Study of Osteo-/Chondropenia Caused by Impaired Chemokine Receptor and for Progressive/Idiopathic Condylar Resorption

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Purpose

So-called Progressive Condylar Resorption (PCR) is defined as diminishing condylar head volume with changes in shape, often discussed with decreased mandibular ramus height, mandibular retrusion and clockwise rotation resulting in progressive Angle's Class II basal bone in relation with anterior open bite, resulting in malocclusion. There are various clinical issues since the etiology of this disease is largely unknown.

So far, we have investigated abnormal bone metabolism with condylar resorption similar to PCR in CC chemokine receptor 5 (CCR5) null mice and CCR1 null mice, sharing chemokine ligands. Although practical application of a drug for the treatment of human immunodeficiency virus (HIV) using CCR5 which functions as a co-receptor of HIV has almost been achieved, the effects of the drug on the quality of life of patients with acquired immune deficiency syndrome (AIDS) such as abnormal bone metabolism and increased risk of fracture have not been evaluated.

In a study last year, our group found a relationship between the pathology of PCR and chemokines based on the finding that chemokines such as RANTES (regulated upon activation, normal T-cell expressed and secreted) that are increasingly expressed in PCR patients can be effective biomarkers.

The purpose of the present study is to develop a new reasonable definition of PCR including its name through collecting and analyzing both domestic and international cases, and to propose treatment measures for each case for further discussion, including predictability.

Methods

1. Survey on PCR in Japan

Letters requesting participation in the survey were sent to 547 departments of oral surgery mainly in universities and hospitals, as well as orthodontic clinics. The survey was carried out by accessing the National Center for Global Health and Medicine (NCGM) website and obtaining answers through the internet. The questionnaire was mainly composed of multiple-choice questions such as number of cases, sex, age, chief complaints, affected sides, diagnoses at first visit, coexisting diseases, and treatments.

The survey was conducted for a maximum of three cases in each institution, but additional questionnaire files were sent to those institutions having more than three cases.

2. Marker search from blood and urine samples

After obtaining informed consent, blood and urine samples were collected from the patients diagnosed as...
PCR in the NCGM hospital. Biomarker molecules of osteoporosis such as deoxypyridinoline (DPD), type I collagen cross-linked N-telopeptide (NTX) and type I collagen cross-linked C-telopeptide (CTX) in the urine samples and typical bone metabolism markers such as tartrate-resistant acid phosphatase (TRACP), NTX, CTX, bone alkaline phosphatase and osteocalcin in the blood samples of PCR patients were measured. Regarding bone metabolism markers, cut-off scores and comparison of general bone-volume reduction and fracture risk covered by health insurance in the cases of osteoporosis were evaluated. In addition, the level of MIP-1α, known as CCL-3, and RANTES, known as CCL-5, as chemokine matrices in blood were measured. Since the standard test values are not determined in the latter indexes, the mean values of blood serum from normal people were compared with the results.

This study was approved by the NCGM ethics committee.

3. Microstructural analysis of CCR1 and CCR5 KO mouse temporomandibular joints

Fixing with formalin, tissues around temporomandibular joints (TMJ) were collected and frontally sliced for observation with Alcian blue, and hematoxylin-eosin staining.

Results

1. Survey on PCR

A survey was conducted on 547 institutions nationwide having oral surgery clinics and orthodontic clinics, and the 94 institutions shown in Table 1 actually participated in this survey (17% response rate).

