UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

BERNARDO CORREIA LIMA

CONDIÇÕES BUCAIS E CONDUTA NO TRATAMENTO ODONTOLÓGICO DE PACIENTES PORTADORES DE ANGIODEMA HEREDITÁRIO ATENDIDOS NO AMBULATÓRIO DE SAÚDE BUCAL ESPECIAL DO HOSPITAL UNIVERSITÁRIO CLEMENTINO FRAGA FILHO

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Orientadoras: Profª. Dra. Michelle Agostini

Profª. Dra. Sandra Regina Torres

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PARECER FINAL referente à defesa de dissertação da(o) mestranda(o) **BERNARDO CORREIA LIMA** intitulada **"CONDIÇÕES BUCAIS E CONDUTA NO TRATAMENTO ODONTOLÓGICO DE PACIENTES PORTADORES DE ANGIOEDEMA HEREDITÁRIO ATENDIDOS NO AMBULATÓRIO DE SAÚDE BUCAL ESPECIAL DO HOSPITAL UNIVERSITÁRIO CLEMENTINO FRAGA FILHO"** do Curso de Mestrado Profissional em Clínica Odontológica.

PARECER FINAL

A(O) candidata(o) cumpriu as exigências do Curso, conforme Regulamento de Pós-Graduação (Stricto Sensu) desta Faculdade.

A Banca Examinadora à defesa de dissertação da(o) **mestranda(o) BERNARDO CORREIA LIMA** resolve conceder o conceito final "A" e recomenda que lhe seja concedido o Grau de **Mestre em Clínica Odontológica.**

Rio de Janeiro, 25 de abril de 2018.

Sandra Regina Torres

Arley Silva Junior

Solange Oliveira Rodrigues Valle

Dedicatória

Dedico este trabalho:

ao meu pai, Luiz Carlos,

por ter me dado todos os valores éticos e morais

necessários para a construção do homem e do profissional

que tento ser, e que mesmo ausente em corpo,

está e sempre estará em minha vida diariamente;

à minha mãe, Ana Lucia,

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são o pilar para qualquer conquista

que se almeje na vida;

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“Impossível é apenas uma palavra grande usada por gente fraca, que prefere viver no mundo como ele está em vez de usar a força que tem para tentar mudá-lo, melhorá-lo. Impossível não é um fato, é uma opinião. Impossível não é uma declaração. É um desafio. Impossível é hipotético. Impossível é temporário. Impossível não é nada.”

Muhammad Ali

RESUMO

O angioedema hereditário (AEH) é uma condição caracterizada pela deficiência quantitativa ou qualitativa do inibidor de C1 (C1-INH), ocasionando crises de edema que podem acometer diversos órgãos, sendo transmitida de forma autossômica dominante causada por diferentes mutações. A morbidade está principalmente associada ao edema de vias aéreas superiores e de alças intestinais. Os fatores gatilhos incluem trauma, estresse físico ou mental, infecções e estrógenos. É uma doença desconhecida por muitos profissionais da área de saúde, sendo muitas vezes subdiagnosticada. Pela proximidade com as vias aéreas superiores e geração de micro traumas, os procedimentos odontológicos representam um risco em potencial para os pacientes portadores de AEH, podendo desencadear episódios graves, com possibilidade de asfixia e morte. Este estudo teve como objetivo descrever as condições de saúde bucal e o manejo odontológico de pacientes com AEH atendidos no Programa de Saúde Bucal Especial do Hospital Universitário Clementino Fraga Filho. Nove pacientes com idade entre 32 e 70 anos (média de 47 anos) com diagnóstico confirmado de AEH foram incluídos no estudo. Dados referentes ao tipo de AEH, severidade da doença, medicação profilática de longa duração, medicação profilática de curta duração, procedimentos odontológicos realizados e ocorrência de crises de angioedema após os procedimentos foram coletados dos prontuários. Além disso, as imagens digitais das radiografias panorâmicas iniciais foram avaliadas para a descrição do número de dentes presentes ou presença de lesões intra-ósseas. A maioria dos pacientes eram mulheres (78%), e AEH do tipo I foi o mais comumente apresentado (78%). Muitos pacientes tinham história de crises graves (67%), com de edema cutâneo (100%), dor abdominal (78%) e edema de laringe (55%). Todos os pacientes faziam uso da medicação profilática de longa duração, a maioria em uso de Andrógenos atenuados (AAs). A média de dentes presentes por paciente foi de 23 (variando de 13 a 30) e 58% apresentavam sinais radiográficos de doença periodontal. Quarenta e três procedimentos odontológicos foram realizados, sendo os mais comuns: exodontias (28%), restaurações dentárias (21%) e remoção supragengival de biofilme e cálculo (21%). Em 67% dos pacientes os procedimentos foram realizados sem alteração da dose da medicação profilática de longa duração. Em 33% um aumento da dose dos AAs (Danazol 600 mg e Oxandrolona 7,5 mg) foi empregado alguns dias antes do procedimento, sendo que em um destes pacientes foi associada a administração de concentrado C1-INH (1000UI) 1 hora antes do procedimento. A maioria das exodontias (67%) foi realizada nos pacientes submetidos a modificação do esquema profilático antes do procedimento, os quais tinham histórico de crises graves. Nenhum dos pacientes (0%) desta série de casos desenvolveu crises de angiodema após a realização dos procedimentos odontológicos. Este é o primeiro estudo que descreve o manejo odontológico de uma série de casos de pacientes Latino Americanos portadores de AEH. A maioria deles apresentou muitos dentes perdidos, dentes com indicação de extração e sinais radiográficos de doença periodontal. Não foram observadas crises de angioedema após diferentes tipos de procedimentos odontológicos, incluindo extrações dentárias, mesmo nos pacientes onde não foi realizada alteração da dose da medicação profilática de longa duração.

Palavras-chave: Angioedema hereditário, C1-INH, tratamento odontológico, terapêutica medicamentosa, doença sistêmica, edema de vias aéreas superiores.

ABSTRACT

Hereditary angioedema (HAE) is characterized by quantitative or qualitative deficiency of the C1 inhibitor (C1-INH), causing attacks of edema that can affect several organs, and it is an autosomal dominant condition caused by different mutations. Morbidity is mainly associated with edema of upper airways and intestinal loops. Trigger factors include trauma, physical or mental stress, infections and estrogen. HAE is unknown to many healthcare professionals and is often underdiagnosed. Because of its proximity to the upper airways and the generation of micro-trauma, dental procedures represent a potential risk for patients with HAE, which can lead to severe episodes with the possibility of suffocation and death. This study aimed to conduct an observational study on oral conditions and management of dental procedures in patients with Hereditary Angioedema (HAE) treated in an Oral Health Program at a University Hospital in Brazil. A total of 9 patients (age range 32 -70, mean age 47) diagnosed with HAE were enrolled in this study. Demographic data, type of HAE, disease severity, long and short-term prophylaxis, dental procedures performed and occurrence of angioedema following the procedures were recorded. Panoramic radiographs were analyzed to describe the number of teeth and presence of intra-osseous lesions. 78% of the patients were women and C1-INH-HAE type I was more frequent (78%). Many patients presented history of severe attacks (67%) with cutaneous edema (100%), abdominal pain (78%) and laryngeal edema (55%). All patients were on long-term prophylaxis, most of them (67%) with attenuated androgens (AAs). The mean number of present teeth was 23 (ranging from 13 to 30) and radiographic signs of periodontal disease were observed in 58% of the patients. Forty-three dental procedures were performed, being the most common: dental extractions (28%), dental restorations (21%) and supragingival removal of biofilm and calculus (21%). In 67% of the patients, the procedures were performed without changing the long-term prophylaxis, In 33% an increased dose of AAs (600 mg of Danazol and 7,5 mg of Oxandrolone) was administrated five days before and three days after the procedure. In one of these patients, the administration of C1-INH concentrate (1000 UI) 1 hour before the procedure was realized. Most of dental extractions (67%) were performed in the patients submitted to the pre-procedure prophylaxis, who had history of severe attacks. None of the patients in this case series developed angioedema attacks (0%) after the dental procedures. This is the first case series on the dental management of patients from Latin America with HAE. Many of them showed several missing teeth, indication of tooth extraction and radiographic signs of periodontal disease. No angioedema attacks were observed after different types of procedures, including dental extractions, even in patients where no modification of long-term therapy has been performed.

