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ScienceDirect
European Journal of Integrative Medicine 2 (2010) 71–77
European Journal of INTEGRATIVE MEDICINE
www.elsevier.com/eujim

Original article

Immune messengers in Neuralgia Inducing Cavitational Osteonecrosis (NICO) in jaw bone and systemic interference

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Received 7 January 2010; received in revised form 24 March 2010; accepted 31 March 2010

Abstract

Aim of the study: In the practice of the author astounding improvements of systemic complaints which accompanied apparently rheumatic, neuralgic and other chronically inflammatory systemic diseases are consistently observed after cleaning pain free, radiographically normal edentulous areas of the jaw. These are marked by fatty-degenerative osteonecrosis of the cancellous bone. Thus far, in dental research there are only few scientifically proven explanations concerning such systemic therapeutic successes.
Methods: In order to clarify systemic interrelations, samples of cancellous bone have been extracted from six subjects. The specimens were then analyzed by bead-based multiplex technology and tested for 27 immune messengers.
Results: All six specimens concordantly showed highest concentration for IL1-ra (interleukin-1-receptor antagonist) and RANTES. In addition, in all samples FGFbasic and PDGF-bb have been distinctly evidenced. A statistically high concentration on IL1-RA and RANTES is noticeable here. The samples' small distribution and specific concentration on IL1-ra and RANTES, despite the high number of 27 tested mediators, is a striking figure.

Keywords: NICO; Immune messenger; RANTES; Proinflammatory cytokines; Osteonecrosis; Systemic interference

Introduction

What is NICO (Neuralgia Inducing Cavitational Osteonecrosis)?

Chronic softenings in the jaw are nothing new in medical history. Already in 1848 textbooks have been published on fatty dissolution of the jaw bone, which exists separately from abscesses or acute inflammation of the teeth. In 1915, G.V. Black – the father of modern dentistry – describes chronic osteitis of the jaw as a preceding chronic progress which produces cavitations and necrosis of bone cells. Black was impressed by the expansions of these medical conditions and suggested surgical removal of such "dead appearing" jaw bone [1]. In 1930, these processes have been specified in the USA for the first time as "cavitations" and "avascular" (lack of inflammation-induced vascular proliferations) and less "infectious". American scientist Dr. Fischer from the University of Cincinnati wrote a book in 1940 titled: "Death and Dentistry" in which he describes chronic osteitis of the jaw as a "metastasis of microorganisms from these bone necroses" [2]. Professor G. Bouquot, American pathologist from University of Pennsylvania gave this cavitation producing osteonecrosis the name NICO (Neuralgia Inducing Cavitational Osteonecrosis). In an analysis of more than 200 samples from patients with trigeminal neuralgia, he noted necrosis of the jaw bone with concomitant irritation of the trigeminal nerve in all cases [3–5]. At least 800 medical papers report on NICO. More than 27 studies concerning osteonecrosis/NICO have been published in peer reviewed journals since 1979.

The term NICO suggests, however, that neuralgia is the only consequence of the osteonecrosis. Possible systemic effects of this osteolysis of the jaw bone on the organism in terms of chronic strain are not covered by this nomenclature. Neverthe-

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doi:10.1016/j.eujim.2010.03.004

less, we will confine ourselves to the term NICO to describe these processes in the following. The author published not only an alleviation of neuralgic complaints of the maxillofacial area, but also striking improvements of systemic symptoms [6,9]. The guiding principles of the present analysis are:

- Can immune messengers, cytokines and growth factors generally be found in tissue samples of NICO sites in the jaw?
- Do immune messenger based inflammatory processes in the NICO sites exist?
- Which immune messengers appear high in NICO tissue? Can they possibly be related to systemic diseases?

Problems of radiological diagnosis of NICO

The existence of NICO is largely denied today in main stream dentistry. The reason is that normal X-ray do not show the process of bone marrow osteolytic NICO. To answer this question the author published the following research in summary [6,9]: healthy parts of the jaw bone ($n = 8$) and softened spongial parts ($n = 29$) were examined in a nuclear absorption spectrometer to view their mineral contents. The following mechanisms seem to happen within a NICO regarding the minerals.