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>The 94 institutions, oral surgery clinics and orthodontic clinics that participated in this survey</th>
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Shizuoka Cancer Center, Nagaizumi, Sunto, Shizuoka
Ogaki Municipal Hospital, Ogaki, Gifu
Yamaguchi University Hospital, Ube, Yamaguchi
The Employees' Pension Welfare Corporation Tamatsukuri Kosei-Nenkin Hospital, Matsue, Shimane
Yamanashi Prefectural Central Hospital, Kofu, Yamanashi
Shinshu University Hospital, Matsumoto, Nagano
Asahikawa Medical University Hospital, Asahikawa, Hokkaido
Okayama University Hospital, Okayama
Division of Maxillofacial Surgery, Iwate Medical University Hospital, Morioka, Iwate
Jinwakai General Hospital, Hachioji, Tokyo
Ebina General Hospital, Ebina, Kanagawa
Tsukuba University Hospital, Tsukuba, Ibaraki
Yokohama City Minato Red Cross Hospital, Yokohama
Aichigakuen University Dental Hospital, Nagoya
Ogaki Central Hospital, Yuzawa, Akita
Komatsu Municipal Hospital, Komatsu, Ishikawa
Kyushu University Hospital, Fukuoka
Japanese Red Cross Society Kaibara Hospital, Tamba, Hyogo
Kyushu Dental College Hospital, Kitakyushu
Kariya-Toyota General Hospital, Kariya, Aichi
Tokushima University Hospital, Tokushima, Tokushima
Tagawa Municipal Hospital, Tagawa, Fukuoka
Tsurumi University Dental Hospital, Yokusuka
Obihiro Daini Hospital, Obihiro, Hokkaido
Kanagawa Dental College Hospital, Yokosuka, Kanagawa
The University of Tokyo Hospital, Tokyo
Yukiguni Yamato Hospital, Minamimaisonuma, Niigata
Tokyo Women's Medical University Hospital, Tokyo
Yamagata University Hospital, Yamagata, Yamagata
SASAKI Dentistry-Oral and Maxillofacial Care Clinic, Tateyama, Chiba
Nagoya University Hospital, Nagoya
Sato Lingual Orthodontic Clinic, Tokyo
Nikko Memorial Hospital, Muroran, Hokkaido
Niigata University Hospital, Niigata
Kimijima Dental Clinic, Saitama
Nagasaki University Hospital, Nagasaki, Nagasaki
Kobe City Medical Center West Hospital, Kobe
Tokyo Kosei Nenkin Hospital, Tokyo
University Hospital, Dokkyo Medical University, Mibu, Shimotsuga, Tochigi
Hitachi, Ltd. Hitachinaka General Hospital, Hitachinaka, Ibaraki
Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka
Secomedic Hospital, Funabashi, Chiba
University of Yamanashi Hospital, Chuo, Yamanashi
Akita University Hospital, Akita, Akita
Saitama Medical University Hospital, Moroyama, Iruma, Saitama
Keio University Hospital, Tokyo
Gunma University Hospital, Maebashi, Gunma
Yokkaichi Municipal Hospital, Yokkaichi, Mie
Division of Oral Surgery, Iwate Medical University Hospital, Morioka, Iwate
Tokyo Metropolitan Geriatric Hospital, Tokyo
Yaizu City Hospital, Yaizu, Shizuoka
Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa
Ogawa Orthodontic Clinic, Fukuyama, Hiroshima
Otsubo Orthodontic Clinic, Tokyo
Meguro-Aobadai Orthodontic Clinic, Tokyo
Itoh Dento-Maxillofacial Hospital, Kumamoto
Maxillofacial Orthognathics, Tokyo Medical and Dental University, Tokyo
National Center for Global Health and Medicine Hospital, Tokyo
tionnaire sheet, the total of each section varies.

We collected a total of 179 cases (male: 104, female: 10, unknown: 65). The reason for unknown gender cases were: loss of detailed data due to time, transfer of doctors in-charge, or in the process of record checking.

In terms of age distribution, the highest group was people in their twenties followed by those in their teens and thirties. The number of people in their forties was low, but it increased again over age fifty, showing a two-phase distribution (Fig. 1).

In addition, 15 out of 26 cases over fifty presented autoimmune diseases such as rheumatoid arthritis and were using steroids. Many cases of over fifty were accompanied with other diseases such as autoimmune diseases and many of the patients had been taking drugs including steroids for a prolonged period (Fig. 2).

Chief complaints at the time of visiting medical institutions are presented in Fig. 3. The number of people with discomfort and imbalance of occlusion was highest (84 cases, 63%) followed by pain on TMJ (25 cases, 19%), open bite without proper anterior bite (14 cases, 11%) and others (esthetic problems and discomfort on TMJ) or unknown (10 cases, 7%).

