based, which makes it unlikely that questions can be answered by looking in pre-existing databases. There is a need for very large population-based longitudinal study. Ultimately, more complex designs and analyses will yield a greater understanding of CN.

Discussion

In general, data on Charcot foot are inadequate to conduct scientifically sound epidemiologic studies. For example, general practitioners in the United Kingdom are not paid to diagnose CN,

only to conduct tests such as the pin-prick. Among populations at risk, especially among people with diabetes, there are no good studies on incidence or prevalence. Neuropathies exist among many people with diabetes that are classified as CN. One strategy is to follow all patients with foot problems to determine how many develop CN, but it still would be useful to follow all patients in the population and the population of those with diabetes.

In order to begin to collect valid data, there must be a set of parameters developed that are distributed to clinicians, and determine some method to have them report the number of patients who meet the parameters. This is the basic challenge in determining CN incidence and prevalence. Another option in the short term may be to include a foot exam in the National Health and Nutrition Examination Survey (NHANES), although there still is a need to have clear definitions and parameters before considering this strategy.

A suggestion is to refocus the conversation from studying “Charcot Neuroarthropathy” to “Diabetic Charcot Neuroarthropathy” because this is where it appears the major population at risk exists, where the amount of data would be greater, and our understanding of the disease is better elucidated.

Submitted Abstract Presentation: Health Status and Quality of Life (QoL) of Patients Affected by Charcot Neuroarthropathy (CN)

Loretta Vileikyte, M.D., Ph.D., University of Manchester, Manchester, U.K.

Dr. Vileikyte’s study of 489 patients from the United Kingdom and the United States at high risk for neuropathic foot ulceration, 71 percent of whom had T2D, employed generic (Short Form, SF-12; Hospital Anxiety and Depression Scale, HADS) and foot problem-specific measures (NeuroQoL) to investigate the impact of CN on health status and QOL. Sixty-seven patients were identified at baseline with CN. Neuropathy severity was assessed by the Neuropathy Disability Score (NDS) and the Vibration Perception Threshold (VPT).

Compared to patients without CN, individuals with CN reported more NeuroQoL-symptoms of reduced feeling (3.8 vs. 2.7, $p < 0.001$) and unsteadiness (2.8 vs. 2.3; $p = 0.007$); more impaired activities of daily living (NeuroQoL-ADLs 3.2 vs. 2.4; $p < 0.001$); and more NeuroQoL-emotional burden (2.8 vs. 2.0; $p < 0.001$). In multivariate regression analyses, controlling for disease, demographic characteristics, NDS/VPT, and foot ulceration, CN was a significant independent predictor of NeuroQoL-emotional burden (beta = .10, $p < 0.05$), poorer foot problem-related QOL (beta = .17, $p < 0.001$), and diminished SF12 physical functioning (beta = -.08, $p < 0.05$), but not mental functioning. Furthermore, no significant association was found between CN and HADS-depression or anxiety.

Conclusions were that these data illustrate the detrimental effects CN has on individuals’ QOL, as indicated by generic and condition-specific measures. CN impacts individuals’ physical functioning, causes emotional distress, and reduces foot problem-specific QOL over and above demographic factors, diabetes severity, and somatic experience of neuropathy (symptoms and foot ulceration). However, only condition-specific measures identified emotional effects. The latter finding emphasizes the importance of condition-specific measures when assessing the emotional state of CN patients. Further research is needed to map the specific pathways by

which CN reduces QoL in these individuals.

Discussion

In the study, the presence of foot ulceration was adjusted for in the analyses. This was not a study of CN *per se*, so there was no way to specify the stages of CN. It is known, however, that all patients had chronic rather than acute CN. Implications of the level of distress are not adjusted for in the data. The SF-12 and HADS scales do not capture the level of emotional distress; therefore, condition-specific measures should be used when examining the impact of CN on emotional functioning.

Submitted Abstract Presentation: The Association between Obesity and Charcot Neuroarthropathy in a Diabetic Population

Elly Budiman-Mak, M.D., M.P.H., Loyola University Stritch School of Medicine and Edward Hines Jr. VA Hospital, Hines, IL

Dr. Budiman-Mak reviewed the facts about CN and noted that delayed diagnosis or mismanagement can lead to fracture, dislocation, foot ulcer, amputation, and permanent disability. The data sources used for the study were from databases of the Veteran Affairs Administration (VA), and included all patients with diabetes seen by the VA in 2003.

The purpose of the study was to estimate the incidence rate of CN among VA diabetics; examine whether obesity is significantly associated with incidence of CN; and test whether the effect of obesity on CN incidence is different in the presence of peripheral neuropathy (PN) and/or peripheral vascular disease (PVD).

Results of the study indicated that 0.12 percent (652/561,597) of patients with diabetes were newly diagnosed with CN in FY 2003. Compared to patients without obesity, PN, or PVD, those with obesity alone were approximately 57 percent more likely, and those with obesity, PN, and PVD were 34-fold more likely to develop CN. The study determined that 1.2 per 1,000 persons in a large veteran population with diabetes have CN. Obesity, PN, and PVD are significantly associated with CN in this model. Incidence rates are likely to increase as diabetes and obesity become more common in aging veterans. In addition, weight and glycemic control could reduce risks of developing Charcot neuroarthropathy, a complication of chronic diabetes.

Heightened awareness about CN would lead to early detection and prevention of disability and amputation. Future studies may include the investigation of the effects of different treatment options on outcomes for patients with CN, and the personal and health system burden of this morbidity.

Discussion

There were approximately 6 percent female patients included in the VA database used for this study. The conditions assessed in the study—CN, PVD, and PN—were determined using ICD codes, and all associations have a p-value less than 0.05. In many of the earlier presentations at this meeting, PN is part of CN, but in this data analysis it appears that PN is outside of CN. There are many questions raised by the results of the study, and some could be accounted for by

the lack of information on the duration of the disease in patients used for the study. There may be a followup study to determine inflammatory cytokines involved in the disease found in these patients.

SESSION II: UPDATE ON CALCIUM AND BONE BIOLOGY

The RANKL-OPG System and the Bone Vascular Interphase

Lorenz Hofbauer, M.D., University Hospital Carl Gustav Carus at the Technical University of Dresden, Germany

(NOTE: Dr. Hofbauer also covered some of the material on “Bone Biology and Control Mechanisms: Normal Bone Turnover, Fracture Healing, and Possible Abnormalities in Charcot Neuroarthropathy” that was to be presented by Dr. Greg Mundy, Vanderbilt University, who was unable to attend.)

Bone metabolism is a dynamic balance of bone formation and resorption, with complete bone turnover occurring approximately once every 7 years. There is growing interest in the factors that affect bone metabolism. As for bone formation, stimulators include bone morphogenetic proteins responsible for the genetic shaping of the bones of the body, and mechanical load and androgens; bone formation inhibitors include aging, immobilization, and leptin. Factors that promote bone resorption include estrogen deficiency, immobilization, and a diet low in calcium or vitamin D. Epidemiological studies indicate that vascular diseases (e.g., myocardial infarction and stroke) are major contributors to mortality among those with osteoporotic fractures. Common etiologies for this association include age, estrogen deficiency, cigarette smoking, diabetes mellitus, renal failure, chronic inflammation (e.g., rheumatoid arthritis), and the presence of reactive oxygen species (ROS) and free radicals.

Arterial calcification (AC) is considered a major risk factor for mortality from atherosclerosis among patients with osteoporotic fractures. Studies have shown that there can be calcification in the smooth muscle cells of the arteries without preexisting atherosclerosis, especially in men with diabetes. Studies have reported on knockout animal models with a phenotype of atherosclerosis and vascular calcification. For example, studies have used knockouts for the genes matrix gla protein (MGP), a matrix protein that is gamma-carboxylated (vitamin K-dependently); fetuin-A (alpha2-Heremans-Schmid glycoprotein), a serum protein forming soluble calciproteins; and osteoprotegerin (OPG), a receptor antagonist for RANK ligand.

Osteoclasts are the primary mediators in perturbations in bone metabolism responsible for bone diseases. There are three factors associated with formation of osteoclasts; (1) RANKL (Receptor activator of NF-kappaB ligand and a member of the TNF superfamily), (2) RANK (Receptor activator of NF-kappaB and a member of the TNF-R superfamily), and (3) OPG (Osteoprotegerin, a soluble receptor antagonist [homodimer] and the antagonist for RANKL). RANKL is sufficient for osteoclastogenesis and an essential cytokine for osteoclasts. OPG is produced and secreted by osteoblasts, neutralizes RANKL, and prevents activation of RANK. RANKL and OPG also have effects on the immune system. For example, activated T cells are

able to secrete RANKL to activate osteoclasts directly. This occurs in rheumatoid arthritis, but there may be some involvement in Charcot foot.

OPG not only blocks RANKL but also blocks TRAIL, an inducer of apoptosis. This demands caution in designing drugs that block OPG. A therapeutic approach is to produce an antibody against RANKL, rather than block RANKL with OPG-analogues.

In studies of a rat model of rheumatoid arthritis, the RANKL-to-OPG ratio is enhanced in arthritic rat joints, which indicates an increase in osteoclastic potency and an increase in TRAP-5 that shows increased bone resorption. Another study showed that blockade of RANKL prevents bone loss in experimental arthritis. When arthritis is induced and OPG is blocked, inflammation still occurs in the bone, but there is suppressed bone resorption and bone loss.

Regulators of RANKL and OPG have been investigated in experimental studies. These studies indicate that glucocorticoids inhibit OPG production. In a small study in patients with Crohn's disease, treatment with prednisolone lowered OPG after a few weeks, although levels increased after that time. Studies of estrogen therapy in small groups of pre-menopausal women, postmenopausal women, and postmenopausal women on hormone replacement therapy (HRT) found that estrogen deficiency upregulates RANKL expression; this was reversed with HRT.

