UNIVERSIDADE FEDERAL DE MINAS GERAIS
Faculdade de Odontologia
Colegiado de Pós-Graduação em Odontologia

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ANOMALIAS DENTÁRIAS E CRANIOFACIAIS NA ANEMIA DE FANCONI: *REVISÃO SISTEMÁTICA DE 158 CASOS E 46 RELATOS ADICIONAIS*

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Dissertação apresentada ao Colegiado de Pós-Graduação em Odontologia da Universidade Federal de Minas Gerais como requisito parcial para obtenção do título de Mestre em Odontologia – área de concentração em Patologia Bucal

Orientadora: Prof (a). Dra. Tarcília Aparecida da Silva
Coorientador: Prof. Dr. Lucas Guimarães Abreu

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PAULA ALVES DA SILVA ROCHA

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“Unir-se é um bom começo, manter a união é um progresso e trabalhar em conjunto é a vitória.”

Henry Ford

RESUMO

Este estudo objetivou realizar uma revisão sistemática da literatura (RSL) sobre anomalias dentárias e craniofaciais em indivíduos com Anemia de Fanconi (AF), além de avaliar a ocorrência dessas alterações em um estudo transversal aprovado pelo Comitê de Ética em Pesquisa. A pesquisa foi realizada em parceria com o Hospital das Clínicas da Universidade Federal de Minas Gerais e o Hospital de Clínicas da Universidade Federal do Paraná, dois centros de referência no Brasil. A AF é uma doença genética rara e carece de estudos sobre características dentárias e craniofaciais. Para a RSL, foram realizadas buscas eletrônicas em seis bases de dados, complementadas por análise manual e da literatura cinzenta. Foram incluídos estudos transversais e relatos de casos. No total, 19 artigos com 158 casos de AF foram analisados. A prevalência estimada de anomalias dentárias variou de 13,3% a 71,4%. Dos 158 indivíduos, 130 apresentavam anormalidades dentárias e/ou radiculares, e 56 tinham maloclusão e/ou anomalias craniofaciais. O estudo transversal foi baseado em avaliação clínico-radiográfica e incluiu 46 pacientes diagnosticados com AF a partir de exames de pesquisa de quebras cromossômicas. Nosso estudo revelou que 93,5% dos pacientes apresentaram anomalias dentárias e/ou craniofaciais, especialmente anormalidades radiculares. Homens apresentaram predominantemente anomalias de erupção/exfoliação. Uma maior ocorrência de anomalias relacionadas ao tamanho do dente foi observada em indivíduos que passaram por transplante de células-tronco hematopoéticas com idade ≥14 anos. A literatura limitada e a variabilidade de anomalias dentárias e craniofaciais na AF destacam a necessidade de expandir e padronizar critérios de diagnóstico e o monitoramento destes indivíduos, o que pode ajudar a mitigar o impacto dessa condição na saúde geral e qualidade de vida dos indivíduos afetados.

Palavras-chave: radiografia dentária; anemia de Fanconi; saúde bucal; manifestações orais; esqueleto.

ABSTRACT

Building upon evidence on dental and craniofacial anomalies in Fanconi anemia: a systematic review of 158 cases and additional 46 reports

The present study aimed to conduct a systematic review of the literature on dental and craniofacial anomalies in individuals with Fanconi Anemia, as well as to evaluate the occurrence of these alterations in a cross-sectional study approved by the Research Ethics Committee. The research was conducted in partnership with two Brazilian reference centers, the Hospital das Clínicas of the Federal University of Minas Gerais and the Hospital de Clínicas of the Federal University of Paraná. Fanconi Anemia (FA) is a rare genetic disease and lacks studies on dental and craniofacial characteristics. For the systematic literature review, electronic searches were conducted in six databases, complemented by manual analysis and gray literature. Cross-sectional studies and case reports were included. A total of 19 articles describing 158 cases of FA were analyzed. The estimated prevalence of dental anomalies ranged from 13.3% to 71.4%. Among the 158 individuals, 130 exhibited dental and/or root abnormalities, while 56 presented malocclusion and/or craniofacial anomalies. Our cross-sectional study was based on clinical-radiographic evaluation and included 46 patients diagnosed with FA through chromosomal breakage tests and/or genetic tests. Our study revealed that 93.5% of the patients presented dental and/or craniofacial anomalies, particularly root abnormalities. that 93.5% of patients presented dental/craniofacial anomalies, particularly radicular abnormalities. Males predominantly exhibited eruption/exfoliation anomalies. A higher occurrence of anomalies related to tooth size was observed in individuals who underwent hematopoietic stem cell transplantation at ≥14 years of age. The limited literature and variability of dental and craniofacial anomalies in FA highlight the need to expand and standardize diagnostic criteria for effective monitoring and mitigation of their impact on health and quality of life.