Key-words: Hereditary angioedema, C1-INH, dental treatment, drug therapy, systemic disease, upper airway edema.

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

AA – Andrógeno atenuado

AEH – Angioedema Hereditário

AEH tipo 1 – Angioedema Hereditário do Tipo 1

AEH tipo 2 – Angioedema Hereditário do Tipo 2

AEH-FXII – Angioedema Hereditário por mutação no gene FXII

AEH-ANGPTI – Angioedema Hereditário por mutação no gene Angiopoietin-1

AEH-PLG – Angioedema Hereditário por mutação no gene Plasminogênio

AEH-UNK – Angioedema Hereditário de origem desconhecida

C1-INH – Inibidor de C1

ECA – Enzima conversora de angiotensina

HUCFF – Hospital Universitário Clementino Fraga Filho

ICC – Insuficiência cardíaca congestiva

IECA - Inibidor de enzima conversora de angiotensina

UFRJ – Universidade Federal do Rio de Janeiro

SUMÁRIO

1. INTRODUÇÃO

O termo angioedema refere-se ao edema da derme e submucosa, sendo subdividido entre histaminérgicos - mediados por histamina – e não-histaminérgicos – mediados por bradicina. O angioedema hereditário (AEH) é uma condição transmitida de forma autossômica dominante causada por diferentes mutações, que é caracterizada pela deficiência quantitativa ou qualitativa do inibidor de C1 (C1-INH) e mediado por bradicina. Não há predileção racial, com proporção homem/mulher de 1:1 e prevalência de 1:50000. Os maiores problemas clínicos estão associados ao edema de vias aéreas superiores e de alças intestinais, pois além de gerar grande desconforto, ocasionam risco de vida no caso do acometimento da laringe, com taxa de mortalidade entre 25-40% em pacientes subdiagnosticados ou subtratados (Van Sickles *et al*., 2010; Jurado-Palomo *et al*., 2013).

Diferentes formas de Angioedema Hereditário (AEH) são atualmente reconhecidas e geneticamente identificáveis: AEH devido à deficiência genética do C1-INH (AEH tipo 1, AEH-1), caracterizado por baixos níveis de C1- INH, correspondendo ao maior número de casos (85%) e AEH devido à disfunção do C1-INH (AEH tipo 2, AEH-2), caracterizado por níveis normais (ou elevados) de C1-INH, porém com baixa funcionalidade, ambas causadas por diferentes mutações no gene SERPING1; AEH com níveis normais de C1-INH e mutação no gene FXII (AEH-FXII); AEH com mutação no gene angiopoietin-1 (AEH-ANGPTI); e AEH com mutação no gene plasminogênio (AEH-PLG). Além disso, alguns pacientes podem apresentar níveis normais de C1-INH e AEH de origem desconhecida (AEH-UNK). (Frank, 2006; Sánchez-Borges *et al*., 2012; López-Lera *et al*, 2013; Bork *et al*., 2014; Moreno *et al*, 2015; Veronez *et al*. 2017; Maurer *et al*., 2018). Em todas as formas a bradicinina desempenha um papel crucial (Cicardi *et al.*, 2014; Wu et al., 2016). Um padrão familiar de herança está presente na maioria dos pacientes com AEH, mas 25% dos casos ocorrem devido a mutações espontâneas (Frank, 2006). As manifestações clínicas são semelhantes, caracterizando-se por episódios recorrentes de angioedema subcutâneo, de vias aéreas superiores ou de alças intestinais, com duração de 2-5 dias.

Além disso, há o tipo adquirido de deficiência de C1-INH, associado com certos tipos de doenças linfo proliferativas ou em pacientes que desenvolvem anticorpos específicos. Nas doenças linfo proliferativas, os anticorpos monoclonais dirigidos contra células tumorais ativam o C1 e levam ao consumo de C1-INH. Na variante autoimune, o anticorpo une-se ao receptor de C1 na molécula C1-INH, levando a diminuição do C1-INH funcional e ao consumo de C1 (Brickman *et al*., 1986).

De maneira geral, há grande variabilidade clínica nas manifestações do AEH. Sabe-se que os ataques podem ocorrer sem nenhum fator precipitante, mas em 50% dos casos este fator é o trauma. Os fatores gatilho incluem procedimentos médicos e odontológicos, estresse físico ou mental, infecções e estrógenos (menstruação, gravidez, uso de contraceptivos orais) (Bork *et al*., 2000; Bork *et al*., 2006; Frank, 2006; Morcavallo *et al*., 2010; Sanuki *et al*., 2014). A frequência, severidade e localização dos episódios variam muito, de paciente para paciente e no mesmo paciente. Em alguns pacientes os ataques de angioedema são precedidos por sintomas prodrômicos de dor, prurido, eritema serpiginoso ou parestesia (Longhurst & Cicardi, 2012). Estes fatores predisponentes fazem com que o AEH se diferencie dos outros tipos de angioedema, como por exemplo, daquele causado por degranulação de mastócitos (causa mais comum de angioedema), que leva a liberação de histamina, ocasionando as alterações clinicas conhecidas. Esta degranulação ocorre principalmente por resposta de hipersensibilidade mediada por IgE devido a drogas, alimentos, plantas, poeira e inalantes, bem como por estimulo físico, como calor, exercício, frio, exposição solar ou significativa vibração (Stone *et al*., 2017). Outro tipo de resposta mediada pelo uso de drogas, que, no entanto, não é mediada por IgE, está associada ao uso inibidores de enzima conversora de angiotensina (IECA), utilizadas para controle da hipertensão arterial ou insuficiência cardíaca congestiva (ICC), tendo como exemplos o Captopril e o Enalapril. O angioedema associado à IECA resulta da diminuição da degradação de bradicinina e outros substratos ECA vasoativos, como a substância P. A bradicinina aumenta a permeabilidade vascular através do seu receptor B2, portanto, em níveis elevados, ocasiona a crise. Numa tentativa de reduzir estes efeitos colaterais, uma nova classe de IECA vem sendo utilizada, a qual tem por foco de inibição a angiotensina II, que são o Losartan e

Valsartan, reduzindo a frequência de angioedema, por reduzir o gradiente de concentração de bradicina. A prevalência deste tipo de angioedema é de 0,1% a 0,2% dentre os usuários de IECA (Brickman *et al*., 1986; Frank *et al*., 2006; Morcavallo *et al*., 2010; Stone *et al*., 2017).