RANKL is now gaining acceptance as a factor in development of Charcot disease because of its relationship to inflammation. A recent study of osteoclastogenesis in patients with acute Charcot's osteoarthropathy and diabetic and healthy controls to determine the effect of the RANKL and OPG found that patients with CN developed more osteoclasts when fed a fixed dose of RANKL. An experimental study in OPG-deficient mice found that in the absence of OPG the mice have increased numbers of osteoclasts, loss of lamellar structure, reduced bone density, and osteoporosis and fracture. In addition, the OPG-deficient mice have vascular calcification that looks like the medial calcification reminiscent of Mönckeberg medial sclerosis.

OPG is expressed in the aorta, kidney, and thyroid. Rats that were given large doses of vitamin D had enhanced bone resorption along with pronounced vascular calcification; when given OPG, bone resorption was reversed as was vascular calcification. Further studies have shown that vascular calcification is not a passive process but is caused by active processes. It is important in the early phases that inhibitors of calcification are present, such as fetuin-A or MPG; OPG probably may not have a direct effect on vascular calcification; its vasculoprotective effect may be related to its antiresorptive effect. However, further study is needed to confirm this. Risk factors that increase inflammation in the vascular wall also contribute to calcification.

Strategies have been developed to block the processes of calcification. RANKL is blocked by denosumab (DMAB), which acts in a manner similar to OPG. A recent study of DMAB in postmenopausal women found that treatment with DMAB increased bone mineral density (BMD). DMAB lowers bone resorption (given every 6 months), and a presentation at another conference indicated that DMAB reduces fracture rate. It has been suggested that a clinical trial of DMAB should be conducted in CN patients to see if inflammation-triggered bone loss in CN can be reduced.

In summary, the RANKL/OPG system is essential for bone homeostasis and modulating vascular function; a variety of factors (e.g., OPG, MGP, and fetuin-A) are involved to inhibit vascular calcification; as in osteoporosis, rheumatoid arthritis, and some tumors, the RANKL/OPG ratio is upregulated in acute Charcot foot; and DMAB is a specific inhibitor of RANKL.

Discussion

There is not much known about the association between neuropathy and calcification. Equivocal findings also are present in the literature on CN and BMD. Some Charcot patients have normal BMD in the lumbar spine but regional osteoporosis, and it is unclear why there is no systemic effect. T2D patients can have normal BMD but poor bone quality; another factor is that fracture-healing in T2D may be impaired as a consequence.

There is no apparent relationship between calcitonin gene-related peptide (CGRP) and RANKL-OPG.

RANKL-OPG is found in arterial wall calcification—this conflicts with some of the literature that says there is no expression of RANKL in cells near calcification, but there is OPG expression.

Submitted Abstract Presentation: Radiographic Correlates of Charcot Neuroarthropathy Deformity Reflect Midfoot Function and Calcaneal Bone Mineral Density

Mary K. Hastings, D.P.T., P.T., A.T.C., Washington University School of Medicine, St. Louis, MO

Dr. Hastings described a study in which she and her colleagues applied three radiographic quantitative measures of midfoot deformity to individuals with diabetes mellitus and peripheral neuropathy. The correlations between the midfoot deformity measures and peak plantar pressure (PPP) and calcaneal BMD were assessed. She reported that the study indicated PPP was negatively correlated with cuboid height, calcaneal pitch, and Meary's angle. In addition, calcaneal BMD was poorly correlated with calcaneal pitch but moderately correlated with cuboid height and Meary's angle. In conclusion, lowering of the midfoot arch is associated with high midfoot PPP and lower calcaneal BMD.

Further studies will determine the BMD of all tarsals and metatarsals and gait kinematics to provide information critical to preventively addressing contributing factors to deformity.

Discussion

Although it is difficult to quantify disease progression, the concept of this study seems relevant. The radiographic measurement tool includes a measure of forefoot abduction and a designation of the location and severity of fractures. The current alignment rating tool does not include a measure of metatarsophalangeal or interphalangeal alignment.

Submitted Abstract Presentation: The Role of the Pro-inflammatory Cytokine TNF- α in Acute Charcot Neuroarthropathy

Michael Edmonds, M.D., King's College Hospital, London, U.K.

One of the crucial questions is how and why an acutely active Charcot foot progresses to the chronic deformed foot in the space of a few weeks. Regarding this pathogenesis, many factors (e.g., inflammation, resorption, and osteoclastic activity) have been investigated. Studies of inflammation in acute CN, chronic CN, and diabetic patients have shown that levels of IL-6, TNF- α , and serum C-terminal telopeptide (CTx) are higher in chronic CN.

Dr. Edmonds presented his abstract on the role of pro-inflammatory cytokine TNF- α and other markers of inflammation in CN and diabetic patients. *In vivo* studies included serum markers of bone turnover (e.g., CTx and bone alkaline phosphatase [BAP]) and serum markers of inflammation (e.g., TNF- α , IL-1 beta, IL-6, and OPG). Nine patients with acute CN and eight diabetic controls were studied. Results indicated that serum levels of CTx were significantly higher in patients with acute CN compared with diabetic patients. There was significant correlation between CTx and hsTNF- α , but although hsTNF- α levels were increased in acute CN, this did not reach significance. hsTNF-levels were significantly associated with osteoclast formation and resorption in cultures with M-CSF+sRANKL, and similarly with osteoclast formation and resorption in cultures with M-CSF+RANKL+OPG). Pro-inflammatory cytokines (including TNF- α) correlate with markers of bone resorption *in vivo* and osteoclastic activity *in vitro*. We believe that these new observations may help to explain the pathogenesis of Charcot osteoarthropathy.

Further studies will include investigating cultures of peripheral blood monocytes (PBMCs) in the presence of neutralizing antibodies to TNF- α to confirm its role. In conclusion, TNF- α may be important as an osteoclastic activator in acute Charcot osteoarthropathy and its inhibition may lead to future therapies.

Discussion

The monocytes from which the osteoplasts develop show greater activity in acute CN patients. There is no sure answer to why this is so, especially why they begin this increased activity before apparent CN progression begins; it may be that the pro-inflammatory cytokines increase the activity through some mechanism we do not understand at this point.

One area of potential investigation is the CD-16 monocytes, characteristic of rheumatoid arthritis, which may play a role in CN progression. It is suggested that the CD-14 monocytes are a factor.

SESSION III: PATHOGENESIS AND DIAGNOSIS

Aetiopathogenesis of Charcot Neuroarthropathy: An Update for 2008

William Jeffcoate, M.D., University of Nottingham and City Hospital, Nottingham, U.K.

The causes of CN are complicated, with many pathways suspected of being involved. The German and French theories have been explained before but there is no consensus on the true causes, although there is currently a synthesis of the two theories that is leading researchers nearer to understanding.

It is known that fracture will cause a 2 to 3 day increase in inflammatory cytokines that cause bone breakdown (to clear the broken pieces), before healing can begin. RANKL and OPG are involved in this process. Lorenz has shown this relationship, and it is osteoblasts that are most likely to express RANKL, although there are other monocytes in other tissues that may express RANKL. RANKL then acts on the nucleus to cause increased expression of NFκB, which causes maturation of the osteoclasts. This also leads to the production of OPG, which acts as a decoy receptor for RANKL and inactivates it. Regulation occurs from various pro-inflammatory cytokines and sex steroids. One interesting regulator is CGRP, but others, such as leptin and IAPP, may be important in diabetes.

There may be several explanations why people with diabetes are predisposed to the process described for fracture, and ultimately, CN. Evidence suggests a change in RANKL and OPG occurs in people with T1D and T2D; they have higher circulating levels of OPG. ROS, oxygenated lipids, advanced glycated end-products, glucose, or insulin each impinge on the RANKL pathway and could be an explanation for overexpression in diabetes.

CGRP leads to underexpression of OPG (thus protecting bones), and may be dependent on loss of nerves such as occurs in neuropathy. Few studies have looked at this relationship; a small study showed that people with diabetes have higher levels of OPG, and it is even higher in people with neuropathy.

Another line of research is the study of the endocannabinoid system. The endogenous ligands for the cannabinoid (CB) receptors CB1 and CB2 are found in both the central nervous system (CNS) and peripheral nervous system (PNS). CB1 and CB2 receptors are widely distributed in bone; CB1 receptors may mediate the effects of leptin and centrally acting neuropeptides on bone; the CB2 receptors are anabolic for bone; and endocannabinoids may modulate the adrenergic control of bone metabolism.

Another issue in CN is AC, although it is known that approximately 20 percent of people with diabetes have AC and approximately 40 percent of also have neuropathy. The prevalence of AC is approximately 80 percent in people with CN. RANKL is associated with AC, and that autonomic neuropathy is associated with increased expression of RANKL.

Although increased RANKL expression may lead to AC, and is increased in people with neuropathy, there still is no clear reason to explain how this predisposition leads to the cycle of inflammation that results in CN. A study in newly diagnosed cases of CN, inflammation is the

one factor that is common among most of these cases.

In summary, predisposing factors for CN may include diabetes, neuropathy, osteopenia (especially in alcoholics), chronic kidney disease, renal transplantation, and body mass index (BMI). Possible predisposing factors may be the use of thiazolidinediones and genetic factors. The precipitating factors for CN include trauma and dislocation. Perpetuation of CN can be caused by inflammation and continued trauma, which may be enhanced by neuropathy.

Discussion

It was noted that recent studies indicate an increase in CN among pancreatic transplant patients.

As to the question of dislocation, there are many hypotheses about the process and how it is initiated. Some researchers think it begins in the LisFranc area, but by an unknown initiating process. Another key research need is to understand why inflammation stops in CN patients after 2 to 3 days; this is especially true in CN with offloading.

The study of neuropeptides has provided valuable information, but there are many areas left unstudied. For example, the association of CGRP in CN has been studied, but in some studies CGRP is decreased in CN patients. These types of questions do not have easy answers without more research in large numbers of patients.

Risk Factors in Charcot Neuroarthropathy

Michael Edmonds, M.D., King's College Hospital, London, U.K.

Predisposing risk factors in nerve, bone, joint, and circulation can lead to CN. There is the possibility of a difference in predisposition to CN between patients with T1D and those with T2D.