Inside the NICO the hydroxyl apatite of the jaw bone split with loss of calcium and phosphate. The originally solid bone structure softens; the clinical image of a rarefying fatty degenerate NICO is expected to develop increased permeability for X-rays and thus a corresponding brightening of the X-ray by the loss of calcium and phosphate. Spectral analysis shows that, parallel to the dissolution of the bone, the trace minerals copper, iron and zinc increase statistically highly significant. Now a fatal overlapping effect comes up in the NICO area: the increased tendency to throw a positive radiological picture by loss of calcium and phosphate is compensated by the increased X-ray-absorption of accumulation of copper, iron and zinc; this in turn leads to a balance in the amount of X-ray permeability. The fatal diagnostic effect: radiological examination of NICO is without positive results. Thus radiological techniques are not apt for the exclusive diagnosis of NICO lesions in the jaw bone. The author documented the extent of this lesions in former publications [6,9].

Complementary diagnosis of NICO by ultrasound imaging

Obviously low bone density of NICO is difficult to detect in the maxillofacial bones via radiographic imaging. To give the practitioner an aid to diagnose the debilitating effects of bone marrow softening inside NICO lesions a computer-assisted through-transmission alveolar transmission through sonography called CAVITAT was developed. CAVITAT precisely images and identifies cavitational porosity in the jawbone. To compare radiology with this new ultrasonography technology, relative to the ability to identify alveolar bone with NICO lesions studies show that in 84% of cases the CAVITAT image changes were more obvious and more readily identified, than the radiograph for the same site. CAVITAT imaging proved significantly superior to radiology for the detection of microscopically confirmed osteoporotic and osteopenic NICO bone [7,8].

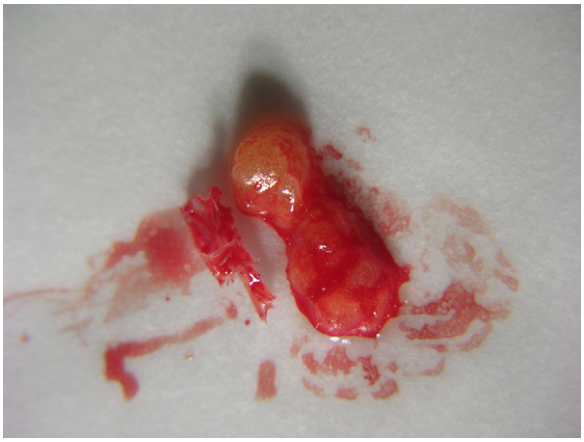

Fig. 1. Sample of fatty and osteolytic spongial bone of lower jaw.

Materials and methods

Sampling method of NICO tissue

Following local anesthetics, six subjects underwent intraoperative folding back of the gingival flap of the affected part of the jaw. The overlying cortical bone was removed. All six cases showed in the spongial area of the jaw bone osteolytic and degenerative fatty tissue. This was typical NICO instead of normal jaw bone. Samples of these osteolytic and fatty-degenerative parts of cancellous bone were removed. In three subjects, the softened cancellous bone tissue was extracted from retro molar and third molar's areas of the mandible, in cases of the other three from the corresponding areas of the maxilla. This cancellous bone tissue could be spooned out in all six cases as fatty-appearing lumps with a volume up to 1/2 cubic centimeter [10]. The pea-sized tissue lumps were immediately put into a dry, sterile storage receptacle (Sarsted Mikro-Tube, Ref. 72.693.005), the screw cap was sealed airtight und stored at −20 °C in the freezer until it was transported to the laboratory [29].