O tratamento do angioedema alérgico, por ser mediado por histamina (histaminérgico) consiste, no geral, em terapia com anti-histamínicos orais. Se o ataque não for debelado, deverá ser ministrada epinefrina intramuscular. Os casos de angioedema por IECA, por não serem mediados pelo IgE, não respondem a terapia com anti-histamínicos e corticosteroides. Os casos de AEH relacionados à deficiência de C1-INH também não respondem a anti-histamínicos, corticosteroides ou terapia adrenérgica. Quando há acometimento das vias aéreas superiores, pode haver necessidade de intubação ou traqueostomia (Frank *et al*., 1976, Frank, 2006).

Existem três tipos de terapia medicamentosa para o AEH descritas historicamente: profilaxia de longa duração; profilaxia de curta duração e terapia para crises agudas (Giavina-Bianchi *et al*., 2011; Sanuki *et al*., 2014). O primeiro tipo pretende reduzir a frequência e severidade dos ataques e é indicada para pacientes com episódios significantes ou frequentes (mais de um episódio por mês). As drogas de primeira escolha para estes casos são os concentrados de C1-INH, como o Berinert ou Cinryse ou, na impossibilidade do uso dos concentrados de C1-INH, principalmente pela dificuldade de acesso a estes medicamentos, as drogas de escolha para o tratamento do AEH são os andrógenos atenuados (AA), agentes antifibrinolóticos ou *Interferon gama.* No Brasil, os mais utilizados são os AA e os agentes antifibrinoliticos. Os AA aumentam os níveis de C1-INH e fração C4 do complemento, reduzindo as crises de angioedema. Os medicamentos utilizados são o danazol, estanazolol e oxandrolona, que são menos virilizantes que a metiltestosterona. O Danazol consiste no andrógeno atenuado mais utilizado no Brasil e mais disponível (assegurado pelo programa de medicamentos de alto custo), além de existirem estudos bem controlados demonstrando sua eficácia clínica, com melhora de parâmetros laboratoriais (Giavina-Bianchi *et al*., 2010). O ácido E-aminocapróico e ácido tranexânico são recomendados como terapias adjuvantes, principalmente em pacientes sem acesso ao concentrado de C1-INH ou com baixa tolerância a esteroides anabólicos (Frank *et al*., 1979). O

segundo tipo de terapia, de curta duração, é recomendado em pacientes que passarão por procedimentos invasivos como os odontológicos, cirurgia oral ou maxilofacial e operação endoscópica. Esta terapia é baseada na administração de uma dose elevada de esteroides anabólicos ou agentes anti-fibrinolíticos de 5 a 7 dias antes da cirurgia e de 2 a 5 dias após, ou administração de concentrado de C1-INH 1 hora antes do procedimento. Alternativamente, plasma fresco congelado pode ser administrado na noite anterior e logo antes do início do procedimento (Morcavallo *et al.*, 2010; Sanuki *et al*., 2014). A terceira opção, com função de debelar crises agudas, consiste em aplicação de infusão intravenosa de narcóticos e drogas anti-inflamatórias, para manter o nível a integridade do trato respiratório e o controle da dor e náusea. Em caso de desidratação e hipotensão causadas por envolvimento abdominal, reidratação é necessária. A resolução do quadro agudo se dá por elevação dos níveis de C1-INH, que pode se dar pela forma de concentrado dessa proteína ou por administração de plasma fresco congelado, o qual é rico neste fator, no entanto, estudos demonstram que a solução concentrada tem efeito mais desejado. O uso de andrógenos não se faz eficaz em crises agudas, pois necessitam de 1 a 2 dias para o início da ação (Donaldson *et al*., 1963; Frank *et al*., 1979; Frank *et al*., 2006).

As recomendações internacionais para o manejo do AEH, incluindo a profilaxia de longa duração, profilaxia de curta duração e terapia para crises agudas estão resumidas no quadro 1 (Zanette *et al*., 2015).

Quadro 1 – Manejo do AEH: recomendações internacionais (Bowen *et al*., 2010; Cicardi *et al*., 2010; Van Sickles *et al*., 2010; Caballero *et al*., 2011; Flocard *et al*., 2012). Extraída de Zanette et al. (2015).

Manejo	Administração/ dose	Observações	Profilaxia de longa duração	Profilaxia de curta duração	Tratamento de crises agudas
Ácido Tranexâmico /*Ácido* épsilon-*aminocapróico* (Transamin)	Via oral/ 0,25 – 1,5 g 2x ao dia/1 -3 g 2x ao dia	Efeitos colaterais; Não seguro na gravidez	Eficaz em 48 h	Eficaz em 48 h	Ineficaz (latência de 48 h*)
17α-ethinyl testosterone (Danazol)	Via oral/ 200-600 mg/dia	Efeitos colaterais; Não seguro na gravidez	Eficaz em 48 h	Eficaz em 48 h	Ineficaz (latência de 48 h)
Icatibanto (antagonista do	Subcutâneo/ 30 mg	Efeitos colaterais;	NA	NA	Eficaz

receptor de bradicinina B2) (Firazyr)		Idade >18 anos; aprovado para auto-aplicação			
Ecallantide	Subcutâneo/ 30 mg	Efeitos colaterais; Idade >18 anos	NA	NA	Eficaz
Concentrado de C1-INH (Berinert); C1-INH recombinante (Rhucin e Ruconest); Concentrado de C1-INH nanofiltrado (Cinryze e Cetor)	Endovenoso / 20 U/kg	Gravidez, parto e formas adquiridas; aprovado para auto-aplicação	Apenas em casos específicos	Eficaz 1 hora antes da cirurgia	Eficaz
FFP	Endovenoso/ 250-500 ml	Efeitos colaterais; transmissão de doenças infecciosas	NA	Eficaz 1 hora antes da cirurgia	Eficaz
Analgesia com opióides/ Hidratação	Via parenteral/ dose apropriada	Durante crises abdominais	NA	NA	Durante crises abdominais
IT/ *cricotireotomia*	Antes da obstrução completa de vias aéreas	Alta taxa de complicação	NA	NA	Apenas para asfixia
[1]Epinefrina, anti-histamínicos, glicocorticóides	Via parenteral/ dose apropriada	Apenas se SAV for necessário	Não eficaz	Não eficaz	Não eficaz

* *Ácido* épsilon-*aminocapróico* e ácido tranexânico podem ser administrados durante ataques agudos para facilitar a regressão de sintomas no período de 48 horas. [1]APENAS se for necessário SAV; SAV: suporte avançado de vida; C1 – INH: inibidor de C1; FFP, Plasma fresco congelado, NA, não aplicável, IT, intubação traqueal.