Neuropathy is an absolute requirement for the development of CN. The various diseases in which CN occurs (diabetes, leprosy, *tabes dorsalis*, syringomyelia, alcoholic neuropathy, congenital insensitivity to pain) all involve neuropathy, and their nature may provide clues as to the type of neuropathy involved (e.g., syringomyelia involves pain and temperature fibers, alcoholic neuropathy involves very severe pain, and congenital insensitivity to pain involves the small fibers).

An illustration was shown of CN in a shoulder joint in syringomyelia, with fragmentation and marked destruction of the humeral head, followed by an attempt at sclerosis. This case illustrates the massive necrosis that can occur in CN and may support the French neurotrophic theory because the shoulder joint experiences less stress than the foot does.

Dr. Martin Stevens and his colleagues have demonstrated that diabetic patients with CN have a very high, abnormal thermal threshold to cold but a variable pattern of response to warm sensation, whereas diabetic patients with ulcerated neuropathy have impairment of both types of temperature perception. The vibration threshold for large fiber neuropathy was found to be similar in CN patients and those with ulcerated neuropathy, both of whom differed from controls.

Dr. Boulton and Dr. Matthew Young and their colleagues, however, found that CN patients had abnormal temperature perception thresholds for both hot and cold, which were indicative of a global neuropathy. Dr. Young also evaluated autonomic neuropathy using the heart rate variation test and found abnormal results in all 17 CN patients tested.

Neuropathy plays a role in CN through the anti-inflammatory reflex, as previously discussed in Dr. Pitocco's presentation. Ischemia or injury leads to cytokine release, which if unbalanced, can lead to severe tissue injury. The autonomic nervous system is important in controlling cytokine release. A reflex goes to the autonomic centers, and from there, via the vagus nerve, there is an efferent response. In the periphery, macrophages are involved in the response. A subunit of the acetylcholine receptor on the macrophage can inhibit cytokine release. Uncontrolled cytokine release occurs in neuropathy and may contribute to the overall poor prognosis of patients with neuropathy.

Abnormalities of the nervous system may interact with those of the bones in CN. It has been established from periodontal work that sympathectomy decreases osteoblastic activity, increases osteoclastic number, and decreases BMD. Dr. Young and his coworkers measured BMD in the lower limbs and found that CN patients had reduced BMD compared with neuropathic control subjects, although BMD in the spine was relatively preserved. Similar findings have been reported by Dr. Alexandra Jirkovská from the Czech Republic.

Dual-energy x-ray absorptiometry (DEXA) scan measurements in the contralateral femoral neck have shown lower bone density in patients with a fracture pattern of CN as compared to those with a dislocation pattern.

In their own research, Dr. Edmonds and his colleagues found that ICPP, a marker of osteoclastic activity, was significantly raised in patients with acute CN compared with those with chronic CN and with diabetic and non-diabetic controls, whereas an osteoblastic marker did not show this pattern. These findings are indicative of an uncoupling between the osteoblast and osteoclast responses. They then evaluated T1D and T2D patients separately and found that both groups had reduced BMD in the Charcot foot. Only the T1D patients, however, had reduced BMD in the unaffected foot. Thus, there is evidence of preexisting osteopenia at the onset of CN in T1D but not T2D; this finding supports Dr. Jeffcoate's concern that CN can develop in patients with normal bone density.

The precursors of osteoclasts, the main cells responsible for bone resorption, are found in bone marrow and the monocytic fraction, particularly the CD14. These cells undergo proliferation and differentiation into large multinucleated cells. Classical culture techniques require both MCSF as a growth factor and RANKL as an osteoclastogenic factor to yield bone-resorbing osteoclasts, but monocytes from CN patients can progress to bone-resorbing osteoclasts with just MCSF in the culture, without RANKL. This is a very high risk factor, but whether it precedes or results from CN is unknown. In addition, a small pilot study has indicated that the proportion of CD14 monocytes in patients with CN is significantly increased in comparison with both diabetic patients and healthy controls.

Joint dislocation is also an important feature of CN, but why it occurs has not been fully elucidated. Weak ankle dorsiflexors, Achilles tendon shortening, increased plantar pressures, and limited joint mobilities may be significant factors. Very high peak plantar pressures have been demonstrated in the affected foot in patients with CN, as compared to the unaffected foot or to patients with neuropathic ulcers. Bone scans indicate a variable number of “hot spots” that suggest avulsion fractures and ligamentous tearing at these areas, with marked inflammation.

Circulation in the Charcot foot is abnormal, with very high systolic and diastolic flow. It must be remembered, though, that the Charcot foot has massive bone and joint destruction, and thus it is unclear whether the circulatory abnormalities represent a cause or an effect. In patients with diabetic neuropathy, vasomotion and blood flow are disordered, but in CN they are preserved, which may be protective against bone resorption but allows bone activity leading to CN. C fiber function has been found to be equally impaired in neuropathic patients with and without CN, but a higher maximum hyperemia distinguishes patients with peripheral neuropathy from those with CN. The affected and unaffected limbs in CN patients have the same neurovascular abnormalities, suggesting that these abnormalities precede CN and are not a result of it. Venous pressure is high in patients with CN, as compared to diabetic controls and normal controls, but it is not significantly higher in CN patients than in those with diabetic neuropathy. High venous pressure is a feature of neuropathy in general.

Precipitating factors for CN may include accident, ulcer, surgery, and osteomyelitis. As previously discussed by Dr. Frykberg, both trauma and predisposition from sensory neuropathy were necessary for the development of CN in a cat model. It is hypothesized that there is a traumatic factor precipitating every case of Charcot foot. In the presence of an autonomic neuropathy, uncontrolled cytokine response to injury leads to inflammation, osteoclastic activation, and bone and joint destruction. The pathologic process may differ, however, between T1D and T2D patients. In T1D, the combination of osteopenia and small fiber neuropathy may lead to fractures, which supports the French neurotrophic theory. In T2D, however, a global neuropathy, without osteopenia but with dislocations promoted by obesity, may be present, which supports the German neurotraumatic theory. Thus, it is possible that both theories are correct, each in a different type of patient.

Discussion

There is some uncertainty about whether the data are sufficient to support the conclusion that T1D patients with CN have preexisting osteopenia but those with T2D do not; the difference in age between the two patient groups is an important confounding factor, and the use of the unaffected foot for comparison with the affected foot in unilateral CN may be less than ideal. Statistical analyses of larger samples are needed to confirm whether substantial bone density differences exist between the two types of patients and to determine whether fractures are more common in T1D and dislocations are more common in T2D. It would also be of interest to have statistical data to confirm or refute the clinical observation of a predominance of forefoot and hindfoot (calcaneal) fractures in CN patients with T1D.

Advances in Understanding of Charcot Disease and Implications for Diabetes in General
William Jeffcoate, M.D., University of Nottingham and City Hospital, Nottingham, U.K.

The relationship between CN and AC and the mechanisms involved are still undecided. RANKL may be involved in AC but the data are not as strong as they could be. Bone breakdown is another factor, and with the release of calcium and phosphate, especially in chronic kidney disease. Osteolysis could be through the loss of CGRP or the cannabinoids.

The prevalence of AC previously has been reviewed and shown to be elevated in other causes of neuropathy, but not to levels as high as in diabetes. As for the processes of new bone formation, the histological appearance of intimal calcification (i.e., ossification) that complicates atheroma is endochondral calcification, whereas the one that occurs in Monkey-Begs calcification has the appearance of membranous bone.

It is difficult to understand published research on bone because much is left unsaid. For example, one would have to know that many of the cells that trigger ossification are the very cells that form the new bone. These cells can be caused by trauma, high blood pressure, metabolic changes, or inflammation; this makes understanding the etiology for calcification difficult to separate into clear processes. All types of factors (e.g., TNF- α , TRAIL, and RANKL) are responsible for inducing apoptosis and setting the stage for mineralization. Once bone-forming cells are produced, alkaline phosphatase, which opposes pyrophosphate, and MGP and OPG tend to have a modulating effect on the bone-forming cells.

Clinical implications of AC can be devastating on the individual. Tests for the sympathetic nervous system may not be accurate in the presence of stiff arterial walls, which cannot restrict. The relevance is in the way Ewing-type tests are conducted; it does not necessarily show that this result is reliable. In AC there is monophasic distal blood flow that causes a higher systolic blood pressure; in fact, high systolic blood pressure (SBP) is a symptom of AC and by treating it there may be a situation where treating one condition can exacerbate another condition.

In a small case series of CN (n = 47), a shocking 44.7 percent mortality was seen. In the study, a comparison of those with CN and those with neuropathic ulcers found that mortality among those with CN was still higher.

What must be investigated is the connection between microvascular and macrovascular disease in CN. It is clear that this connection exists in some form, but no one seems to know how to address this issue is unclear.

In summary, it is unclear if AC is the cause or consequence of CN. There are metabolic factors, but there may be nerve-dependent factors seen in those with diabetes and CN. Whether peripheral calcification is OPG-dependent is an area for future research, as is understanding the role of RANKL. Among the consequences of CN, research must address the role of systolic hypertension in calcification and whether it is made worse by the pre-existing loss of peripheral resistance, and whether abnormal distal (and coronary) blood flow are made worse by antihypertensive therapy and/or dialysis.

Discussion

Although many patients with CN have AC, it may be interesting to look at CN patients who do not. This area would need to have interdisciplinary groups working together to address the question.

Amputation rates among people in the U.K. are much lower than in the United States, and these were not thought to be a factor in the high mortality rate seen in the data from the small case series study. The cause for death was not classified in the study, but the presumption is that most of the deaths were a result of CVD.