Macroscopic clinical features of the NICO bone samples

All six samples showed a surprisingly high degree of osteolysis of the cancellous bone. The softening is so distinct, that the marrow space can be sucked and spooned out. Degeneration of the cancellous bone extends in the mandible areas as far as to the canal of the infraalveolar nerve. Bouquot describes NICO-induced necrotic, softened cancellous bones as follows: Hollow cavitations with soft tissue that had undergone fatty dystrophic changes and demyelination of the bony sheath of the infraalveolar nerve [3,4]. The six NICO samples present themselves clinically and macroscopically as fatty lumps of tissue. Fig. 1 shows such a specimen with predominantly fatty transformation of the jaw bone.

Microscopic features of the NICO bone samples

Every sample was examined histopathologically. The changes of the bone are similar to those seen in osteoporosis. The trabeculae are thin with a loss of their bony interconnections. The widened intertrabecular spaces often contain small necrotic bone fragments. The fatty marrow shows a mucoid degeneration with an interstitial edema and an accumulation of acid mucopolysaccharides staining positively using alcian blue. These chronic degenerative changes are intermingled with foci of recent areactive adipocyte necrosis with granular dissolution of cytoplasma. The amount of fat cells is constantly strikingly increased: They show "foamy" changes as sign of an energetic imbalance of micro-metabolism. Small groups of foamy makrophagocytic cells are to be seen. Fibrosis is restricted to small amounts of collagen fibers adjacent to the bony trabeculae. Small nerve fibers are a striking feature in most biopsies of the jawbone. Nerve fibers are situated in close contact to degenerated and necrotic fatty tissue. Typical signs of inflammation, especially of an inflammatory cell response are missing. There are no significant leukocyte infiltrates, only few lymphocytes and mast cells. It is rather the fatty degenerative and osteolytic aspect, which overweighs. Thus all specimen show degenerative changes of fatty marrow and bone tissue due to insufficient supply, that is a chronic trophic disorder [30].

Laboratory treatment of the bone samples

After unfreezing, the samples were mixed in the Micro-Tube with 150 μl sterile, phosphate buffered saline (Sigma–Aldrich, Dulbeccos Phosphate Buffered Saline, Lot. 108K2334), 10 s vortexed and finally centrifuged (1 min, 5000 rpm, Eppendorf 5415D). 50 μl from the protrusion has been put apart for an analysis of immune messengers.

Measurement of immune messengers

Determination of human messengers (G-CSF, GM-CSF, IFN-gamma, IL1beta, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10 IL12(p70), IL13, IL15, IL17, IP10, MCP1, MIP-1alpha, MIP-1beta,TNF-alpha, Eotaxin, FGFbasic, IL1-ra, PDGF-BB, RANTES, VEGF) was performed via a bead-based assay (Bio-Plex Human Group I Cytokine Broad Range Panel, Ref. 171-A11127) on a BioRad Luminex System according to manufacturer's instructions. Quantification of the messengers followed standard curves included in the Bioplex software.

Results

Regarding to immune messengers IL1-ra und RANTES, all six samples show levels exceeding 800 pg/ml. The interleukin 6 level as well averaged clearly above 1000 pg/ml. However, this is due to one exceptionally high reading in only one of the six specimens. In the range from 97 to 298 pg/ml FGFbasic could be evidenced in all samples, MCP-1 and PDGF-BB were present at an average concentration above 100 pg/ml. The concentration of messengers IL1b, IL2, IL8, Eotaxin, G-CSF, GM-CSF, IFN-gamma, IP10, MIP1b and TNF-alpha averaged in the specimens at levels between 30 and 90 pg/ml. Messengers IL4, IL5, IL7 and IL9 were hardly detectable, their average readings lying below 15 pg/ml. IL10, IL12(p70) IL13, IL15, IL17, MIP1a, VEGF were contained as well in very low concentrations (<15 pg/ml). Fig. 2 shows the results from the 27-parameter luminex measuring in six processed NICO samples. Readings are in pg/ml, OOR < below detection limit, OOR > above detection limit with extrapolated reading.