Os procedimentos odontológicos representam um risco em potencial para os pacientes portadores de AEH, pois geram micro traumas, não apenas pelo contato com os instrumentos, como também pela saída de ar comprimido em alta pressão dos micromotores odontológicos, além da proximidade com as vias aéreas superiores, ocorrendo a possibilidade de asfixia e morte (Sanuki *et al*., 2014). No passado, a taxa de mortalidade pós-procedimentos odontológicos de rotina era de 30% a 40% em pacientes em AEH. De fato, um

grande número de atendimentos foi realizado sem o conhecimento da condição, seja por desconhecimento por parte do paciente ou deficiência na coleta de dados durante a anamnese por parte do cirurgião-dentista. Além disso, os cirurgiões-dentistas muitas vezes não sabem como realizar o manejo adequado da condição para o tratamento odontológico e a falta de conhecimento por parte da equipe médica pode levar a um diagnóstico incorreto (Van Sickles *et* al., 2010; Morcavallo *et al.,* 2010; Christensen *et al*., 2012; Jurado-Palomo *et al*., 2013; Sanuki *et al.,* 2014; Zanette *et al.,* 2015; Forrest *et al.,* 2017).

Forrest *et al.* (2017) descreveram a necropsia de uma paciente de 50 anos com *causa mortis* de asfixia por edema em vias aéreas superiores após a exodontia de dois molares inferiores. Na necropsia foi constatada a presença de edema em região submandibular e do pescoço do lado direito. A paciente foi atendida em uma unidade de emergência dois dias após as exodontias evoluindo para óbito no hospital. O diagnóstico inicial foi de Angina de Ludwig, o qual foi descartado devido à ausência de sinais de infecção evidenciada na necropsia. A paciente havia recebido um diagnóstico de “edema angioneurótico” alguns anos antes deste procedimento, e acreditando se tratar de uma condição psicológica não procurou tratamento. Apesar de ter recebido esta informação na anamnese, o dentista realizou o procedimento que desencadeou o episódio fatal de angioedema.

Baliga *et al*. (2011) relatou um caso de uma paciente de 42 anos com episódio de angioedema em região de face (submentoniana e submandibular bilateral), após pulpectomia em um pré-molar inferior. A paciente desconhecia a condição de AEH, portanto foi tratada em atendimento de emergência de hospital com protocolo para reação alérgica. Na história clínica, a paciente relatou dores abdominais e desenvolvimento de angioedema após picada de mosquito anos antes deste episódio. Desta forma, a hipótese de AEH foi considerada e o exame para verificar os níveis de C1–INH foi realizado, confirmando AEH por deficiência de C1-INH. O edema regrediu espontaneamente em 48 horas.

Não há um esquema profilático único para pacientes portadores de AEH que serão submetidos a procedimentos odontológicos. De acordo com Jurado-Palomo *et al*. (2013), a profilaxia de curta-duração deveria ser

administrada para todos os pacientes com AEH anteriormente a realização de procedimentos odontológicos, independente da severidade da condição. De acordo com estes autores, as três principais opções são: 1- aumento da dose de AAs, ou introdução deste medicamento (para os pacientes que não fazem a medicação de rotina), antes e após o procedimento, 2 - administração de C1-INH antes do procedimento ou 3 - manutenção da terapia de longa duração (sem alteração) para os pacientes que já fazem a medicação rotineiramente. Na série de casos estudada por Jurado-Palomo *et al.* (2013), a pré-medicação com AAs (aumento da dose ou introdução do medicamento), a administração de concentrado de C1-INH derivada de plasma humano, ou ambos, foram boas opções para o manejo ambulatorial de procedimentos odontológicos em pacientes com AEH do tipo I. Além disso, os autores afirmam que medicação para crises agudas deveria estar disponível no consultório odontológico para uso imediato no caso de ocorrência de edema de laringe.

Christensen *et al*. (2012) relataram sucesso na realização de cirurgia ortognática em paciente com AEH de 16 anos de idade, sem intercorrências no trans e pós-operatório. Para tal procedimento o paciente recebeu 1000 UI de C1-INH na manhã da cirurgia e mais 1000 UI com 48 horas de pós-operatório. Já Cifuentes *et al*. (2013) relataram uma crise severa de angioedema em um paciente asiático de 18 anos de idade após a realização do mesmo tipo de procedimento. Neste caso o paciente não sabia ser portador da condição e desta forma, não foi realizado nenhum esquema profilático.

Farkas *et al.* (1999) relataram 12 cirurgias orais menores em 12 pacientes, sendo 11 exodontias e uma cirurgia de seio maxilar, e não observaram nenhuma crise de angioedema com administração de Danazol 200 mg de 8 em 8 horas, 4 dias antes e 4 dias após os procedimentos. Protocolo semelhante foi relatado por Van Sickles *et al.* (2010) para a realização de exodontia de 4 terceiros molares, os quais também não observaram ocorrência de angioedema no trans e pós-operatório.

Zanette *et al.* (2015) relatam o uso de concentrado de C1-INH uma hora antes do procedimento em 9 pacientes que foram submetidos a cirurgias de exodontias (5 com instalação de implantes osseointegrados), mesmo nos 5 pacientes que faziam uso de terapia de longa duração (4 em uso de Danazol e 1 em uso de Ácido Tranexânico). Apenas um dos pacientes apresentou uma

crise de angioedema no antebraço após a colocação do “garrote” para a administração concentrado de C1 INH. Este paciente era um dos 4 que não fazia uso de terapia de longa duração. Sanuki *et al.* (2014) também utilizaram concentrado de C1 INH (Berinert) uma hora antes do procedimento para a realização de exodontias múltiplas (quatro terceiros molares e primeiros pré-molares inferiores) em paciente com AEH, que foram executadas em centro cirúrgico para maior controle e segurança, não havendo intercorrências no trans e pós-operatório. Bork *et al*. (2011) na maior série de casos de extração dentária em pacientes com AEH relata na literatura de língua inglesa, mostram que a administração de concentrado de C1-INH antes do procedimento reduz significativamente o risco de angioedema após o procedimento. No entanto, os mesmos autores relatam que edema facial e edema de laringe podem ocorrer mesmo quando da administração do medicamento. No relato de Morcavallo *et al.* (2010) uma paciente portadora de AEH foi submetida a tratamento periodontal agressivo, com elevação de retalhos muco periósteos para raspagem subgengival e exodontia de dentes comprometidos com administração de Danazol 200 mg 8/8 h por 5 dias antes do procedimento e 5 dias após o mesmo. A cirurgia foi realizada em centro cirúrgico, sob anestesia geral com intubação nasotraqueal. Apesar do uso da terapia profilática, o paciente apresentou edema com 24 horas de pós-operatório em região de face cavidade oral, principalmente nos sítios cirúrgicos.

Considerando as especificidades relacionadas ao tratamento odontológico de pacientes portadores de AEH, estudos que relatem o perfil dos pacientes, protocolos utilizados e ocorrências trans ou pós-operatórias são de extrema importância para uma melhor compreensão da condição bem como para o estabelecimento de práticas seguras para os pacientes. No presente estudo são relatadas as condições de saúde bucal e a conduta no tratamento odontológico dos pacientes com AEH atendidos no Serviço de Saúde Bucal Especial do Hospital Universitário Clementino Fraga Filho (HUCFF) da Universidade Federal do Rio de Janeiro. Os pacientes foram encaminhados para tratamento odontológico pelo Serviço de Imunologia do HUCFF, o qual é considerado um centro de referência de atendimento aos pacientes com AEH. Um estudo realizado neste serviço (Alonso *et al*., dissertação de Mestrado em Clínica Médica - UFRJ, 2017) descreveu o perfil de 138 pacientes

diagnosticados com AEH atendidos na unidade entre 1989 e 2016. Os resultados coletados mostram que 70,3% dos pacientes eram mulheres e 29,7%, homens. A idade variou entre 12 e 77 anos, e o tempo de diagnóstico entre 0 e 61 anos. História familiar de AEH estava presente em 89,9% dos casos. Os autores encontraram predominância do AEH com deficiência de C1-INH (77,5%) e uma frequência importante de AEH com níveis normais de C1-INH com mutação no gene do FXII. Com relação à severidade dos ataques, a maioria dos pacientes apresentou crises graves (52,2%) ou moderadas (23,2%). 13,8% dos pacientes eram assintomáticos. Portanto, os resultados do presente estudo contribuirão com um dado novo, pois informações relativas às condições de saúde bucal e ao tratamento odontológico destes pacientes nunca haviam sido avaliadas.