Goals of Therapy of Charcot Fractures and Assessment of Outcomes

Peter R. Cavanagh, Ph.D., D.Sc., University of Washington, Seattle, WA

Goals of therapy for Charcot fractures include prevention, QOL, and biomechanical intervention. Prevention should focus on preventing progression, ulceration (or re-ulceration), or bilateral disease. One of the most challenging aspects of prevention is preventing re-ulceration. Data indicate that re-ulceration in non-CN neuropathic patients is extremely high (4-year ulcer-free survival is 0 percent), but there are no published data on recurrence in CN patients. Very little is known about bilateral disease. The best current estimate of previous contralateral CN is 15 percent (from unpublished data), and there may be a higher incidence of bilateral disease in younger people, women with eating disorders and diabetes, and in renal transplant patients.

QOL goals include the ability to continue working, to be independently mobile, and to wear shoes. Various assessment instruments are available to measure the physical and mental state of CN patients. Some have been described in earlier presentations. The SF-36 is one of the most common QOL instruments from CN research, but there are other instruments that can be more useful in specific studies. No instrument is the best in all situations. Part of being able to have a good QOL is the ability to move about freely. To this end, development of functional biomechanical boots for CN patients is a critical area for development. Not only should the shoe/boot be functional, it must allow the patient to feel that the style is appropriate for their lifestyle. Interestingly, a study on the needs of CN and diabetic patients regarding biomechanical boots found that CN patients were much more concerned with functionality and comfort, whereas diabetic patients wanted the boot to be stylish.

Assessment in CN usually begins with temperature of the limb for staging and progression; this is conventional wisdom, but may not be accurate. Most studies use temperature as one of the measurements, but the evidence for its use is equivocal. For example, a 2004 study by Jude showed that temperature does decrease over a 24-week treatment period, but in looking at the data, it was not a dynamic indicator during the 24 weeks. In addition, in the Alendronate study the treatment group and control group did not have a difference in temperature over the life of the trial. Other studies have shown the same thing. Results of these studies indicate that temperature may not be as important as previously thought.

Imaging is useful in staging and following the progression of CN. It may be that this assists in classification but not in quantification. Studies that use structural changes in X-rays for joint

dislocation and bone disruption have not been validated and, thus, it is unclear as to whether they should be used in assessment or staging. In a study among people with diabetes and calcaneous bone density, there appeared to be a lower bone density in the T1D CN patients compared to the T1D controls; this difference was not observed in comparisons of people with T2D CN and T2D controls.

In the Alendronate study, investigators used DEXA scanning to measure BMD in postmenopausal women. The study found that in total foot mineralization in the distal phalanges and proximal femur, the treatment had an effect, but is not surprising given what is known about Alendronate therapy.

The MRI is another imaging technology used in studies of CN. It has been found to be relatively useful in describing progression, and this may indicate its ability for use in quantification. Most of the MRI studies have been conducted for a differential diagnosis. A drawback to gallium-contrast MRI is that the imaging technique is not useful in the presence of infection. One of the most interesting advances in Charcot imaging is the use of high-field strength magnets, which can give greater details with the use of stronger magnets. This technique, if widely available, may offer the opportunity to see details not seen previously and the ability to build better models for representing disease status, progression, and quantification.

Among serum and urine markers for measuring progression and quantification, recent trials have used traditional markers with some interesting results. For example, in the Pamidronate trial, the traditional markers of bone-specific alkaline phosphatase and deoxypyridinoline, a marker of bone collagen breakdown, were both different at different times during the treatment. In the Alendronate trial, of the 15 markers studied, two interesting markers that were identified as having promise for use in assessing treatment were a telopeptide of type 1 collagen (ICTP) and urinary hydroxyprolin. Nontraditional bone markers relate to some aspect of newer theories of pathogenesis that are emerging from recent research, although not enough information on them has been collected to know if they will ultimately be useful.

Biomechanical measures are important in CN research because they relate to treatment success and QOL. Early studies found there was no difference in peak pressure between the affected and the unaffected foot in patients who had CN, and that peak plantar pressure was on the forefoot, suggesting that the forefoot may function as a lever, forcing collapse in the midfoot. What is not known is whether the barefoot pressure or in-shoe pressures are subject to change.

In summary, CN research is on the threshold of a number of new approaches. At present, there are many methods of characterization but few have been shown to be sensitive and specific to progression and/or treatment. This impacts the planning for future clinical trials in CN because of the need to develop good outcome measures before conducting trials.

Discussion

There was some discussion of ligament damage and deterioration in the progression of CN. Most studies that looked at ligaments using MRI found that ligament destruction and separation had to do with bone deterioration first as the cause of ligament failure.

As for the impact of reducing pressure on the foot to reduce foot ulcers or the recurrence of ulcers, there are few studies that address this problem. This is a key issue that needs further studies to gather accurate information.

An overriding, unanswered question is how long to treat CN in clinical trials, given the average time of 10 months (7-15 months) for resolution of CN. This is likely to be a problem in planning a long trial that asks patients to wear a boot or cast for extended periods. It is not clear if there are advantages for extending the length of time for restricting movement in eventual resolution of CN. Activity level also may be important, but studies that tried to measure the association between activity level and treatment outcome have not been conclusive. It may be that physicians do not have enough data to know when to stop an intervention.

Submitted Abstract Presentation: Association between Osteoprotegerin G1181C and T245G Polymorphisms and Charcot Neuroarthropathy

Dario Pitocco, M.D., Catholic University, Rome, Italy

Dr. Pitocco described the four principles that govern research on CN:

- The pathogenesis of CN is still unknown;
- The difference between the higher prevalence of diabetic neuropathy and the lower prevalence of CN and their different clinical features support the hypothesis of a non-complete role of diabetic neuropathy and the probable involvement of other factors;
- A feature of CN is bone reabsorption, as in other diseases (e.g., osteoporosis) where there is an imbalance between osteoclast and osteoblast activity; and,
- The RANK-RANKL-OPG system plays an essential role in osteoclast activation, and OPG polymorphisms have been associated with bone reabsorption in osteoporosis.

His abstract described a study of an investigation of polymorphisms in the OPG and whether they are involved in the pathogenesis of CN. The two polymorphisms include the G1181C polymorphism located in exon I and the T245G polymorphism located in the promoter region of the OPG gene. Participants in the study included 59 with diabetic CN, 41 with diabetic neuropathy without CN, and 103 healthy controls. Genotyping was carried out by a PCR-RFLP protocol.

Results indicated that among those with diabetic CN, there is an association with the G allele and with the G/G genotype of the G1181C polymorphism when compared to the controls, and a negative association with C allele and with the C/C genotype. For the T245G polymorphism, there was an association with the G/G genotype and G allele, and a negative association with the T/T genotype and T allele in CN when compared to the controls; double homozygosis is linked with a strong risk to develop CN. Comparison of allele and genotype frequencies did not reveal any significant difference between those with diabetic neuropathy without CN and controls. These findings suggest that genetic variations in qualitative and quantitative production of OPG influence susceptibility to CN and may explain the difference between the prevalences of diabetic neuropathy and CN.

It is anticipated that further studies will involve investigations of polymorphisms in RANKL and the involvement of the RANK-1 OPG axis, and a trial with denosumab in acute CN.

Discussion

CN was defined in the study by diagnosis, with no record of duration of the disease. Both T1D and T2D patients were included in the study. There was no measurement of OPG levels or the relationship to CN.

Submitted Abstract Presentation: Atlas-Based Quantitative Imaging in Charcot Neuroarthropathy

David R. Sinacore, Ph.D., P.T., F.A.P.T.A., Washington University School of Medicine, St. Louis, MO

Acute CN can be considered the trigger for inflammatory osteolysis—a unilateral red, hot, swollen foot—that does not look or function like the other foot. Dr. Sinacore described a highly precise, quantitative visual method for quantifying whole-bone and sub-regional volumetric BMD for all bones in CN based on high-resolution CT. The 3D atlas allows acquisition of sub-region densities constructed from segmented whole bones and surfaces of each bone. Bones are represented as octahedral and tetrahedral meshes that are partitioned into sub-regions of interest. Although this is a time-consuming process, bone segmentation and atlas construction have been semi-automated. Atlas-based imaging is particularly useful to compare involved and uninvolved feet, since it is possible to derive percent difference in BMD and to identify and quantify localized areas of bone loss. Atlas-based imaging allows for comparison of scans over time, providing the ability to detect changes in specific sub-regions. In CN there appear to be areas that lose large amounts of bone and areas that lose very little bone.

In conclusion, atlas-based quantitative imaging of all the foot bones throughout the stages of CN may be useful to track inflammatory-related osteolysis in CN. It may be that past studies have underestimated the severity of inflammatory osteolysis due to acute CN. Precise methods of assessing inflammatory osteolysis will allow early interventions to prevent foot deformity onset, progression, and associated sequelae.

Discussion

The study described will continue with longer followup times (up to 2 years) in 35 patients and will include serum markers and conventional DXA measures of BMD. The fact that so much edema accompanies acute CN makes atlas-based CT imaging superior to ultrasound and MR imaging, allowing detection of differences in BMD as small as 1.6 percent.

An advantage of atlas-based CT imaging is that it allows true volumetric bone densities of all the foot bones, replacing DXA scans as a more accurate followup tool.

Submitted Abstract Presentation: Outcome Evaluation of Charcot Reconstruction by Monitoring Dynamic Behavior of Plantar Pressure Distribution

Bijan Najafi, Ph.D., Rosalind Franklin University of Medicine and Science, North Chicago, IL

Joint deformities that arise as a result of Charcot lead to gait modification. Early diagnosis is challenging, but early recognition could allow intervention to prevent development or worsening of such deformities. The goals of this study included development of a protocol by which gait modification could be objectively characterized and screened after surgery to fix the joint deformity. CN develops most commonly in the midfoot, which can lead to the characteristic “rocker-bottom” deformity. A single score that demonstrates the abnormal gait—based on distribution of plantar pressure—associated with this deformity, as compared to the healthy foot, could be used to screen for CN and to screen progress after treatment.