The proportion of affected sides was as follows: bilateral cases (90, 50%) were the most predominant followed by left side cases (15, 8%) and right side cases (7, 4%). As described above, 67 unknown cases (38%) remained due to insufficient records.

Diagnoses at first visit were as follows. Fifty-one cases (38%) were diagnosed as temporomandibular disorder. The number of cases diagnosed with jaw deformities, PCR, malocclusion, and others including infectious disease and diffuse sclerotic osteomyelitis were 40 (29%), 28 (21%), 14 (10%) and 3 (2%), respectively.

Coexisting diseases of these patients were as follows. Fifty-four cases (59%) showed no underlying disease, whereas there were 23 cases (25%) of autoimmune diseases and 14 cases (16%) of other diseases including oropharyngeal cancer, depression and progressive muscular dystrophy.

Lastly, the treatments for these patients were as follows: treatment equivalent to those for temporomandibular disorders was conducted in 43 cases (33%). Orthognathic surgery was conducted in 32 cases (24%). Orthodontic treatment only was conducted in 24 cases (18%). Other treatments such as intermaxillary traction with screw anchorage, prosthodontic treatment and condylar resection were conducted in 10 cases (8%). No treatment was conducted in 22 cases (17%).

2. Marker search

Regarding diagnostic criteria, after analyzing blood samples from a small number of patients, high levels of NTX and DPD indicating osteoporosis were observed. In addition, the level of RANTES, which is considered as a chemokine, fluctuated from the standard value (data not shown).

The number of samples was small this year. Although gene samples were collected, they were not analyzed in view of cost-effectiveness.

3. Microstructural analysis of temporomandibular joint

To elucidate the secondary effects of anti-HIV drugs, we revealed in CCR5-deficient mice and CCR1-deficient mice an osteopenia and/or chondropenia due to impaired functions of osteoclasts and osteoblasts, and/or chondroblasts. An analysis of bone histomorphometrics indicated decreased bone volume in the metaphyseal region in both CCR5- and CCR1-deficient mice. Especially, Ccr1−/− mice have fewer and thinner trabecular bones and low mineral bone density in cancellous bones. The lack of CCR1 affects the differentiation and function of osteoblasts.

A histological analysis revealed that in CCR1 and CCR5 KO mice the alignment of chondrocytes in the end of long bone was disarranged. We attempted to conduct
further analysis of bone tissue and TMJ in model mice. However, the temporomandibular joints of mice are so small that it was difficult to conduct appropriate sample fabrication and data collection (data not shown).

Discussion

The clinical goal of our study is to establish objective diagnostic indexes for the existence and probability of onset of PCR using simple methods such as blood and urine collection. The second goal is to standardize the diagnosis of PCR which is not sufficiently recognized among dentists and to spread the name of PCR as a refractory disease. We therefore set up a research unit to establish the criteria for progressive condylar resorption, for pathogenesis, and for effective authorized therapy.

1. PCR survey

A survey was performed on institutions of oral surgery nationwide, as well as some orthodontic clinics, to grasp the actual status. However, the response rate was less than 20% (17%) in spite of efforts to simplify the questionnaire items and answering methods.

There may have been several reasons for the low response rate. One reason is that there is a mix of names and definitions of diseases causing condylar deformation such as degenerative temporomandibular joint disease, osteoarthrosis, progressive condylar lysis, hypoplasia of condyle and idiopathic condylar resorption (ICR), and the definition of each disease is not consistent. For example, in some cases, ICR is considered to be different from PCR, resulting in fewer cases in our survey.3,4.
In many cases of PCR, there is no symptom, so it is not easy to detect PCR without radiographic observation. In addition, some patients visit orthodontists rather than oral surgeons due to their imbalance of occlusion.

The low response rate of our survey may have been due to the abovementioned facts that diagnostic criteria vary among dentists and their understanding of PCR is not high.

Nevertheless, we obtained valuable information from the survey. We collected a total of 179 cases: 10 males, 104 females, and 65 unknown cases. This result supports the previous finding that female patients of PCR are predominant in international studies. Our finding suggests that by simple extrapolation, there are at least 1000 PCR patients in Japan.