2. OBJETIVO GERAL

- Avaliar as condições de saúde bucal e a profilaxia antes do tratamento odontológico em pacientes com AEH atendidos no Serviço de Saúde Bucal Especial do Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro.

2.1 OBJETIVOS ESPECÍFICOS

- Caracterizar o perfil demográfico dos pacientes com AEH atendidos no Serviço de Saúde Bucal Especial do HUCFF/UFRJ;
- Descrever as condições de saúde bucal destes pacientes com base nos registros do exame físico extra e intra-oral e na análise de radiografias panorâmicas;
- Descrever os procedimentos odontológicos realizados nestes pacientes;
- Descrever as condutas preventivas adotadas no tratamento odontológico para reduzir a possibilidade de crises em vias aéreas superiores;
- Verificar a ocorrência de episódios de edema em vias aéreas superiores após a realização do tratamento odontológico nestes pacientes.

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3. ARTIGO

Oral Surgery Oral Medicine Oral Pathology Oral Radiology (Anexo 3)

HEREDITARY ANGIOEDEMA: DENTAL MANAGEMENT OF NINE PATIENTS FROM A UNIVERSITY HOSPITAL FROM RIO DE JANEIRO, BRAZIL

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ABSTRACT

Objective. To conduct an observational study on oral conditions and management of dental procedures in patients with Hereditary Angioedema (HAE) treated in an Oral Health Program of a University Hospital from Brazil.

Study Design. A total of 9 patients (age range 32 -70, mean age 47) diagnosed with HAE were enrolled in this study. Demographic data, type of HAE, disease severity, long and short-term prophylaxis, dental procedures performed and occurrence of angioedema following the procedures were recorded. Panoramic radiographs were analyzed to describe the number of teeth, horizontal and vertical alveolar bone loss and presence of intra-osseous lesions.

Results. Most of the patients were women (78%) and C1-INH-HAE type I was more frequent (78%), with 67% of patients presenting history of severe attacks. All patients were on long-term prophylaxis, most of them (67%) with attenuated androgens (AAs). The mean number of present teeth was 23 and radiographic signs of periodontal disease were observed in 58% of the patients. Forty-three dental procedures were performed, being the most frequent: tooth extractions (28%), dental restorations (21%) and supragingival removal of biofilm and calculus (21%). In 67% of the patients the procedures were performed without modification in the long-term prophylaxis. However, in 33%, an increased dose of AAs and/or C1-INH concentrate was administrated before the procedure, being most of dental extractions (67%) performed in these patients. None of the patients in this case series developed angioedema attacks (0%) after the procedures.

Conclusion. This is the first case series on the dental management of Latin American patients with HAE. Many of them showed several missing teeth, indication of tooth extraction and radiographic signs of periodontal disease. No angioedema attacks were observed after different types of procedures, including dental extractions, even in patients where no modification of long-term therapy has been performed.

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by different mutations, characterized by sudden recurrent episodes of swelling of the skin (mainly in extremities, face and genitals), gastrointestinal tract, upper airways and other organs.[1,2,3] HAE is classified in : 1) HAE with genetic Deficiency of C1 inhibitor (C1-INH) that includes C1-INH quantitative deficiency (C1-INH-HAE type I); and C1-INH functional defect (C1-INH-HAE type II); 2) HAE with Normal C1-INH and mutations in Factor XII gene (Hageman Factor) (FXII-HAE); 3) HAE with normal C1-INH and mutation in the angiopoietin-1 gene (HAE-ANGPTI); 4) HAE with normal C1-INH and mutation in the plasminogen gene (HAE-PLG), and a type of HAE with normal C1-INH but unknown origin (Unknown-HAE = U-HAE).[3,4,5] The pathophysiologic mechanism underlying HAE is mediated by bradykinin and is therefore a nonhistamine-mediated process.[6] Because of this, traditional medications associated with the treatment of allergic disorders (anti-histamines, corticosteroids) are ineffective or have limited effect in the treatment of HAE.[5] Management of HAE include long-term and short-term prophylaxis and treatment for acute attacks.[7,8,9]

The HAE is a disease that is unknown to many healthcare professionals and is often underdiagnosed, with a delay between symptoms onset and diagnosis and is associated with high morbidity and mortality.[3] A familial pattern of inheritance is characteristic and should alert to the possible diagnosis of HAE, but in 20-25% of cases it is absent and spontaneous mutations can be observed. HAE attacks can be precipitated by local trauma, psychological stress, medical and dental procedures, estrogens and infections.[3,10] Microtraumas caused by dental-oral procedures carry a high risk of causing such attacks and increasing the risk of death due to asphyxiation, since they are performed close to the upper-airway.[11,13] In the past, overall mortality after dental surgery without adequate treatment was around 30-40% in patients with HAE.[10] Short-term prophylaxis for management of invasive dental procedures is indicated to patients with HAE regardless of their severity score. It is generally done by the administration of human C1- INH concentrate before the procedure; increasing the dose of attenuated androgens (AAs) or antifibrinolytic drugs, and/or administration of fresh frozen plasma. However, the risk of developing angioedema because of dental-oral procedures cannot be completely avoided with preoperative prophylaxis. [7,8,9,13]

The aim of this study was to conduct an observational study on oral health conditions, long-term treatment, prophylaxis protocol used for dental treatment and the occurrence of post treatment episodes in 9 patients affected by HAE.

METHODS

We carried out a retrospective review of the clinical histories of patients with confirmed HAE in follow-up at the HAE outpatient clinic of Immunology

Service of the University Hospital Clementino Fraga Filho (Federal University of Rio de Janeiro – Brazil, HUCFF-UFRJ), which were referred for dental care to the Oral Health Program of the same Institution between 2012 and 2017. This referral occurred because of patients complains about difficulties for dental assistance. This study was approved by Ethics Committee of the HUCFF-UFRJ (protocol 76177317.2.0000.5257).

Information evaluated from the charts was gender, age at the time of the dental care, type of HAE, disease severity, long-term prophylaxis, short-term prophylaxis, dental procedures performed and occurrence of angioedema following the dental procedures. Digital images of the initial panoramic radiography of each patient were analyzed to describe the number of teeth, signs of horizontal and vertical alveolar bone loss and presence of intra-osseous lesions.

The collected data were systematically transcribed into a worksheet of the Microsoft Office Excel 2007 program for better organization and were subjected to a descriptive analysis.