Efforts to develop a reliable outcome measure for objective assessment of plantar loading post-reconstruction relied on two hypotheses: (1) the statistical distribution of plantar pressure during stance is independent of gait speed; and (2) any biomechanical change (or joint deformity) will affect the pattern of plantar pressure profile during gait. A pilot study was performed using a mathematical model (regression factor [RF]) to compare plantar pressure distribution (PPD) to a customized normal distribution curve. To see if the RF score was speed independent, pressure profiles were measured for healthy subjects walking at multiple speeds. The results showed that within subjects the RF score was consistent regardless of gait speed, age, gender, or weight.

In order to test if the RF score was affected by CN-induced joint deformity, a comparison of total peak plantar pressure for a typical healthy subject versus a typical CN patient before and after reconstructive surgery was made. Results showed that the RF scores for healthy subjects and post-operative Charcot cases were similar, and the score for the pre-operative Charcot case differed significantly. This indicates that the abnormal pattern of plantar pressure profiles may be returned to normal with reconstructive surgery.

Discussion

The normal pressure distribution of gait usually shows two peaks, one originating from the heel and the other from the forefoot. The peaks associated with a rocker-bottom foot differ significantly, primarily due to a large peak at the midfoot. This alteration in peaks results in a plantar pressure profile with a statistical distribution that greatly differs from a normal curve. The results of these RF score investigations suggest that a reliable and speed-independent score can be used to demonstrate gait improvement following foot reconstruction. Future studies should investigate whether the same principles may be used with intelligent insoles and telemonitoring for early recognition of Charcot.

THURSDAY, SEPTEMBER 18, 2008

SESSION IV: MANAGEMENT

Methods for Early Diagnosis of Charcot Foot

Prof. Luigi Uccioli, University of Rome, Tor Vergata, Rome, Italy

Charcot foot is a progressive, destructive disease affecting the bones and joints of the foot. Delays in diagnosis are not uncommon and can lead to advancing deformity, infection, and increased risk for amputation. Several methods are under investigation to determine the best approach for distinguishing Charcot foot from conditions such as osteomyelitis, inflammatory arthritis, cellulitis, trauma, deep vein thrombosis, and gout.

X-rays are inexpensive and provide useful anatomic information but are not sensitive enough to diagnose CN in its early stages or to distinguish between changes associated with CN versus infection. X-rays have been used since 1966 to classify CN stages. In the proposed Stage 0, no radiographic changes are observed, but the foot is warm and red. Recognition of Stage 0 may be important for reducing delays in diagnosis and thus reducing risk of progressive deformity and further deleterious effects.

Radionuclide imaging has been proposed as a method for improving diagnosis. The three-phase bone scan using technetium (Tc-MDP) is positive for all three stages of CN and reflects the increased turnover of bone. The four-phase bone scan is more specific, but fractures, tumors, and severe degenerative changes can give false positive results. These scans also cannot distinguish between CN and osteomyelitis, and have not significantly influenced patient management. One study of the three-phase bone scan found no significant differences in amputation rates for patients with confirmatory, indeterminate, or non-confirmatory bone scan findings.

Scans of white blood cells (WBCs) also have been proposed for diagnosis of CN. WBCs do not usually accumulate at sites of new bone formation unless infection is present. However, in cases of recent onset, rapidly advancing CN, labeled WBC scans can be positive in the absence of infection, due to localization of the labeled WBCs at acute fracture sites that may not be visible with plain x-rays. However, the use of WBC scans has been criticized because it shows poor definition, involves handling of blood products and a complicated labeling process, and is not rapid. Specific monoclonal antibodies that are easier to label and bind antigens on the leukocyte give comparable results within 2 hours and afford better resolution. Complementary marrow scanning using TC-nanocolloid in conjunction with labeled WBC scans may be useful for distinguishing between Charcot foot with or without osteomyelitis.

CT scanning can detect sequestra, cortical destruction, periosteal reaction, and intraosseous gas, which might not be detected by MRI. However, MRI is superior for soft tissue imaging and provides a higher level of anatomic detail and diagnostic accuracy and thus has largely replaced CT scanning. Because MRI can allow visualization of damage in the soft tissue, joint, and bone marrow, it is important for early diagnosis. In Stage 0 CN, MRI shows advanced stress injuries

and edema in the bone, and also edema of adjacent soft tissue and joint effusion, although it may not be as useful for distinguishing between Charcot foot and infection.

Recently, 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET), in which the 18F-FDG tracer accumulates at sites of increased cellular glucose metabolism (e.g., infection and inflammation) has been tested for utility in diagnosis of CN. 18F-FDG-PET scans are highly sensitive but less able to define the anatomic location of increased 18F-FDG accumulation. To address this issue, a hybrid PET/CT technology, which provides precise registration of metabolic and structural imaging data obtained in the same imaging session on a single device, has been developed to improve diagnosis and localization of infection and inflammation. Images from PET/CT scans can be examined visually for focal abnormalities, and data generated from the scan also can be assessed quantitatively by calculating the maximum standard uptake value (SUV max).

The ability to calculate the SUV max makes PET/CT scans useful for distinguishing between Charcot foot and osteomyelitis. The average SUV max for Charcot foot is 1.8; the average SUV max for osteomyelitis of the foot is 5.4. A study of 20 patients with uncomplicated diabetes, 17 patients with Charcot foot, and 5 with osteomyelitis found detectable differences in SUV max values for Charcot foot versus osteomyelitis. However, the patients in this study all had chronic Charcot foot rather than acute cases. PET/CT scans also may be useful for diagnosing Stage 0 Charcot foot by confirming the presence of an area with increased metabolism and quantification of this increase.

A clinical evaluation of the use of PET/CT scans in acute Charcot foot enrolling diabetic patients with clinical suspicion of acute Charcot foot is in progress. The protocol involves standard clinical evaluation including temperature recording, MRI and PET/CT scan of the foot at commencement of the protocol, offloading until clinical resolution, and MRI and PET/CT scan at clinical resolution (or lacking that, re-evaluation of the patient prior to the appointment for a final assessment).

Preliminary results indicate that MRI confirmed CN in 9 of the 10 patients, as did PET/CT scan. Analysis of SUV max values of the patients in this study compared to clinical resolution found a decrease in the mean SUV max value in patients with clinical resolution, but no change in patients in which the disease process was ongoing. This study suggests that PET/CT scanning in conjunction with MRI may be useful for diagnosing acute CN. PET/CT scanning provides visualization of the location of the disease process and its extension at baseline; visual information of the evolution of the original location and new locations in the same or contralateral foot at followup; and quantification of metabolic activity that can be used as a parameter to evaluate disease progress.

Discussion

In the above study, exclusion of patients with a history of osteomyelitis enabled confirmation of the relationship between MRI and PET/CT for diagnosing CN. PET/CT may be more useful for followup than diagnosis because it provides an objective value—SUV max—for monitoring disease progress. Changes in SUV max also could be used to monitor the effects of new drugs

on CN. PET/CT scanning does not replace MRI; instead, it provides additional clinical information.

Current Medical Management of Acute Charcot Neuroarthropathy

Jan Ulbrecht, M.D., The Pennsylvania State University, University Park, PA

Agreement on the characteristics of different stages of CN is important for research purposes and also has therapeutic and prognostic implications. The traditional Eichenholtz stages provide perspective on the progression of the disease and inform prognosis and treatment. Stage 0 CN is characterized by obvious inflammation but no radiographic changes. Stage 0 also could be considered a part of stage 1 that occurs earlier than the onset of changes observable by x-ray. CN patients with risk characteristics and inciting events also could be considered to be in Stage 0. Diagnosis is important because it can influence treatment decisions. For example, a patient with dense sensory neuropathy and a traumatic fracture of the fifth metatarsal or badly sprained ankle could be considered to be Stage 0, but the best treatment option for such a patient is not clear; currently such a patient likely would be offered protection and monitoring.

Determining whether a patient has active (ongoing bone disintegration and remodeling) or healed CN (stage 3 fixed deformity, no further inflammation, and completion of ankylosis and remodeling) also will impact treatment decisions. The goals of CN therapy include a foot that supports the functional goals of the patient, which may be different for a young and active patient versus a patient who already uses a wheelchair. Mechanical protection to treat active CN is the most “natural” way to stop abnormal weight-bearing and inflammation in the injured bone. Other potential therapies include pharmacologic treatments directed at osteoclast activation and osteopenia and also use of anti-inflammatory drugs such as tumor necrosis factor- α blockers (e.g., entanercept [Enbrel] and infliximab [Remicade]).

Early diagnosis of CN is essential for successful therapy; one study found that the average time from onset to correct diagnosis of CN was 7 months. In patients with normal x-rays and no deformity but evidence of bone damage with MRI, one study of 11 patients found that casting for 2 to 12 months resulted in complete resolution and no development of deformity; however, the study did not include objective measures of deformity. Although treatment of CN using nonsurgical techniques is not uncommon, there are no studies comparing devices (e.g., total contact cast [TCC], bivalve TCC, removable cast walker, or Charcot Restraint Orthotic Walker [CROW]) used for offloading. The Charcot in Diabetes in the U.K. (CDUK) study compared removable versus non-removable devices and found a slight, statistically significant difference that healing, as determined by clinicians, occurred sooner when non-removable devices were used. Evidence also is lacking concerning whether weight-bearing or non weight-bearing devices promote better healing.

Accurate measures of disease progress and healing are needed. MRI and PET/CT scanning are promising for monitoring the healing process. Blood tests featuring markers of bone turnover (e.g., C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) monitor systemic bone turnover and are not sensitive enough to detect changes related to CN, but more localized measures of bone turnover and inflammation may be useful. Temperature changes also may provide information about the disease process. Although not perfect, x-rays are affordable and it

should be possible to use x-rays in objective ways to document healing by monitoring ankylosis and measuring angles in the feet.

Studies to determine the appropriate duration of active treatment are lacking. Most centers use clinical judgments, such as a combination of temperature, swelling, x-ray images, and perhaps also MRI to monitor treatment. Determining the necessary duration of treatment also is hampered by a clear definition of “healing” for CN. Healing could be defined as no recurrence after treatment, but “recurrence” also is poorly defined. Perusal of a number of reports found treatment durations of between 2 and 4 months, in contrast with the median duration of 7 months reported earlier in this meeting. This difference could be attributed to differences in the definition of “healing” used by different clinicians. Because CN treatments are cumbersome, clinicians should consider the earliest potential progression from cumbersome to less cumbersome treatments as the ability to assess healing is improved.