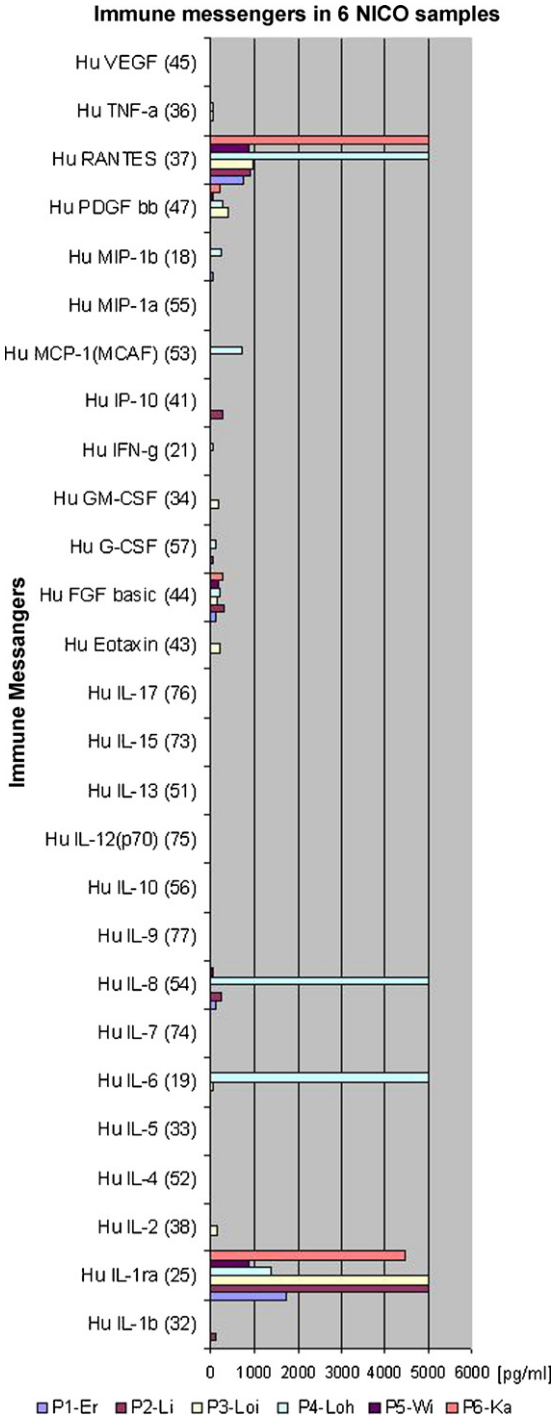

Fig. 2. Readings of 27-parameter of six NICO samples show high levels in RANTES (CCL5) and FGFbasic.

Discussion of the immunological results

The present research is the first to analyze immune messengers on a broad level within the scope of a screening of processed samples of degenerated jaw bone tissue (NICO). There is no study with similar purpose and extensiveness known to the authors.

Inflammatory and proinflammatory messengers

Primarily striking are the messengers that showed the highest concentrations, thus IL1-ra and RANTES, as well as FGFbasic and PDGF-BB. In this context it stands out, that except of RANTES, no other proinflammatory messenger, as interferon-gamma, interleukin 6, interleukin 8 or TNF-alpha, was detected in such distinctively elevated levels.

RANTES (CCL-5) signifies "regulated on activation normal T-cell expressed and secreted" and belongs to the group of chemotactic cytokines with proinflammatory effects. RANTES affects leukocytes chemotactically, especially T-cells, eosinophils and basophil granulocytes. Synthesis of RANTES in circulating T-cells is induced by TNF-alpha and IL1-alpha. Increased RANTES concentrations in the serum are described in a large number of inflammatory diseases, e.g. autoimmune diseases, cardiovascular diseases, chronic infects etc. [11–14]. RANTES levels up to approximately 20 ng/ml in the serum are regarded as normal [14]. Proceeding on this assumption, the concentrations of ca. 1 ng/ml metered in the samples have to be considered as relatively low. However, RANTES "standard levels" for normal jaw bone specimens are not available yet and can therefore not be evaluated. A systemic proinflammatory effect seems unlikely, because the RANTES concentration is relatively low in relation to the serum level.