RESULTS

Seven (78%) patients were female and two (22%) were male. The age ranged from 32 to 70 years (mean age= 47 years). The mean age at onset of manifestations was 22 years and at the time of diagnosis was 37. Seven (78%) patients had C1-INH-HAE type I, and 2 (22%) had HAE with normal C1-INH and mutation on Factor XII (FXII-HAE). Seven (78%) patients reported family history of HAE, and the other two (22%) not. Cutaneous edema (100%), abdominal pain (78%) and laryngeal edema (55%) were the most common manifestations

of HAE and the majority of patients had severe attacks (67%). All patients were on long-term prophylaxis, 6 (67%) using AAs (oxandrolone or danazol), 2 (22%) Tranexamic acid, and 1 (11%) Epsilon-aminocaproic-acid.

Panoramic radiography was available for 7 patients and the mean number of present teeth was 23 per patient (ranging from 13 to 30). Five (71%) patients had 9 or more missing teeth. Two patients (29%) presented signs of vertical alveolar bone loss and other two (29%) showed signs of horizontal alveolar bone loss and indicates signs of periodontal disease in these patients. Besides that, there were observed six periapical lesions, five of them in the same patient in teeth with indication of extraction. The other lesion was associated with a tooth with indication of endodontic treatment. Two impacted third molars were also observed. No reports of lesions in the oral mucosa were found in the records.

There were performed 43 dental procedures, all in the dental chair, including 12 (28%) tooth extractions, 9 (21%) dental restorations, 9 (21%) supragingival removal of biofilm and calculus, 5 (12%) suture removal, 4 (9%) subgingival removal of biofilm and calculus, 3 (7%) dental prophylaxis and 1 (2%) endodontic treatment. All procedures were performed on days where, if necessary, patients could receive medication for acute attacks at the Immunology Department of the Hospital.

In 6 patients (67%) the procedures were performed without changing the dose of the long-term medication, with 3 patients taking oxandrolone (7.5 mg/day), 2 using Tranexamic acid (500 and 1 g/day, respectively) and 1 using Epsilon-aminocaproic acid (1 g/day). Four dental extractions were realized in one patient taking oxandrolone and an endodontic treatment and subgingival

removal of biofilm and calculus were performed in patients taking Tranexamic acid. In 3 (33%) patients taking danazol as long term-prophylaxis, a dose increase of the medication was performed (600 mg/day 5 days before e 3 days after the procedure). In one of them, who underwent 6 dental extractions, 1000 UI of C1-INH concentrate (Berinert) was also administrated 1 hour before the procedures. Considering all the dental extractions, most of them (67%) were performed in the patients who underwent modification in the therapeutic regimen before the procedure (short-term prophylaxis). All of them had history of severe attacks.

None of the patients in this case series developed angioedema attacks (0%) after the dental procedures. The data of each patient are described in the Table 1.

DISCUSSION

Although HAE is a condition without preference by gender[3], in the present study most of the patients were women, what was also observed in other two series of cases[12,13,14], which involved patients with HAE undergoing dental treatment. A fact to be considered is that the individuals enrolled in this kind of study were those who sought dental treatment, and the literature indicates that there is a greater concern of women with health and body care than men.[15] The C1-INH-HAE type I was the most common type of HAE presented by our patients, which is described in approximately 85% of the affected patients.[3,12] Almost all patients reported familial history, also a similar finding described in the literature.[3] Two patients were affected by FXII-HAE, one without a family history, what probably represents a spontaneous mutation, which is attributed to 25% of the cases.[3]

Most of the patients in our series had a history of severe attacks, and, in fact, all of them were taking long-term prophylaxis, indicated for patients with significant or frequent episodes.[13,16] Long-term prophylactic treatments include plasma-derived C1-INH concentrate such as Berinert or Cinryse; AAs such as danazol, stanozolol, and oxandrolone; and antifibrinolytics, such as Tranexamic acid and E aminocaproic acid.[17,18] The most frequently used medications in our patients were oxandrolone and danazol. An important fact to say is that in Brazil, the access to C1 INH is restricted the use of AAs is more frequent, with no cost for patients.

There are no studies published in the English literature that specifically address the oral health conditions of patients with hereditary angioedema. In the present study, there were a great number of missing teeth. Precarious dental conditions in patients with HAE have been describe in reports of some isolated cases.[8] In the series reported by Bork *et al*.[14], 801 tooth extractions were performed in 171 patients with HAE, a mean of almost 5 teeth per patient. In fact, in our study tooth extraction was the most common dental procedure (28%). In the study of Jurado-Palomo *et al*.[12], involving 24 patients with HAE, the most common dental procedure was also tooth extraction, corresponding to 56% of the dental procedures performed. Signs of alveolar bone loss, probably associated with periodontal disease, were common in our patients (58%). Data on periodontal disease in patients with hereditary angioedema are not available in the literature. Interestingly, Roberts *et al.*[19], reported aggressive periodontal disease with gingival edema in a young patient with HAE. New studies are needed to understand if patients with HAE tend to present worse oral health conditions. Some studies show that given the impact of HAE on health-related

quality of life, it is hardly surprising that patients may also suffer from depression, anxiety, and phobias relating to trigger situations such as medical and dental procedures.[20,21] In a survey on their perception of their dental care experiences and needs, more than half (58%) of the group of patients with HAE perceived a need for dental care. Many patients reported experiencing attacks of HAE after receiving dental treatments and difficulty in obtaining dental appointments, in about one in two cases.[22] Zanette *et al*.[13] discuss the role of anxiety in patients with HAE in the development of attacks after oral surgery and states that a proper dental management involves conducting a careful psychophysical assessment and thoroughly informing the patient.

The HAE is a disease that is unknown to many healthcare professionals and is often underdiagnosed.[3,10] HAE has considerable implications for dental health care providers, since dental procedures may trigger severe and even life-threatening episodes.[12] In the past, overall mortality after dental surgery without adequate treatment was around 30-40% [10] and a significant number of dental-oral procedures were carried out even before the disease was diagnosed.[12] However, even today, there are cases of death after dental procedure [13,17,23,24], mainly related to the development of upper airway edema after dental extractions that can occur in 24-48 hours after the treatment, causing fear in this group of patients, that constantly avoid dental care, and only seek when in precarious oral conditions.[23] Dental extractions represented a considerable percentage of the dental procedures performed in HAE patients, as reported by Jurado-Palomo *et al*.[12] and also observed in the present study. Therefore, patients are subject to complications after treatment, with the

majority of cases of angioedema of the upper airways being observed in patients where adequate preparation for the procedure was not performed.

Management of HAE include long-term and short-term prophylaxis and treatment for acute attacks.[7,8,9] Short-term prophylaxis for management of invasive dental procedures is indicated to patients with HAE regardless of their severity score. It is generally done with administration of human C1-INH concentrate before the procedure, increasing the dose of AAs or antifibrinolytic drugs, and/or administration of fresh frozen plasma.[4,25,26] However, the risk of HAE attacks associated with dental treatment is not fully prevented by short-term prophylaxis.[13] According to the results of Attikson & Frank[11], attacks occurred independently of the disease activity and the trauma of the dental procedure. Success with the use of increased doses of Danazol has been reported in invasive dental procedures.[8,12,27] But Morcavallo *et al*.[25] have reported the occurrence of angioedema even with the use of short-term prophylaxis with danazol in a periodontal surgery. Bork *et al*.[14] reported that short-term prophylaxis with C1-INH concentrate significantly reduces the risk of angioedema attacks after dental extraction, but facial swellings and laryngeal edema may occur despite prophylaxis. Short-term prophylaxis with C1-INH concentrate before the procedure was also successfully employed by Christensen *et al*.[26], Sanuki *et al*.[23] and Zanette *et al*.[13] in invasive dental procedures.

