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HOT TOPIC

Neuralgia-inducing cavitational osteonecrosis: a status report

JJ Sciubba

The Milton J. Dance Head & Neck Center, The Greater Baltimore Medical Center, Baltimore, MD, USA

Neuralgia-inducing cavitational osteonecrosis remains controversial several years following the initial description. Changing etiologic concepts have led to confusion as well as the significant departures from the concept first defined by Ratner which served as the basis for the explaining the pain syndrome with features of trigeminal neuralgia. Since the earliest publications on the subject by Bouquot and colleagues there have been many challenges and counterclaims to the concept introduced, with a discussion of these included. Finally, absence of any form of research design and approval by institutional review panels remains a weakness in terms of acceptance of the information provided in the literature said to support the stated etiology of this entity.

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Introduction

Bouquot introduced the highly controversial and now established name and concept of neuralgia-inducing cavitational osteonecrosis (NICO) in 1992 Bouquot *et al*, 1992. Early studies described intramedullary bony alterations represented by alveolar bony cavities that were related to the clinical manifestations of a trigeminal neuralgia-like syndrome. At the time of introduction, this theory, concerning the possible notion of an intramedullary anatomic alteration within a jaw bone that could be or in fact was directly related to neuralgia, was controversial and remains so over 16 years later. Proponents of this concept have labored to describe an association between intrabony radiolucent cavitations, which include facial pain, phantom bone pain, headaches, and neuralgia. A precise and widely accepted definition of NICO has not been provided and consistently promulgated since the original report of Bouquot's early papers on the subject, while Ratner's views from which the NICO concept originally evolved were definitive with respect to the presence of an infectious process that was related to the clinical syndrome of pain with trigeminal neuralgia type qualities and chronic pain Ratner *et al*, 1979, 1996. The publication by Ratner and colleagues too was based on a descriptive series of observations with a paucity of investigative rigor, but it did alert clinicians to a possible link between intrinsic bone pathology and pain syndromes, with Bouquot's later work initially adhering to Ratner's concept. Management of the alveolar bone abnormalities with surgery and antibiotics by Ratner and his colleagues was effective in most cases. Others including Goldstein and Epstein have noted the often shifting etiologic opinions and pathogenesis of NICO that were based on anecdotal case reports and analysis from a single laboratory without corroborative, biochemical, histopathologic, neuropathologic, or reproducible and diagnosable clinical features that satisfy standards of proof Goldstein and Epstein, 2000. Numerous debates have been had since the initial publication concerning characterization and understanding of the very difficult circumstances where a patient presents with a chief complaint of facial pain that often has failed earlier diagnostic or therapeutic approaches.

The claims described by Bouquot and others are considered to offer a rationale for the explanation of facial pain characterized as neuralgia and at other times a neuritis, which over time have evolved to encompass a widening series of pathologic and neuropathologic concepts as well as coagulopathic disorders. The confusion persists and in fact has grown.

Counterclaims to the NICO concept have been offered by many, some of which are characterized by dry humor and others by more direct derision. Some have gone to the extreme end of pejorative rhetoric where the term 'NICO' has been reckoned to represent 'Non-existent idiotic concept of osteopathology', an unfortunate barb published in a widely read textbook,

Correspondence: James J. Sciubba, The Milton J. Dance Head & Neck Center, The Greater Baltimore Medical Center, 6569 N. Charles Street, Baltimore, 21204 MD, USA. Tel: 443 849 8940, Fax: 443 849 8965, E-mail: sciubbajj@comcast.net
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believing that the term is 'totally bogus' and is essentially a restating of an earlier concept termed 'Ratner bone cavities' Marx and Stern, 2003. One claim is that NICO has never been clearly defined by Bouquot or others, which in turn may have led to the impassioned statement of opinions. In such cases, Ratner treated these cavities with minor surgery and antibiotics, with the majority of cases healing normally with associated resolution of pain. Analogy is extended further in a somewhat less than professional or constructive fashion by stating that the NICO concept is the classical 'fog wrapped in an enigma, surrounded in a mist'. Further adding to the confusion of terminology and description of the entity is noted in a widely read oral and maxillofacial pathology textbook where low grade, non-suppurative and radiographically invisible osteomyelitis may be present in at least some patients presenting with symptoms of facial pain or trigeminal neuralgia, Neville *et al*, 1995a. The so-called 'invisible' quality of radiographic images has been later contradicted by Bouquot (see below).