Anti-inflammatory messengers

In contrast to RANTES, IL1-ra (interleukin-1-receptor antagonist) acts strongly anti-inflammatory by blocking signal transduction at the interleukin-1 receptor, by inhibiting IL2-secretion and IL2-receptor expression on the cell surface. IL1-ra can be generated by a variety of cells, e.g. macrophages, monocytes, neutrophils, fibroblasts and ephitelial cells. Due to strong immunosuppressive effects of IL1-ra, recombinant human IL1-ra is used successfully by patients with rheumatoid arthritis (e.g. Kineret®). In regard to IL1-ra, serum concentrations are noted up to a maximum of 1000 pg/ml in normal subjects [15], compared to that, the concentrations of up to 21,000 pg/ml detected in the specimens appear as salient. Growth factors FGFbasic and PDGF-BB are generated, amongst others, by fibroblasts and stimulate the migration of osteoblasts and the formation of collagen. Both are assigned an important role in osteogenesis [16,17]. FGF concentration in the specimens can be estimated as relatively high, compared to serum concentration of normal subjects (FGFbasic ca. <2 pg/ml) [18,19]. On the other hand, PDGF-BB concentration is distinctively below the expected level of normal subjects (ca. <1.5 ng/ml) [20].

Conclusion

Concluding, it has to be recorded that the present messenger diagram of the analyzed samples, in comparison to reference levels in serum, accounts for a growth promoting, anti-inflammatory milieu. That is consistent with the lack of inflammation at the histopathologic analysis [3,4,6]. The assumption, that the samples high local IL1-ra levels have a systemic effect in terms of an overweight of immunohomoeostatic processes with a consequent tendency to chronic inflammation, has to be substantiated in further researches. It is supposed as immunological fact that any raised immune messenger is a proof for inflammatory activity. Inflammation is defined not only by inflammatory and proinflammatory mediators but also by anti-inflammatory mediators. In spite of the above limitations of this research NICO can be defined as sort of inflammatory focus.

A determination of messenger levels, in particular those of IL1-ra, PDGF-BB, FGF and RANTES, in serums of NICO affected patients would be appropriate to provide indications of systemic effects of the local NICO messengers. This research was only targeting NICO as a possible source of immune messengers, with the striking outcome of high levels of IL1-ra and RANTES. Naturally the question comes up: How far are the levels of immune messengers in the fatty degenerated NICO probes to compare with levels in healthy jaw bone? The NICO probes are by itself altered tissue which has no corresponding structure in normal bone; similar to pus where a healthy reference is also not existent.

Salutogenetical aspects of NICO treatment in complementary medical practice

The reasons for initiating the present study are systemic phenomena which have been described repeatedly under the keywords: "osteitis of the jaw" and "maxillary disturbance fields". On the one hand, positive therapeutic outcomes of such interference field elimination are well known. On the other hand there are only few verified explanatory models and validated mechanisms referring to the presumed links between systemic diseases and NICO. Meridian based relations of organs and teeth; originating from traditional Chinese acupuncture do exist. In this research the authors' purpose is to develop an immunological based explanatory model of systemic phenomena caused by NICO jaw surgery.

Case 1: male patient, age 38

Clinical symptoms

Initial complaints: pain in the right knee joint for 12 months. Previous diagnosis: rheumatic arthritis. Previous medical treatment: prescription of oral Prednisolon and Metotrexat.

Postsurgical findings after NICO treatment

After NICO treatment in the left part of the upper jaw on September 8th, 2008, the knee pain ceased promptly. In March 2009 the patient gives the following account:

From February to May 2007, the pain in my knee increased to such an extent that I went to see my family doctor. He referred to a rheumatologist. Until the appointment in the mid of Juno 2007, the state of my health worsened, so that I had difficulties to get out of bed in the mornings and down the stairs. My hands became increasingly stiff as well. The rheumatologist diagnosed rheumatoid arthritis. The treatment consisted of medication with Prednisolon and Metrotexat. Because of the adverse effects I would have had to expect and the statement of the rheumatologist "I would be able to live a relatively normal life once adjusted to the medication", I turned to complementary medicine. I decided to seek alternative treatment besides orthodox medicine. I contacted Dr. L. in March 2008 to have an examination for disturbance fields in the head area. In March 2008 you diagnosed NICO lesions in all four wisdom tooth's regions. After every operation, four in total, my condition improved. In the beginning of May 2008 I stopped the intake of Prednisolon and Metrotexat. Today–in March 2009 - I'm 95% free of pain, especially when getting up in the mornings.