Two studies in England and Italy have examined the use of Pamidronate (a bisphosphonate) in CN patients because bone turnover is increased in active CN. The English study was a double blind, placebo-controlled randomized trial in which 39 active CN patients were randomized to 90 mg Pamidronate by intravenous route or standard care. At 12 months, patients receiving Pamidronate had slightly superior improvement in pain, discomfort, and swelling. Decreases in bone alkaline phosphatase activity also were observed, although because bone turnover is suppressed systemically by Pamidronate, the effect of these decreases on CN is unclear. No differences were observed for surface temperature and no data on deformity, function, or duration of immobilization were reported. It is unclear whether bisphosphonate therapy significantly affected duration of therapy or quality of life outcomes. The Italian study randomized 11 patients to Alendronate (70 mg orally per week for 6 months) and 9 to placebo. All patients received TCC for 2 months, and an AirCast™ for 4 months. The results were similar to those of the British study; use of Alendronate resulted in improvements in bone density, markers of bone turnover, and pain, but did not significantly influence deformity or function. Data from the CDUK study in which patients received bisphosphonate orally or by intravenous route suggested that healing, as judged by clinicians, was slower in patients receiving bisphosphonate; these data suggest that bisphosphonate can impair the healing process. A study in Prague tested calcitonin in 32 patients with CN. Bone turnover was suppressed by calcitonin, although healing was judged to be superior. Patients receiving calcitonin also received less casting and spent less time in CROW, but had fewer instances of recurrence. A randomized controlled trial of calcitonin is needed. Use of bone growth stimulators also is increasing and should be studied more carefully.

Studies also are needed to clarify which CN patients require surgery. In one study, patients with very early CN (non-fragmented Stage 0 disease) were treated with internal fixation. The follow-up nonsurgical treatment received by these patients was more aggressive than typical medical treatment (casting for 6 to 9 months, no weight bearing for many months) but the outcomes of this study were positive. An alternative to surgical reconstruction for patients with healed, no longer inflamed, deformed Stage 3 CN is custom footwear to decrease midfoot pressure; this approach appears to be clinically successful but data are not available to determine if these patients would have benefited further from surgical reconstruction.

There is evidence that current CN treatment protocols are effective, but data concerning the essential components of these therapies and what constitutes “enough” therapy is lacking. The lack of clear definitions for healing and recurrence also hamper evaluation of therapies. Use of immobilization, bisphosphonates, calcitonin, and bone growth stimulation all may contribute to CN treatment, but more rigorous trials of these therapies are needed. Above all, the choice of surgical versus conservative treatment for a deformed and poorly functioning foot should involve the patients’ goals and wishes and be free of provider bias.

Discussion

Trials of CN need objective measures to monitor progress. MRI has potential to provide such measures, but objective ways to assess x-rays also should be considered. Bisphosphonates show promise, but should not be used except in experimental settings. The benefit of non-weight bearing versus weight-bearing therapies also needs to be evaluated in controlled trials.

Lack of recurrence may indicate healing, but may not be applicable to patients with positive bone scans and MRIs but no sign of inflammation or trouble walking.

The Surgical Management of Diabetic Charcot Arthropathy: Evidence-based Medicine or Lack Thereof?

Dane Wukich, M.D., University of Pittsburgh Medical Center, Pittsburgh, PA

Patients with CN score lower on the SF-36 QOL assessment tool than do patients with Parkinson’s disease, heart failure, or hemodialysis. The goals of CN surgery are to create a foot that is plantigrade, stable, shoeable or braceable; heals without ulcers and does not have recurrence of ulcers; has decreased or no pain; allows ambulation; and avoids amputation. Deformities that are unacceptable elsewhere in the body are accepted by neuropathic patients; a good outcome is defined by preservation of the limb, some walking capacity, and lack of ulcers. The success of surgery depends on geography, the skill of the medical team, the available technology, and the expectations of the patient. Surgical treatment remains controversial because of the current lack of sound scientific evidence to support or refute surgical management of CN. CN surgery is a multidisciplinary approach involving plastic surgeons, vascular surgeons, orthopedists or podiatrists, infectious disease specialists (to treat osteomyelitis), endocrinologists (to manage perioperative blood sugar), internists, and cardiologists (many CN patients also have cardiovascular disease).

CN surgery is one of the most technically challenging areas of surgery for orthopedists. Failures of fixation occur, and CN patients often develop pseudoarthrosis and wound infections. Wound infections can lead to amputation, but with proper pre-surgical assessment and appropriate patient selection, limb salvage rates should be higher than 90 percent. Although indications for surgery are not well defined, deformities that cause instability that cannot be addressed using orthotics, impending compromise of the skin, or non-healing or recurrent ulcers due to mal-alignment are usually better managed with surgery. Approximately 25 to 50 percent of patients with pain and instability will require surgery. The presence of ulcers significantly affects amputation rates; amputation rates are 7 percent if no ulcer is present, 28 percent if ulcers are present, and 31 percent in patients with recurrent ulcers. Therefore, preventing ulceration will

prevent a large number of amputations. Surgery also is not recommended during the acute inflammatory stage except in cases of impending compromise.

Surgical options for Stages 2 and 3 non-inflamed CN include exostectomy, osteotomies, and realignment arthrodesis. In patients with forefoot problems, Achilles lengthening can temporarily decrease forefoot pressure and allow ulcers to heal. Other surgical options include gastric slide, first MTPJ arthrodesis, correction of hammertoes, and metatarsal head excision. Some of these procedures can be performed as prophylaxis to prevent ulcers. Midfoot problems that indicate surgery include a non co-linear talar first metatarsal angle associated with ulcer. Exostectomy is technically simple and provides benefits for medial column ulcers. Complications associated with this procedure include iatrogenic instability arising from removal of bone, recurrent ulceration, delayed wound healing, and infection. This procedure often is combined with tendo-Achilles lengthening; significant bleeding requiring drainage before reconstruction often occurs with this procedure. Midfoot reconstruction should be performed after ulcers heal, but because some patients have long-standing ulcers that cannot heal because of the deformity, operating while the ulcer is open can be necessary. The presence of an open ulcer increases the risk of infection; use of external fixation rather than internal screws can mitigate this risk. Other indications for external fixation include active soft tissue infection, osteomyelitis, poor bone quality, decreased BMD due to renal osteodystrophy, and obesity.

In cases of a highly negative talo-first metatarsal angle and declined calcaneus (rocker-bottom foot) with ulcer, patients cannot use a CROW to aid healing. This condition can be treated by osteotomy and realignment in which the foot is plantar flexed and adducted, and external fixators and percutaneous pins are placed. This results in significant stability and allows immobilization and treatment of ulcers and open wounds. Negative pressure therapy can be useful if infection occurs. Complications of external fixation include pin track infections, cellulitis, pin breakage, and tibial fracture. Between 80 and 100 percent of diabetic patients will experience at least a minor complication, but in 90 percent of these cases the complication will not interfere with treatment.

Problems at the Chopart and subtalar joints are more difficult to manage than midfoot or forefoot deformities because of their inherent instability due to proximity to the long axis of the leg. In such cases, exostectomy often is required; if an ulcer is present, arthrodesis often is performed. External fixation can be useful to allow the patient to stand without interrupting the local flap. Ankle Charcot also is difficult to manage once deformity develops because the area becomes unstable and prone to ulcers. Patients with this deformity are prone to ulceration over the medial and lateral malleoli, especially if they have used CROW or a removable boot that is not custom-made. If the area is not infected, the joint can be salvaged using an intramedullary (IM) nail and an electrical bone stimulator, because these patients are at high risk for non-union. In a compilation of multiple studies of 100 patients who underwent arthrodesis with IM nailing, an 85 percent fusion rate was achieved. Frequent complications occurred, but limb salvage was greater than 90 percent. In a study of 11 patients with ankle Charcot and open ulcers in which external fixators were used, the limb salvage rate was 92 percent. Fifty percent of the patients achieved bony unions, 33 percent had stable fibrous “unions,” and 8.5 percent had unstable fibrous “healing.”

To determine the state of evidence-based medicine for surgical management of CN, a literature search of Medline (PubMed) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) was performed. Four hundred thirty articles were identified, and 85 articles met the inclusion criteria: patients with Charcot arthropathy due to diabetes, localized to the foot and ankle. In this group of 85 articles, 45 percent were expert opinion or case reports and 55 percent were case series; there were no randomized or prospective trials and no control groups. The total number of patients among the 85 articles was 981, with a range of 1 to 121 patients per report; the mean number of patients per study was 20 and the median was 14. Perusing the articles for anatomic location of surgery found that the site could be identified for only 783 of the 981 patients. In articles for which surgery site could be identified, 32 percent involved the ankle, although the ankle represents only 10 percent of CN cases. This suggests that the more proximal the deformity, the more likely that surgery will be needed. Procedures reported in these articles included amputations, arthrodesis, debridement, incision and drainage, and exostectomy. Four surgeons performed the procedures for 54 percent of the patients.

Analysis of the literature for surgical procedures for CN has determined that exostectomy is useful for relieving pressure due to bone that cannot be accommodated with prosthetics and/or orthotics. This procedure receives a Grade C Recommendation from the Oxford Centre for Evidence-Based Medicine and is supported by consistent Level IV studies. Arthrodesis with realignment is useful in patients with pain, instability, or recurrent ulcers who fail non-operative treatment; this procedure also received a Grade C Recommendation and is supported by conflicting or poor quality evidence in Level IV and V reports. Achilles tendon or gastrocnemius lengthening reduces forefoot pressure and improves the alignment of the ankle/hindfoot to the midfoot/forefoot and allows forefoot ulcers to heal. This procedure receives a Grade C, or possibly Grade B Recommendation and is supported by consistent Level IV studies; this procedure is more effective for managing ulcers. There is inconclusive evidence to recommend internal over external fixation in patients who do not have infections; supporting studies are heterogeneous and not comparable. There also is inconclusive evidence concerning whether surgery is better than amputation or limb salvage.