Etiology

From a more constructive perspective, Bouquot's early studies states that NICO is not histologically unique and not an osteomyelitis, unlike Ratner's bone cavities, where persistent osteomyelitis was described and successfully managed. Earlier discussions dealing with this topic emphasize that the concept over time has been built on expanding vagueness or at least shifting and multiple models of pathogenesis, where initially infection and later ischemia were deemed to be the causative factors, but later expanded to be more in keeping with hereditary coagulopathies, and still later, an autoimmune concept, based on antibodies to peripheral nerve myelin in one study and the presence of anticardiolipin antibodies, thrombophilia, and hyopfibrinolysis in another.

An additional explanation of the pathogenesis was offered in 2000 where it was stated that NICO resulted from edema of bone marrow with non-suppurative osteomyelitis secondary to marrow ischemia within the background of a hypercoagulability state that was evident by magnetic resonance imaging (MRI) and histopathologic studies Bouquot and McMahon, 2000. Whether bone marrow edema is a radiologic or image-based concept remains to be proven. The proponent of the concept has been the primary diagnostician making this pathologic diagnosis within his own laboratory, without further or concurrent blinded analysis by other pathologists or in separate confirmatory studies by others. Absent within the analysis of imaging and histopathology is a peer review or concurrent analysis of pathologic specimens or cases within a single laboratory or between laboratories where independent and unbiased analysis could be obtained and subsequently published. It would thus appear from the data published that surgically derived specimens are received, subsequently analyzed, diagnosed by a single pathologist (the major proponent of the NICO concept), the results of those analyzes pooled, and later published as data, but without any statistical rigor or analysis nor has this research methodology or execution of concept been vetted by the institutional review committees of the institutions which the concept's proponents hold academic appointments.

Proponents of the NICO concept have labored diligently and in a scholarly fashion to formulate the scientific basis of their claims, which have been wide-ranging and shifting over the years. Following the early publications of Bouquot where osteomyelitis was stated to be present in the absence of a definitive inflammatory process (see below), there was an abandonment of this notion in favor of a genetically determined coagulopathy and local intramedullary ischemia as being central to the evolution of this condition. While there may be controversy concerning information available on web-based sites, there have been several instances where the NICO concept has been presented and discussed beyond the evidence-based environment and practitioners of the so-called NICO surgery identified Barrett, 2008.

From an epidemiologic standpoint, the prevalence of this condition is unknown, with Ratner and colleagues noting 800 patients treated over a 9-year time frame Ratner *et al*, 1996. Most studies state an approximate 3:1 female to male predominance and an affected patient range of 40–60 years Roberts *et al*, 1979; Bouquot and Christian, 1995.

Radiography

Of note, the bony alterations within the jaws have been stated to be radiographically 'invisible', with a stated relationship to a systemic disease, an inherited hypercoagulopathy, which leads to focal marrow ischemic alterations and the formation of focal trabecular destruction and cavitation Glueck *et al*, 1996. Other individual publications and descriptions, however, have described several definitive but evident radiographic findings as being associated with the neuralgia-like pain syndrome, another apparent reversal or contradiction of earlier-published clinical descriptions by members of the same group, thus further adding to the confusion of the clinical presentation of the entity. These have been described as a subtle 'fragmentation' of lamina dura at prior dental extraction sites, so-called 'ischemic osteosclerosis', 'bull's eye sclerotic rings', and 'laminar rain' alterations within the walls of extraction sockets Neville *et al*, 1995b.