Histological findings

The histological diagnosis of the NICO area 28/29 on September 12th, 2008 showed the following result:

Bone tissue consistently vital with preserved osteocytes. The marrow spaces show exclusively fat tissue, on the one hand a very small area with a recent fat tissue necrosis which shows a lack of adipocyte nuclei, individual, immigrated neutrophil granulocytes, extravasates of erythrocytes. On the other hand, areas in where the width of the adipocytes' caliber is varying, and a foam cellular or fine fibrillar transformed cytoplasm edge. In the remaining marrow spaces, here a small area with a more recent ***fat tissue necrosis****, other areas with varying calibers and* ***partly lipoid degeneration*** *of the cytoplasm in the way of a* ***trophic dysfunction****. No hemopoietic bone marrow, no relevant inflammation, no atypias. Presented findings definitely (provided with concurrent clinic and radiology) are described as NICO.*

Evaluation of pathologic analysis data

The RANTES level of the NICO bone sample of this particular case of region 28/29, amounting to 911.39 pg/ml, is considerable increased in the range of the limit of detection. Where are the connections between local increased RANTES levels and joints? RANTES is secreted by human fibroblasts in the synovia and therefore can be part of a progressing inflammatory process which accompanies rheumatoid arthritis [21,22]. Synoviocytes produce synovia fluid and secrete effector molecules, which advance inflammations and joint destruction [23]. They form part of complex network of autocrine and paracrine factors. A hypothetic causal relationship regarding the increased RANTES secretion in NICO reads: Corresponding individual set-up provided, a permanently increased level of NICO-RANTES could exert negative impact in terms of joint inflammation, articular effusions and rheumatoid arthritis.

Case 2: male patient, age 39

Clinic symptoms

Initial complaints: massive exercise-induced asthma. Previous diagnosis: exercise-induced asthma of unknown origin. Previous treatment: cortisone spray, meaning a medically prescribed lifelong intake.

Postsurgical findings after NICO treatment

After NICO treatment in the right part of the lower jaw in September 2008 regio 48/49, the pain in the knee ceased promptly. In January 2009, the patient reports:

I wanted to give a short feedback on my previous state of health and on how I am now. About four years ago, I suddenly started having problems cycling. On a longer cycling tour of about 100 km, including many mountain stages, all of a sudden there was absolutely no power left in my legs. I did not recover over three months. I went from one doctor to another and it was declared that I suffered from massive, exercise-induced asthma. Since then, I had to inhale cortisone spray every time before I went on a cycling tour. The doctors could not tell me why I got this asthma, nor where it came from, but they did tell me that I had to take this spray for the rest of my life. I had surgery in the jaw bone. Since the treatment of my teeth, I never had any problems with my maxillary sinus and I did not need the asthma spray once in the entire summer. I hope, that it continues like this for the rest of my life.

Histological findings

The histological findings of the NICO area 48/49 show the following result:

An excised osseous specimen (regio 48/49) with cancellous bone which shows partially fibrosed, yellow marrow, which is situated intertrabecular and has increasingly "meandering", vital blood vessels and nerve branches. The yellow marrow shows distinctive, mucoid degeneration. This mucoid degeneration suggests a chronic, trophic disorder and belongs to those findings that are repeatedly seen in the context of NICO. No inflammatory infiltrates and no atypias.