In the present study, most of the invasive procedures (tooth extractions and subgingival removal of biofilm and calculus) were performed in patients where increased dose of Danazol (600 mg/day) was administered 5 days before and 3 days after the procedures. In one of them, which was submitted to the

largest number of dental extractions, C1-INH concentrated was also administered 1 hour before the procedures. All of these patients presented history of severe attacks. In 67% of our patients, the procedures were performed without changing the dose of the long-term medication, most in use of oxandrolone. One patient underwent 4 tooth extractions and had history of severe attacks. Reports of dental procedures performed exclusively with the maintenance of long-term therapy are not frequent, especially with oxandrolone. In the case series reported by Jurado-Palomo *et al.*[12] some invasive dental procedures were performed only with the maintenance of the dose of long-term therapy with danazol and stanozolol, without modifications.

None of the patients in the present case series developed angioedema attacks (0%) after the dental procedures. Bork *et al*.[14] reported facial swelling, potentially life-threatening laryngeal edema or both in 21,5% of the dental extractions performed in patients that do not received prophylaxis (short or long-term prophylaxis). In the same study, similar symptoms were recorded in a lower proportion of patients undergoing dental extraction after short-term prophylaxis with pdhC1-INH (plasma derived human C1 inhibitor concentrate). The prevalence of upper airway angioedema after dental procedures in the series of Jurado-Palomo *et al*.[12] was very low (4,5%), and none patient developed angioedema after dental extractions. Patients who experienced upper way angioedema during the 24 hours following the procedure were not taking AAs, antifibrinolytic agents, or pdhC1-INH as long-term prophylaxis, nor had they taken short-term prophylaxis. In the present study, the fact that we did not observe the occurrence of any case of angioedema after the procedures

could be attributed to the use of long-term prophylaxis by all the patients and that all types of dental procedures were included, not just extractions.

CONCLUSIONS

This is the first case series on the dental management of Latin American patients with HAE. Many of them showed several missing teeth, indication of tooth extraction and radiographic signs of periodontal disease. All patients were in use of long-term prophylaxis during the execution of the procedures and not all received additional short-term prophylaxis, which was mainly performed in those who underwent tooth extraction. No angioedema attacks were observed after different types of procedures. The results are important for a better understanding of the condition and the establishment of safe dental practices in the affected patients.

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Table 1 – Patients with HAE submitted to dental treatment in the Oral Health Program of Hospital Clementino Fraga Filho (Federal University of Rio de Janeiro – Brazil, HUCFF-UFRJ).

Patient	Age	Gender	HAE type	Familial history of HAE	HAE Severity	Long term prophylaxis	Panoramic radiography	Dental procedures (N)	Short-term Prophylaxis for dental treatment	Angioedema attack after dental treatment
1	45	F	C1-INH-HAE type I	Yes	Severe	AA (Oxandrolone 7.5 mg/day)	- 22 teeth -Localized Horizontal bone loss	Dental Prophylaxis (1)	No change in long-term prophylaxis	No
2	70	F	C1-INH-HAE type I	Yes	Severe	AA (Danazol 100 mg/ every 3 days)	-13 teeth -Advanced periodontal disease -5 periapical lesions	SPGRBC (1) SBGRBC (1) Tooth extraction (6) Suture removal (5)	Danazol 600mg/day 5 days before and 3 days after + C1-INH Concentrate 1 hour before	No
3	32	F	C1-INH-HAE type I	Yes	Severe	Epsilon-aminocaproic-acid (1g/day)	Not available	Dental Prophylaxis (1)	No change in long-term prophylaxis	No
4	32	F	FXII-HAE	Yes	Moderate	Tranexamic acid (1g/day)	-30 teeth -1 periapical lesion	SPGRBC (2) Endodontic treatment (1) Dental restoration (2)	No change in long-term prophylaxis	No
5	64	M	C1-INH-HAE type I	No	Severe	AA (Danazol 300mg/day)	-22 teeth -Generalized horizontal bone loss	SPGRBC (2) SBGRBC (1) Tooth extraction (2)	Danazol 600mg/day 5 days before and 3 days after	No
6	64	F	C1-INH-HAE type I	Yes	Moderate	Tranexamic acid (500 mg/day)	-23 teeth -Advanced periodontal disease	SPGRBC (3) SBGRBC (2)	No change in long-term prophylaxis	No
7	34	F	C1-INH-HAE type I	Yes	Moderate	AA (Oxandrolone 7.5 mg/day)	-30 teeth	Dental restoration (6)	No change in long-term prophylaxis	No
8	43	F	C1-INH-HAE type I	Yes	Severe	AA (Oxandrolone 7.5 mg/day)	-23 teeth	Tooth extraction (4) Dental restoration (1)	No change in long-term prophylaxis	No
9	42	M	FXII-HAE	No	Severe	AA (Oxandrolone 7.5 mg/day/ Danazol 400 mg/day)	Not available	Dental Prophylaxis (1) SPGRBC (1)	Danazol 600mg/day 5 days before and 3 days after	No

SPGRBC – Supragingival removal of biofilm and calculus; SBGRBC – Subgingival removal of biofilm and calculus.

DETALHAR PROJETO DE PESQUISA

DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: CONDIÇÕES BUCAIS E CONDUTA NO TRATAMENTO ODONTOLÓGICO DE PACIENTES PORTADORES DE ANGIODEMA HEREDITÁRIO ATENDIDOS NO AMBULATÓRIO DE SAÚDE BUCAL ESPECIAL DO HOSPITAL UNIVERSITÁRIO CLEMENTINO FRAGA FILHO
Pesquisador Responsável: BERNARDO CORREIA LIMA
Área Temática:
Versão: 2
CAAE: 76177317.2.0000.5257
Submetido em: 10/10/2017
Instituição Proponente: UNIVERSIDADE FEDERAL DO RIO DE JANEIRO
Situação da Versão do Projeto: Aprovado
Localização atual da Versão do Projeto: Pesquisador Responsável
Patrocinador Principal: UNIVERSIDADE FEDERAL DO RIO DE JANEIRO

PLATAFORMA BRASIL COORDENADOR PLATAFORMA BRASIL

Comprovante de Recepção: PB_COMPROVANTE_RECEPCAO_972470

DOCUMENTOS DO PROJETO DE PESQUISA

- Versão Atual Aprovada (PO) - Versão 2
  - Pendência Documental (PO) - Versão 2
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      - Comprovante de Recepção - Submissã
      - Folha de Rosto - Submissão 5
      - Informações Básicas do Projeto - Subm
      - Outros - Submissão 5
      - Projeto Detalhado / Brochura Investigac
      - Recurso Anexado pelo Pesquisador - S
      - TCLE / Termos de Assentimento / Justi
    - Apreciação 5 - UFRJ - Hospital Universitári
  - Projeto Completo

Tipo de Documento	Situação	Arquivo	Postagem	Ações

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Apreciação	Pesquisador Responsável	Versão	Submissão	Modificação	Situação	Exclusiva do Centro Coord.	Ações
PO	BERNARDO CORREIA LIMA	2	10/10/2017	28/10/2017	Aprovado	Não	