Clinically NICO is stated to be represented as a painful condition of the jaws that is considered not to be a rare finding, is commonly multifocal and bilateral in nature, and may present with a very gradual to abrupt onset. The concept of ischemic bone disease with associated necrosis is stated to be noted in almost every bone, being most common in the hip, knee, and jaws and other sites, being present in 1/3 of all hip replacement specimens. Bouquot has indicated several pathologic diseases or conditions of bone to be similar to jawbone osteonecrosis and thus related to ischemic

osteonecrosis, including but not limited to Legg-Calve-Perthe's disease (transient ischemic osteoporosis of the femoral head), Osgood-Schlatter disease (tibial tuberosity), Freiberg's disease (metatarsal head), Kohler's disease (navicular), femoral epicondylar osteonecrosis, Thiemann's disease (proximal phalangeal), mandibular condyle, Scheirman's disease (vertebral body), malignant otitis externa, and mandibular condylar osteonecrosis. Whether some or all of these states of pathology will withstand further scrutiny as being related to ischemia alone or not is an open question. For instance, the claim that malignant otitis externa is akin to what is proposed for NICO is highly questionable, where the otolaryngology literature and standard textbooks consider this condition to represent a virulent, aggressive and potentially fatal infectious necrotizing process (*Staphylococcus aureus, Pseudomonas aeruginosa*, cutaneous staphyloccal species and aspergillus species, where immediate and aggressive medical management including antibiotic and possibly hyperbaric oxygen treatment be instituted Ruckerstein, 2005. Assuming the concept to be a valid one, there are many stated events or factors that may lead to the formation of ischemic bone disease including, but not limited to, coagulopathy, estrogen therapy and pregnancy, sickle cell disease, cancer chemotherapy, arteriosclerosis, infection, trauma, smoking, corticosteroid therapy, serum sickness, metastatic disease, bisphosphonate therapy, radiation therapy, alcoholism, osteomyelitis, starvation, and others.

Bony lesions of NICO are stated to occur between and apical to teeth where, upon histopathologic examination, there are stated to be areas of inter-trabecular myelofibrosis, widened inter-trabecular spaces, osteoporotic change, and chronic ischemia. These ischemic bony alterations are referred to by at least 72 alternate terms. In the jaws Bouquot equates NICO to Ratner's cyst, Roberts' cyst, cavitation, and chronic osteitis, though the osteocavitation process is not of infectious origin according to Bouquot, in contrast to Ratner's original description and that later by Roberts and Person, where the presence of an infection within a dental extraction-related bone cavity was postulated as the initiator Ratner *et al*, 1979; Roberts and Person, 1979. Here again a shift in etiopathogenesis has been noted. NICO-like alterations are stated to occur at either end of long bones, in particular the hip, with increasing age, with jawbone equivalents to long bone ischemia-susceptible sites being the retromolar, maxillary tuberosity, and condylar and mandibular angle regions. Stated to be the major pathophysiologic problem by way of etiology is sluggish marrow blood flow where stagnation occurs, thus increasing the risk of clot formation that is exacerbated by inherited hypercoagulopathies (thrombophilia; hypofibrinolysis), therefore, increasing the risk of bone infarct formation and resultant cavitation. The cavitation is not the disease itself, as Bouquot states, but rather the result of the disease (chronic bone marrow ischemia), with normal overlying mucosa present. Bouquot's analysis of pathologic specimens of stated NICO cases states the presence of a broad array of changes, including plasmostasis, fibrin sludge, dilated capillaries, ischemic myelofibrosis, fat microvesicles (fat cysts), necrosis, and a minimal inflammatory cell infiltration which is lymphocytic in nature, with no evidence of acute inflammatory cells unless an accompanying and active infection was present. Stated is the theoretical role of thrombophilia and hypofibrinolysis leading to an impaired venous circulation and jawbone venous hypertension with subsequent development of osteonecrosis with resultant facial pain. The call for adequately designed double-blind, placebo-controlled, crossover studies was made by the authors of this preliminary study for validation purposes, although this is yet to be done Glueck *et al*, 1996.