Complications from surgical management of Charcot arthropathy are common, but typically do not require treatment plans to be altered. Limb salvage rates should approach 90 percent, or surgery should not be performed. The co-morbidities associated with Charcot arthropathy, such as peripheral arterial disease and immunopathy, must be appreciated by surgeons. Although there is a lack of evidence-based outcomes, surgical treatment for Charcot arthropathy is an evolving field and will continue to improve.

Discussion

In cases of apparent dorsiflexion at the midfoot, a half pin can be inserted in the calcaneus and the Achilles cut and the half pin pulled down, thus ensuring lengthening of the Achilles and not the midfoot.

Decisions regarding amputation must be made by the patient. In the vast majority of cases, the patient wishes to save the leg, but a well-done amputation can be beneficial and many patients do well with a prosthesis. Dr. Wukich sends prospective amputation patients to speak with

clinicians and patients in the amputee clinic to help them make their decisions. Amputations are performed only when the patient is ready, except in cases of severe infection.

In cases of primary dislocation in the absence of bone dissolution, Dr. Wukich would perform a primary arthrodesis. If the patient has a hot swollen foot, a full contact cast can be used. In some cases, hospitalization for suspected cellulitis permits the patient to stay off his feet and allows edema to resolve so that surgery can be performed. Primary fusion is a good treatment for dislocation.

It was suggested that the medical charts kept by the five surgeons who performed the majority of CN arthroplasty surgery could be used in a retrospective study of outcomes associated with the various surgical procedures. However, such a study would be nearly impossible because of Institutional Review Board policies and patient privacy issues.

Submitted Abstract Presentation: Reconstruction of the Charcot Ankle Utilizing External Ring Fixation

Howard M. Kimmel, D.P.M., M.B.A., Louis Stokes Department of Veterans Affairs, Cleveland, OH

The goals of Charcot ankle reconstruction include a plantigrade foot, prevention of future ulceration and amputation, and increased life expectancy. This type of surgery can be challenging, and significant co-morbidities often exist in these patients, further complicating surgery and recovery.

Dr. Kimmel described a case in which a 65-year-old male with a previous amputation of the contralateral limb, elevated HbA1c, non-compliance with hypoglycemic medications, a history of alcohol abuse, evidence of autonomic dysfunction (erectile dysfunction and bladder control problems), and peripheral vascular disease with calcifications presented with an infected ulcer that led to ray resection. After the ulcer had healed, the patient returned to the clinic 2 months later noticing that his food was turning in. X-rays were taken and revealed a medial malleolar fracture and severe varus deformity, leading to a diagnosis of acute phase CN.

The patient was placed in a non weight-bearing cast that was changed weekly to decrease the varus deformity and treat the Charcot. Surgery to reduce the medial malleolar fracture took place 6 weeks later. This surgery failed, and on x-ray, the patient was noted to have severe osteopenia and bony adaptation of the varus deformity. The decision was made to attempt reconstruction or fusion of the ankle.

Because of the patient's co-morbidities, extensive pre-operative planning took place. The patient was noted to have decreased albumin levels, which are associated with slower healing, and thus was switched to insulin rather than an oral hypoglycemic. A vascular consultation was sought to ensure the patient would not suffer from a vascular episode, and pre-operative anesthesia and pain management consults determined that regional anesthesia (popliteal block and PCA pump) was preferable to general anesthesia, in part because of the patient's history of alcohol abuse and previous drug-seeking behavior.

Radiographs showed a severe fixed varus deformity and significant osteopenia in addition to the severe fixed varus deformity. Pre-operative computer surgical planning was used to determine the amount of surgical correction needed, and the plan was to use an external fixation device. The advantages of an external device are that it can be adjusted after surgery to change the amount of compression when needed and that it also allows for earlier weight-bearing. The external fixation device consisted of four rings on a frame and a foot plate. A wire was used to go through the talus and distal aspect of the tibia. The middle rings were used for compression, and stability was provided at the distal and proximal rings. Because of the large amount of bone that was removed, a combination allograft/autograft was used to promote incorporation of the graft. A femoral head allograft was performed to preserve limb length.

Partial weight-bearing was allowed 3 days after surgery in a reverse wedge post-operative shoe. An external bone stimulator also was used. The patient developed pin track infections within 2 weeks, perhaps due to overzealous cleaning of the pin tracks. Wound dehiscence subsequently occurred, likely due to the patient's decreased albumin level and the tension created by taking the foot out of varus. Numerous forms of treatment (negative pressure therapy, enzymatic debridement, and porcine and synthetic skin grafts) were used to treat this problem. Delayed incorporation of the allograft also was observed. By 4 weeks after surgery, wound dehiscence (reopening of the wound) had doubled, likely due to inappropriate weight-bearing. Alignment was intact at this time, but by 8 weeks the graft had moved posterior. The compression was tightened, and the patient was told not to put weight on his foot. By 12 weeks, both K wires at the proximal ring had broken. The wires were removed, but the graft remained in place. By 16 weeks, the tibia showed signs of hypertrophic bone formation and the foot was swollen. The frame was removed at this point. The patient had a medial ulcer and pyogenic granulomas. The patient was placed in a non weight-bearing cast for a week, which resulted in a dramatic decrease in ulcer and granuloma size and edema.

In retrospect, although a plantigrade foot was achieved, changes could have been made to potentially avoid some of the complications that arose. The procedure could have been staged, an adjustable frame used to decrease the soft tissue varus, and the patient definitely should have avoided any weight-bearing for at least 2 to 4 weeks. Use of a frame with motors might have decreased the chance of wound dehiscence. The protocol for pin care also has been changed to avoid infection. Bisphosphonates prior to surgery also may have been useful.

Discussion

Dr. Kimmel chose the frame used in this procedure based on his previous experience with it. To avoid increased costs that would be incurred, motors were not used on the frame to gradually decrease the varus correction. An iatrogenic tarsal tunnel could have been created due to the amount of varus correction at the time, which could have been treated by nerve decompression on the medial side; Dr. Kimmel lengthened the tendon at the time. The decrease in albumin appeared to be a nutritional problem rather than an inflammatory response because levels rose when the patient changed his eating habits.

Submitted Abstract Presentation: Charcot Foot and Nerve Compression

D. Scott Nickerson, M.D., F.A.A.O.S., Consultant to Northeast Wyoming Wound Clinic, Big Horn, WY

Dr. Nickerson described his experience with patients with acute, early-stage CN. The first patient was a 62-year-old female, with diabetes for more than 10 years, who presented with painful diabetic sensory-motor polyneuropathy (DSP) with bilateral sensory impairment. A right foot nerve decompression achieved good pain relief, but while the patient was waiting to receive the same treatment for the left foot, she developed acute CN with regional bone loss. Regional bone loss is most commonly associated with Sudek's bone atrophy, leprosy/Hansen disease, and diabetic Charcot neuro-osteoarthropathy. Common denominators of these conditions include regional expression of pathology; nerve damage via injury, infection (leprosy), or entrapment (diabetic CN); pain; and a combination of sensory damage, sympathetic function alterations, bony resorption, and soft tissue changes (in different patterns). There are differences among the three conditions. In Sudek's bone atrophy, the overall architecture of the bone is not lost; some epiphyseal resorption and diaphyseal changes are observed. In leprosy, terminal resorption of the bone is observed, but there is often less disruption of the talus and other structures in the midfoot as occurs in CN; however, ulceration does occur in these patients.

Because the patient was in significant pain, nerve decompression was offered to attempt to reverse the pain and bone resorption that occur in early-stage CN in diabetes and preserve the normal foot architecture. This recommendation was made based on the similarities of CN bone changes to CRPS/RSD/Sudek's bone atrophy; the patient's significant pain; the patient's excellent contralateral comfort response to nerve decompression; clinical evidence that nerve decompression reduces ulcer incidence and recurrence, suggesting tissue homeostasis benefits; and surgeon experience with successful surgical relief of chronic pain from nerve injury. The surgical nerve decompression hypothesis postulates that unrecognized nerve entrapment, generated by metabolically induced nerve enlargement, which can produce changes in nerve and fibro-osseous tunnel size match, commonly coexists in DSP, and is responsible, in part, for extremity neuropathy symptoms. Thus, nerve decompression at fibro-osseous tunnels provides entrapment relief and should improve subjective symptoms such as pain or sensory loss and reduce objectively measured complications such as neuropathic foot ulcer, ulcer recurrence, and loss of balance. This entrapment hypothesis is not inconsistent with Schaper's recent review of neurally controlled and induced changes in tissue homeostasis and wound repair with neuropathy. It is, however, inconsistent with the hypothesis that Length Dependent Axonopathy alone is responsible for the changes observed in DSP neuropathy.

Prior to surgery, the patient had evidence of absorption at the metatarsal-phalangeal areas, metatarsal bases, and significant bone loss along the medial talar neck and at the proximal navicular bone. Nerve decompression surgery was performed at this point. Bone reconstitution in the metatarsal-phalangeal areas and medial navicular region was remarkable, and the patient has maintained the shape of the foot and shows no loss of the arch 4 years after surgery.

The second patient was a 66-year-old diabetic female. No abnormalities were observed at the onset of symptoms, except for some absorption at the point of Lisfranc's ligament insertion and an undisplaced fracture of the cuboid bone. Surgery was performed 6 weeks after onset. Three

weeks after surgery, areas around the ligament insertion had filled in, and the cuboid fracture was no longer visible. Four months after surgery, bony reconstitution at the second metatarsal was maintained and the cuboid fracture was gone; this result has been maintained for 3 years.