HISTÓRICO DE TRÂMITES

Apreciação	Data/Hora	Tipo Trâmite	Versão	Perfil	Origem	Destino	Informações
PO	28/10/2017 13:24:13	Parecer liberado	2	Coordenador	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	PESQUISADOR	
PO	27/10/2017 12:25:42	Parecer do colegiado emitido	2	Coordenador	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	23/10/2017 12:08:26	Parecer do relator emitido	2	Membro do CEP	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	18/10/2017 17:25:41	Aceitação de Elaboração de Relatoria	2	Coordenador	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	18/10/2017 17:25:22	Confirmação de Indicação de Relatoria	2	Coordenador	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	18/10/2017 17:25:03	Indicação de Relatoria	2	Coordenador	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	11/10/2017 10:44:22	Aceitação do PP	2	Secretária	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	10/10/2017 13:13:51	Submetido para avaliação do CEP	2	Pesquisador Principal	PESQUISADOR	UFRJ - Hospital Universitário Clementino Fraga Filho da	

« « Ocorrência 1 a 10 de 22 registro(s) » »

Apreciação	Data/Hora	Tipo Trâmite	Versão	Perfil	Origem	Destino	Informações
						Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	
PO	06/10/2017 13:04:29	Rejeição do PP	2	Secretária	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	PESQUISADOR	Pendências corretas entregues ao pesquisador
PO	06/10/2017 12:40:10	Submetido para avaliação do CEP	2	Pesquisador Principal	PESQUISADOR	UFRJ - Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro / HUCFF- UFRJ	

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(*) Apreciação

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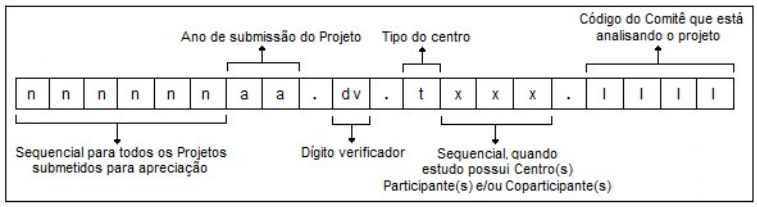
(*) Formação do CAAE



Voltar

ANEXO 2

Nome	Nº Prontuário	Idade	Genero	Tempo de Diagnóstico/Tipo de AEH	Histórico Familiar	Medicamento de Rotina

ANEXO 2

Medicamento Profilático	Frequencia / Severidade dos Episodios	Procedimentos Odontológicos Realizados	Exame de Imagem	Esquema de Profilaxia	Ocorrência de Edema Pós Tratamento

ANEXO 3

Normas de Publicação da Revista Oral Surgery Oral Medicine Oral Pathology Oral Radiology

Types of Papers

1. Original Research Article. Reports of original research (preclinical, clinical, or translational) that are well-documented, novel, and significant. Original research manuscripts will be organized into six parts: (1) Abstract; (2) Introduction; (3) Materials and Methods; (4) Results; (5) Discussion; (6) References.

2. Review article. Manuscripts that review the current status of a given topic, diagnosis, or treatment. These manuscripts should not be an exhaustive review of the literature but rather should be a review of contemporary thought with respect to the topic. Systematic reviews and meta-analyses manuscripts should follow PRISMA (http://www.prisma-statement.org) and the Institute of Medicines' guidelines (http://www.iom.edu/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Systematic-Reviews/Standards.aspx).

3. Clinicopathologic Conference (CPC). Manuscripts that document interesting, challenging, or unusual cases that present unexpected or interesting diagnostic challenges. The presentation should simulate clinical work-up, including the formulation of a detailed and well thought out differential diagnosis. The complete diagnostic evaluation, management, and follow-up must be included. CPC articles must be organized into six parts: (1) Title: Provide a descriptive clinical title that does not reveal the final diagnosis. (2) Clinical presentation: Describe the clinical and imaging characteristics of the lesion. Use clinical photographs and radiographs as appropriate. (3) Differential diagnosis: List and discuss lesions to be considered as reasonable diagnostic possibilities. The authors are reminded that the most important part of the CPC manuscript is the clinical differential diagnosis, where the authors guide the readership through their own diagnostic thought process. This will require the formulation of a list of the most probable diagnostic possibilities (ideally at least 5-6 entities) based on the clinical presentation, medical history, and/or radiographic studies. (4) Diagnosis: Histopathologic findings illustrated with appropriate photomicrographs. (5) Management: Describe the treatment of the patient and response to treatment. (6) Discussion: Concentrate on the most interesting aspect(s) of the case. No abstract is needed for CPC manuscripts. Limit the number of references to no more than 25.

4. Medical Management and Pharmacology Update (MMPU). This section is intended to provide concise, current reviews of medical problems and how they relate to dentistry. Manuscripts should include a good review of the clinical aspects of the disease, stressing the impact of the disease on the dental

management and dental treatment of the patient. Emphasis should be placed on new developments, new research, or new approaches to therapy or management. Manuscripts should not be an exhaustive review of the literature but rather a review of contemporary thought with respect to the topic. Likewise, the bibliography need not be all inclusive but rather should include only seminal, contemporary references deemed by the author to be most pertinent. The desired format for manuscripts submitted for the MMPU section includes: (1) abstract; (2) topic introduction/overview; (3) epidemiology/demographics; (4) etiology and pathogenesis; (5) clinical presentation/physical findings; (6) diagnosis (laboratory tests, diagnostic imaging, etc.); (7) medical management and treatment; (8) complications; (9) prognosis; oral manifestations/dental implications and significance; and (10) dental management (of patients with the disease). Manuscripts should not exceed 12 pages in 12-point, double-spaced Times New Roman (tables and figures count toward the 12-page limit).

5. Pharmacology Update is a component of the MMPU section that offers the reader the opportunity to obtain concise information regarding drugs used in the practice of medicine, clinical dentistry, and dental specialties. Manuscripts should present clearly and concisely the background information regarding the disease or condition that is managed, the indications, rationale for and approved uses of the specific drugs or class of drugs, the advantages and benefits of the drug or drug class over previous drugs, mechanism of action, criteria for selection, usual dosage, pharmacokinetics, adverse effects, drug interactions, and oral health and dental management considerations. Emphasis should be placed on new developments, effectiveness in clinical trials, therapeutic outcomes, and safety. Manuscripts should reflect contemporary thought with respect to the topic. Use of figures to illustrate the mechanism of action and tables to present therapeutic outcomes, drug interactions, and adverse effects are encouraged. Manuscripts should utilize the MMPU categories for formatting the paper. Text should not exceed 3,000 words. Font should be 12-point, double-spaced Times New Roman. A maximum of 50 references is recommended.

6. Case Reports. These types of publications often add little to the scientific knowledge base. However, excellent case reports may be published as online only papers if they meet certain criteria, such as: (1) rare or unusual lesions/conditions that need documentation, (2) well-documented cases showing unusual or "atypical" clinical or microscopic features or behavior, or (3) cases showing good long-term follow-up information, particularly in areas in which good statistics on results of treatment are needed. A case report should either present unique features of the condition or lesion, novel treatment regimens, or provide the basis for a new plausible medical theory about the pathogenesis of a particular disease or condition so clinicians can provide better care regarding patients with chronic and painful conditions relevant to medical disorders and/or medical therapy.

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