Diagnosis

Diagnosis is stated to require a multifaceted approach that includes palpation, diagnostic anesthesia testing, radiographs, computed tomography scan, MRI, Tc-99 scan, and a controversial type of ultrasonography, with many false negative results noted. The latter form of diagnostic study has not been vetted in peer-reviewed fashion beyond publication in abstract form and presentation at meetings Bouquot *et al*, 2001a, 2002.

Bouquot has further noted that between 75% and 79% of patients with atypical facial neuralgia/pain have demonstrated 'hot spots' with technetium-99 m scanning in two of his studies, published as abstracts Bouquot *et al*, 2001b, 2004.

Bouquot also analogizes hip and jaw pain with respect to a stated or apparent ischemic etiology, indicating that the clinical characteristics are essentially identical. Additionally, a study published in abstract form has stated possible autoimmune alterations in NICO samples by use of affinity labeling assay, where the presence of anti-peripheral nerve myelin antibodies has been demonstrated McMahon *et al*, 1994. The contribution of this yet to be independently corroborated and published finding to the evolution of this condition is unclear, not only from an etiologic standpoint, but also from a clinical symptom perspective.

Final thoughts

Evident within the concept of NICO, is vast confusion and controversy over its etiology, pathology and management. Dr. Bouquot and his colleagues are earnest and thoughtful as they continue to investigate, promote, and explain the overall NICO concept. What is hoped is that the clinicians performing the so-called 'NICO surgery', with at times unsuccessful results, do no harm to their patients. This does not, however, impugn the efforts of Bouquot and colleagues; it is simply to make a difference in how the scientific and practicing communities in both surgery and pathology as well as medicine interpret and implement the data thus far presented, with an obvious need to achieve a consensus, as more balanced information is made available and results are duplicated by others by way of well-designed studies with proper controls, investigator blinding or calibration, analysis, and published after rigorous evaluation in peer-reviewed journals.

The practical implementation of this information remains a difficult clinical conundrum to the patient presenting with long-standing jaw or face pain, usually with a long history of failed attempts to produce an acceptable clinical result utilizing standard and accepted modalities. Clinicians, in particular oral and maxillofacial surgeons, may wish to review further valid scientific publications prior to adopting a management philosophy, if indeed the concept of NICO withstands scrutiny and rigorous, properly designed scientific studies with proper diagnostic criteria, analysis of clinical outcomes, use of control groups, randomization and allowance for placebo effect(s), and appropriate statistical analysis are developed. Strict clinical criteria justifying surgical or invasive entry in such chronic pain patients as well as widely accepted non-biased histopathologic criteria and a definition for this stated condition must be developed.

Most recently, McMahon and colleagues have, in a letter to the editor, urged clinicians to consider the multifactorial etiology of osteonecrosis, where they called attention to numerous factors that contribute to an ischemic threshold, which includes reversible and irreversible injury, 'marrow cell necrosis', and 'bone cell necrosis', which are impacted by what is termed bone cell stressors. Precise definitions of these factors were imprecise; however, they state that many cases of jaw osteonecrosis may be in part attributable to stresses of chemotherapy and bisphosphonate therapy, and further suggest that heritable thrombophilia be ruled out prior to embarking on these therapies in an effort to lessen the risk of ischemia-related osteonecrosis. Here again one witnesses a possible opportunity to define an area of clinical investigation where a specific question or concept could be proposed and tested and contribute to the ischemia-based concepts of bone necrosis pathogenesis and ultimately jaw and face pain McMahon *et al*, 1994. Again offering untested theories based on earlier work, or through likewise untested or accepted concepts, may further obfuscate. While any theory may be seemingly rational and persuasive as an *a priori* judgment, only the design of proper clinical studies to test its validity can lead to better understanding of and offer change to existing thought.

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