Nerve compression in DSP may be one of the candidate “triggering events” postulated by Professor Jeffcoate’s etiologic schema. If nerve decompression surgery can arrest and reverse the osteoclasts observed in Charcot foot, it may be of use in achieving the therapeutic goal of preservation of the normal bony architecture of the foot; tissue protection could be an additional benefit. Nerve decompression surgery would be most beneficial to patients with early stages of Charcot foot (Eichenholz Stages 0 and 1); however, clinical and radiographic information to support this theory is available only for a small group of Charcot foot patients. The role of nerve entrapment and therapeutic decompression in diabetic peripheral neuropathy is controversial. Most publications focus on subjective results such as relief of pain and improvement in sensation, but some recent studies have shown balance improvement and reduction in ulcer recurrence rates. Based on this evidence, it is recommended that a small prospective pilot study of objective results after nerve decompression surgery be considered in early-stage Charcot foot syndrome, using biochemical, temperature, or quantitative bone imaging, as outcome measures are developed. The results would contribute information about both the CN neuro-inflammatory process and the involvement of nerve entrapment in diabetic foot complications.

Discussion

In these cases, x-rays were the only measures of osteoclasts. No pre-operative treatment occurred for these patients, and post-operative treatment consisted of use of a removable cast boot with an arch orthotic for 6 weeks, with full weight-bearing allowed. It was suggested that the pain experienced by the first patient was atypical for CN, and this combined with x-ray evidence suggests that the patient had Sudek’s bone atrophy rather than CN. However, the significant clinical response (pain relief) to decompression surgery suggests CN, because nerve decompression generally is not effective for Sudek’s atrophy.

Achieving Therapy for Rare Diseases

William Gahl, M.D., Ph.D., National Human Genome Research Institute, Bethesda, MD

Developing and obtaining approval for therapies for rare diseases requires extensive knowledge of the condition and the effects of treatment, effective interactions with the Food and Drug Administration (FDA), and sound clinical trial data. Dr. Gahl described efforts to develop and test treatments for four rare diseases.

Cystinosis is an autosomal recessive disease involving accumulation of cystine in lysosomes due to a defect in a cystine transporter. These patients develop renal disease by 10 years of age, and after transplant go on to develop additional complications. Cysteamine can be used to treat cystinosis by providing an alternative mechanism by which cystine accumulation can be reduced. The National Collaborative Cysteamine Study took place between 1978 and 1985 and enrolled 71 children who were treated for more than 1 year with cysteamine. This study had only a historical control group (from an ascorbic acid study) and no concurrent control group. This practice was contested, but because the natural history of renal disease arising from cystinosis

was well known, the trial was allowed to proceed with this control group. Creatinine clearance was used as an outcome measure, and the study found that cysteamine treatment resulted in improved creatinine clearance.

A second, retrospective analysis of every cystinosis patient followed at NIH between 1960 and 1992 examined urine collection data, nursing notes, and admissions patterns and divided the patients into those who had been treated well, those whose condition had not been treated well, and those who had received no treatment. This analysis found that, with good treatment, the renal function of young children with cystinosis can be sustained and in fact improves as the patient grows; thus, cysteamine treatment allowed close to normal kidney growth and function. These results were published in 1993 and presented to the FDA; approval for use of cysteamine in pre-transplantation patients was approved in 1994. Rigorous animal studies were not required for cysteamine; previous animal studies of oral cysteamine used levels sufficient to cause gastric ulcers in animal models used for studies of gastric ulcer treatments. The cost of the drug has been reasonable because the company agreed to charge little for this life-saving treatment.

Alkaptonuria (AKU) is an autosomal recessive metabolic disorder characterized by buildup of homogentisic acid, which causes blackness in the connective tissue, prostate, and kidney stones; darkening of urine; cartilage discoloration; characteristic lesions in the eye sclera; and loss of disc space and subsequent loss of height. Nitisinone can be used to replace the enzyme that is defective in AKU. Nitisinone was approved for use in tyrosinemia type 1, a fatal disease characterized by the accumulation of toxic compounds in the liver. Although an Institutional Review Board (IRB)-approved protocol was in place in August of 1997, Dr. Gahl was unable to obtain the drug from the Swedish Orphan International AB until 2002, presumably because the group feared that side effects arising from treatment of AKU patients would prevent approval of nitisinone for tyrosinemia.

Treatment of AKU patients with nitisinone resulted in a decrease in homogentisic acid levels and clearing of the urine. Tyrosine levels rise in these patients, but do not cause symptoms except for occasional eye pain. Demonstration of biochemical efficacy was followed by a study designed to determine clinical efficacy. A single-blinded clinical trial of 40 patients (20 treated, 20 not treated) is underway. The primary outcome measure is total hip rotation, which declines by approximately 6 percent per year in AKU patients; this characteristic could be used as an outcome measure because enough is known about the natural history of AKU with respect to hip rotation to assure regulators that halting the decline in hip rotation could not occur without drug treatment. An interim analysis at 16 months was promising; thus, the study will continue and is scheduled to end in April 2009.

Hermansky-Pudlak Syndrome (HPS) is an autosomal recessive condition characterized by tyrosinase-positive albinism and abnormal bleeding due to the absence of platelet dense bodies. There are eight genetic subtypes of HPS, some of which are associated with pulmonary fibrosis. In HPS, biogenesis of intracellular vesicles from existing membranes is impaired, leading to failure to form lysosome-like organelles such as melanosomes or dense bodies, which are involved in pigment formation and platelet aggregation, respectively. Certain subsets of HPS patients develop untreatable pulmonary fibrosis that is fatal by age 30 to 40 years.

A potential therapy for HPS pulmonary fibrosis is pirfenidone, an Investigational New Drug (IND) made by InterMune that shows antifibrotic activity in cell and animal systems. The initial study, Effect of Pirfenidone on Forced Vital Capacity (FVC), was a randomized controlled trial that enrolled 21 patients. This study found that FVC declined faster in the placebo group compared to the treated group. A current pirfenidone trial will enroll 40 patients and will track rate of decline in FVC as a primary outcome. Subject accrual is challenging because patients must be enrolled after the decline in lung function begins but before FVC declines to 50 percent of the expected capacity. If the data from this trial are sound, it will be used for FDA registration. Complicating registration is the desire of InterMune to use pirfenidone to treat idiopathic pulmonary fibrosis, which is not a rare condition.

Hereditary Inclusion Body Myopathy (HIBM) is an adult onset, autosomal recessive condition characterized by slowly progressive muscle weakness and atrophy. The causative gene for HIBM, *GNE*, encodes two enzymes that function in the sialic acid synthesis pathway. *GNE* mutations decrease sialic acid production. Sialic acid is found on the glycoprotein alpha-dystroglycan, which is involved in interactions between the extracellular and intracellular environments of muscle cells; disruption of these interactions results in myopathy. A *GNE* knock-in mouse carrying the *GNE* variant common in the Iranian Jewish population dies by postnatal day 3 of severe renal disease. Treatment of the mothers with N-acetyl-D-mannosamine (ManNAc), a sialic acid precursor, prevents death of the neonates. ManNAc is essentially the sugar mannose carrying an acetyl group.

A double-blind, randomized, placebo-controlled two-period crossover study of ManNAc in 20 HIBM patients featured incremental dosing to 10 grams per day, a fairly large amount. The primary outcome of this study was quadriceps muscle strength. The NIH Clinical Center Pharmaceutical Development Service provided drug analysis for the ManNAc purchased from New Zealand Pharmaceuticals; although ManNAc could be sold as a nutritional supplement without further regulation, marketing it as a “drug” required FDA regulation. Single dose studies of five individuals revealed no toxicity at 5 and 10 grams of ManNAc, and several HIBM patients have taken 5 to 20 grams of ManNAc per day on their own without toxicity. The National Human Genome Research Institute’s (NHGRI) IRB approved the trial protocol. However, FDA placed a full clinical hold on the trial because of a lack of repeat-dose toxicology studies in two species (rodent and non-rodent) of a duration similar to or greater than that proposed for humans. This meant that NHGRI would be required to perform preclinical studies of ManNAc before the trial could proceed. Unfortunately, the cost of these studies is prohibitive. The Rapid Access to Investigational Drugs program is considering providing assistance with these studies. This decision has delayed the trial by approximately 2.5 years.

Trial design and supporting data are critical for achieving approval of drugs for both rare and common conditions. Large numbers of patients often are not needed to demonstrate efficacy; if the trial is performed correctly and differences are significant, the data are sound and likely will be accepted by FDA. Safety must be demonstrated to the same degree for drugs for rare conditions as for those for non-rare diseases. Approval of an existing drug registered for another indication can be straightforward if all involved parties cooperate; an existing Drug Master File can mean that additional preclinical studies will not be needed before the drug can be tested in a

clinical trial. Receiving IND approval is more difficult now than in the past but has resulted in better protections for the American consumer.

Discussion

CN is a rare disease, and research on this condition could be facilitated by the development of collaborations. A caveat is that investigators must be cautious about potential differences in data collection and quality from different sites. It may be advantageous to designate one central site to run the study and see patients, although this can make recruitment difficult.

Understanding the natural history of a condition is crucial when defining outcomes for a trial. It is essential to select outcomes that have a known course and variance within the patient so that there is no question that the outcome could occur only with treatment. For example, HPS patients with pulmonary fibrosis die within 18 months once they decline to an FVC that is 35 percent of predicted. The rate of decline has an extremely small amount of variance. If the rate of decline varied significantly (i.e., some patients die within 6 months and others within 5 years), the FDA might not accept rate of decline as an outcome parameter.

WRAP-UP AND ADJOURNMENT

Dr. Jones thanked the workshop chair, Dr. Boulton, the organizing committee, and speakers for their efforts in making the workshop so exciting and interesting. She commented that the clinical stories in CN are so compelling that there is a need to expand research and knowledge in this area to better understand how to diagnose and treat this condition. Because CN involves so many facets of physiology, such as the bones, nerves, and joints, it takes experts from many fields to address the disease.

Dr. Jones noted that a summary report of the workshop will be developed from the presentations and discussions, and it is hoped that a journal article will subsequently be produced to highlight what is known about CN and what areas show promise for future research. Select members will meet immediately following the workshop to discuss future plans.