The age distribution of the patients showed a two-phase distribution. Young PCR cases tend to occur idio pathically, whereas many cases of over fifty have other diseases such as autoimmune diseases and many of the patients had been taking drugs including steroids for a prolonged period. These results suggest that the pathology, which has been roughly defined as PCR for a long time, can be divided into two types.

These results should be carefully examined after considering the reason for the small number of patients in their forties and fifties. The people in this age group tend to be busy with work and family, and not to visit medical institutions unless they have serious problems. It is almost impossible to confirm the validity of this “two-phase distribution” for now; we need to accumulate more data from future studies.

The most frequent chief complaints at the time of visiting medical institutions is discomfort and imbalance of occlusion (84 cases, 63%) followed by pain on TMJ (25 cases, 19%). Deformed TMJ with pain is classified as Type IV temporomandibular disorder in the classification of the Japanese Society for Temporomandibular Joint. This complex diagnostic process reflects the difficulty in treating this disease.

In addition, chief complaints based on esthetic reasons such as prominent anterior teeth were found, indicating no functional problems in these patients. Other chief complaints were sleep apnea due to mandibular retrusion, infectious diseases and improper anterior bite.

In terms of the affected side, bilateral cases (90, 50%) were the most predominant followed by left side cases (15, 8%) and right side cases (7, 4%). The latter side was less affected than the former side, but the difference is negligible. From this result, PCR is considered to occur bilaterally and this disease is affected by systemic factors rather than local factors.

The most popular diagnosis of these patients at first visit was temporomandibular disorder (51 cases, 38%). For the diagnosis of temporomandibular disorder, one or more symptoms of “temporomandibular joint sound”, “pain on TMJ or masticatory muscles” and “trismus” or “abnormal jaw movement” must have been found; three cases were diagnosed as “degenerative temporomandibular joint diseases”. We should note that typical symptoms of temporomandibular disorders can be observed as related symptoms of PCR based on the result of this survey. This result also suggested the possible existence of PCR patients in the medical institutions that did not respond or that answered “no case” in this survey.

There were 40 cases (29%) with diagnosis of jaw deformities at first visit. The reason for this diagnosis was considered to be that many PCR patients show Angle’s Class II malocclusion with anterior open bite. According to the result of the survey, this diagnosis was frequently made when patients complained of “problems in mastication” or “malocclusion”, suggesting a relationship with malocclusion (14 cases, 10%). The total of these two diagnoses was 54 cases (44%), which was the almost the same as the number of cases diagnosed with temporomandibular disorders. As a result, it was revealed that some type of malocclusion including abnormality of TMJ and imbalance of jaw anatomy existed. On the other hand, 28 cases were diagnosed as PCR at first visit. Although 14 of them were diagnosed at our institution, it is notable that 14 cases were diagnosed as PCR, including unknown mandibular condylar resorption.

Some cases were diagnosed as diffuse sclerosing osteomyelitis of the mandible or infectious diseases at first, and then accompanied PCR seemed to be found in some of those cases.

In the section of coexisting underlying diseases, 54 people (59%) did not have underlying diseases. Autoimmune diseases were found in 23 cases (25%), of whom 20 were taking steroids. One of the three cases not taking steroids was taking Rheumatrex®, known as MTX, methotrexate, suggesting a history of steroid use.
There were 14 cases (16%) of other underlying diseases including oropharyngeal cancer, depression, varicose veins, osteoporosis, respiratory diseases, hepatitis C, progressive muscular dystrophy, hyperlipidemia, renal diseases, atopic dermatitis and allergic rhinitis.

Except for diseases, bad habits such as resting the cheek on the hand, bad sleeping position, rounded back, and mouth breathing were pointed out in three cases.

The most popular treatment for PCR was cure equivalent to temporomandibular disorders (43 cases, 33%) such as functional training and splint therapy. Stabilization of occlusion by using splints is considered to be effective for treating or stopping the progress of PCR. The abovementioned treatment options are based on this principle. In addition, prosthodontics treatment, splint therapy, intermaxillary traction with screw anchorage and rubber traction were noted in some answers.