Evaluation of pathologic analysis data

The RANTES level of the NICO bone sample of this particular case of area 48/49, amounting to extrapolated OOR >20,000 pg/ml, is considerably increased above the range of detection. Where is the connection between local increased RANTES levels and allergological-pulmonary disorders? RANTES is chemotactic for T-cells, eosinophils and basophils and takes an active part in mobilizing leucocytes in inflammatory changed areas. As a result, it is assumed that a general cellular activation is taking place, which can often be linked with diseases like asthma and allergic rhinitis [24,25]. RANTES is as well a potent activator of the oxidative metabolism, specific for eosinophils [26]. RANTES activates basophils and thereby causes the releasing of histamines. A hypothetic causal relation of the increased secretion of RANTES in the context of NICO reads: Given a corresponding, individual set-up, a constantly

increased NICO-RANTES level could exert negative influence by advancing chronic-inflammatory processes in other parts of the organism.

Pathogenetic aspects of NICO: approach to a mediator-based hypothesis of systemic-causal relations

Discussion of systemic relations of the RANTES readings

The issue which gave reason to analyzing the immune messengers in the six NICO samples had risen from complementary medical experience of "disturbing fields" in the jaw area. Where is the explanatory link between local, operative removal of NICO and the undeniable healing successes in "disturbed fields" of organic symptoms and clinical presentation? Could it be the chronically elevated RANTES level from NICO sites in the jaw bone?

The crucial point of a systemic interpretation of the results lies in the understanding that NICO is an insidious, chronic subliminal effect. Although RANTES level of all six NICO samples were noticeably high, they appear rather low in comparison to RANTES readings which can occur with acute arthritis in serum. These high serum-levels of RANTES in acute stages should not be admitted to hide the fact that acute stages of arthritis (case 1) or asthma (case 2) are actually the late or final stage of a chronic, asymptomatic promoting phase. Factoring chronicity into the considerations, increased RANTES level in the local NICO area lead to the conclusion that the cytokine-regulated signaling in the body in the course of disturbance field processes is a chronic challenge for the immune system. The RANTES increase in NICO can persist for years, is usually clinically unnoticed and causes a displaced increased development of RANTES level. Where the local complaints manifest themselves – knee joint (case 1) or in the bronchial tubes (case 2) depends on genetic and other individual stress factors. As RANTES is found in many other systemic diseases it is worth to discuss further aspects of possible pathogenetic effects of NICO lesions:

RANTES and its role in MS

RANTES has been detected in brain lesions of multiple sclerosis (MS) patients. IP-10 and RANTES CSF levels were elevated in MS patients compared with controls. Because both IP-10 and RANTES are potent T-cell chemoattractants, it is reasonable to postulate that the elevated levels of these chemokines during active episodes of MS induce accumulation of T-cells into the CNS. RANTES is a chemo attractant for both T-cells and macrophages and could be a key proinflammatory factor in the pathogenesis of MS [27].

RANTES and its role in cancer metastasis

The body's own stem cells stimulate cancer cells to mutate, to spread and to form tumors in other organs. A particular sort of stem cells is required for cancer metastasis. Mesenchymal stem cells from the bone marrow have been suspected for some time past. Scientists of Whitehead-Institute Cambridge, Mas., USA assume that those stem cells with the aid of messengers transmute tumor cells into metastasizing cells. These scientists have already found a molecule which stimulates metastasis: chemokine CCL5, also called RANTES: The breast cancer cells stimulate de novo secretion of the chemokine CCL5 (also called RANTES) from mesenchymal stem cells, which then acts in a paracrine fashion on the cancer cells to enhance their motility, invasion and metastasis. This enhanced metastatic ability is reversible and is dependent on CCL5 signaling through the chemokine receptor CCR5 [28].

Concluding, the presented hypothetic model of systemic NICO-impacts can be reduced to a challenge- and stimulation pattern. There is no direct, monocausal relationship between disturbance field and disturbance. Interesting, though, is the author's longtime clinical experience that in dental therapy practice a removal of the proinflammatory NICO lesion usually leads to disappearance of various inflammatory clinical presentations in our patients.

Authors

All research done by the authors.

Financial support

None.

Conflict of interest

No conflict of interest declared.

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