The next most popular treatment was orthognathic surgery (32 cases, 24%) followed by orthodontic treatment (24 cases, 18%). Since many patients mainly complained of abnormal occlusion and discomfort, and visited medical institutions mainly to receive surgery for jaw deformities, their treatment options were directly aiming at resolving these problems. Besides these answers, some institutions reported resection of the mandibular condyle based on the diagnosis of temporomandibular arthrosis.

The findings of the present survey lead to various suggestions.

In many cases, PCR is not clearly distinguished from temporomandibular disorders. The concept of temporomandibular disorders in Japan is considered to be unique. Specifically, the results of the survey have an impact on the diagnosis of degenerative temporomandibular joint diseases in this country. Systematic diagnosis and treatment options for PCR have not been established. Thus, patients complaining of discomfort in occlusion tend to be diagnosed as having temporomandibular disorders or jaw deformities. As a result, suspected cases of PCR just receive "the best treatment that each institution can give".

However, in the institutions that did not respond to the survey, there may be patients who did not receive proper treatment due to misdiagnosis such as simple temporomandibular disorders, jaw deformities or malocclusion.

It is strongly recommended that health professions be kept informed about the pathology of PCR.

2. Marker searching using blood and urine samples

The number of samples was very few this year, resulting in a small amount of data collection.

Regarding diagnostic criteria, after analyzing blood samples from a small number of patients, a result indicating osteoporosis was observed. In addition, the level of RANTES, which is considered as a chemokine, fluctuated from the standard value (data not shown). These test values characterize PCR and can be useful biomarkers to identify the pathology of PCR. The PCR of young patients tends to be a high turnover bone disease, presenting high values of both bone formation and resorption rates. However, patients in their fifties and older are categorized into low-turnover bone disease, with lower values of bone formation and resorption rates. This two-phase distribution obtained from epidemiological studies was reproduced by the analysis of bone formation and resorption markers. This objective result is an important accomplishment in terms of PCR profiling. It is also significant that we obtained data suggesting a relationship between abnormality in TMJ observed in chemokine KO mice and the pathology of human PCR.

3. Microstructural analysis of TMJ

After conducting further microstructural analyses of bone tissue and joints in model mice, we recognized that proper sample fabrication of mouse TMJ is extremely difficult due to their small size.

Conclusion

We conducted this first survey in Japan, and although the response rate was low, we obtained the following results:

1) Subjective symptoms were not always observed in PCR patients.

2) Some PCR patients visited orthodontists rather than oral surgeons based on the symptoms of occlusal imbalance.

3) The previous finding that PCR is more common among females was supported by this survey in Japan.

4) PCR showed a two-phase distribution composed of idiopathic young patient cases and cases over fifties with concurrent diseases such as autoimmune diseases.
5) Occlusal imbalance was a more common chief complaint than abnormality in TMJ in PCR patients.
6) Bilaterally affected cases were more common than unilateral cases, suggesting systemic effects.
7) The most common diagnosis by medical professionals at the first visit of PCR patients was temporomandibular disorders, indicating difficulty in distinguishing them.
8) The most popular treatment for PCR was treatment equivalent to that for temporomandibular disorders. Many institutions seemed to struggle to treat PCR, suggesting a lack of systematic diagnosis or treatment.
9) There may be patients who did not receive proper treatment due to misdiagnosis such as simple temporomandibular disorders, jaw deformities or malocclusion.

After analyzing blood samples, results indicating osteoporosis were observed. In addition, the level of RANTES, which is considered as a chemokine, fluctuated from the standard value. These test values characterize the pathology of PCR.

From the results of the present study, various aspects regarding PCR were revealed. Presently, diseases causing condylar resorption of mandibles such as PCR are treated as complex concepts. We believe that to reasonably classify these diseases, epidemiological and clinical materials in addition to basic and molecular biological data need to be provided. These data could also provide the basis for developing diagnostic criteria of diseases causing condylar resorption.

PCR can be classified by the following three aspects.
1. Originated from low formation
2. Secondary resorptive changes due to autoimmune diseases or their medications
3. Others: Disorders in TMJ discs, etc.

Based on this point of view, differentiation from temporomandibular disorders or modification of the classification may be needed in some cases.

Acknowledgements

Acknowledgements: The participation of the 94 institutions listed in Table 1 in this survey is greatly appreciated.

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References