Keywords: dental radiography; Fanconi anemia; oral health; oral manifestations; skeleton.

LISTA DE FIGURAS

LISTA DE ABREVIATURAS E SIGLAS

AF	Anemia de Fanconi
CCECP	Carcinoma de Células Escamosas de Cabeça e Pescoço
CCEO	Carcinoma de Células Escamosas Oral
COEP	Comitê de Ética em Pesquisa
CONEP	Comissão Nacional de Ética em Pesquisa
DEB	Diepoxibutano
DHC	Deficiência de Hormônio do Crescimento
DNA	Deoxyribonucleic Acid
DOPM	Desordens Orais Potencialmente Malignas
DP	Desvio Padrão
et. al.	E Colaboradores
FA/BRCA	Fanconi Anemia/Breast Cancer Gene
HC-UFMG	Hospital das Clínicas da Universidade Federal de Minas Gerais
HC-UFPR	Hospital de Clínicas da Universidade Federal do Paraná
IMO	Insuficiência da Medula Óssea
LMA	Leucemia Mielóide Aguda
MIC	Microcefalia
MMC	Mitomicina C
PHENOS	skin **P**igmentation, small **H**ead, small **E**yes, **N**ervous system, **O**tology, **S**hort stature
PRISMA	Systematic Reviews and Meta-analyses
TCTH	Transplante de Células-Tronco Hematopoiéticas
UFMG	Universidade Federal de Minas Gerais
UFPR	Universidade Federal do Paraná
VACTERL-H	**V**ertebral, **A**nal, **C**ardiac, **T**racheo-esophageal fistula, **E**sophageal atresia, **R**enal, upper **L**imb and **H**ydrocephalus

SUMÁRIO

1 INTRODUÇÃO

A Anemia de Fanconi (AF) é uma doença genética rara com transmissão autossômica recessiva ou ligada ao cromossomo X e afeta cerca de 1 em 100.000 a 160.000 pessoas (Auerbach 1995, 2009). Apesar de não haver uma definição universal para doenças raras (Richter et al., 2015), o Ministério da Saúde define que uma doença é considerada rara quando afeta até 65 pessoas a cada 100.000 indivíduos. (https://www.gov.br/saude/pt-br). Segundo os dados epidemiológicos disponíveis publicamente Orphanet, um banco de dados dedicado a doenças raras, 71,9% das doenças raras são de origem genética e cerca de 69,9% têm início exclusivamente na infância. (http://www.orphadata.org/cgi-bin/epidemio.html)

A obtenção de dados epidemiológicos sobre a AF no Brasil é limitada; isso se deve pela falta de estudos multicêntricos com essa finalidade. No entanto, pesquisas regionais que analisam os perfis clínicos e genéticos dos indivíduos, além dos resultados de tratamentos como o transplante de células-tronco hematopoiéticas, têm contribuído significativamente para o avanço do conhecimento sobre a AF tornando o Brasil referência mundial no diagnóstico e tratamento da doença.

A AF é caracterizada clinicamente por malformações congênitas, baixa estatura, hiperpigmentação cutânea, falência progressiva da medula óssea e risco elevado de desenvolvimento de câncer (Auerbach 1995, 2009), apresentando uma proporção masculino/feminino de 1,2:1,0. A idade média de diagnóstico é aproximadamente aos 7 anos (Shimamura; Alter, 2010).

Cerca de dois terços dos indivíduos afetados apresentam pelo menos uma anormalidade física congênita (Shimamura; Alter, 2010). Esses indivíduos também apresentam significativa heterogeneidade fenotípica, levando à sua classificação dentro da *associação* VACTERL-H *(**V**ertebral, **A**nal, **C**ardiac, **T**racheo-esophageal fistula, **E**sophageal atresia, **R**enal, upper **L**imb and **H**ydrocephalus)* (Alter; Giri, 2016) bem como alterações adicionais categorizadas sob a sigla *PHENOS (skin **P**igmentation, small **H**ead, small **E**yes, **N**ervous system, **O**tology, **S**hort stature)* (Fiesco-Roa et al*.,* 2019). Ambas as classificações têm sido fundamentais para orientar e facilitar o diagnóstico e acompanhamento precoce desses indivíduos.

As pessoas com AF podem apresentar fácies típica, caracterizada por uma forma triangular, associada a microcefalia, micrognatia, hipoplasia facial média, pregas epicânticas bilaterais, microftalmia e base nasal larga (Auerbach, 2009;

Kerviler et al., 2000; Moreno et al., 2021). Entretanto, apesar da extensa avaliação fenotípica desses indivíduos, a literatura científica carece de pesquisas abrangentes sobre os achados odontológicos associados a essa condição.

Os estudos disponíveis, em geral, apresentam amostras limitadas, investigam um único aspecto da doença e oferecem um seguimento inadequadamente documentado A investigação de anomalias dentárias e craniofaciais na AF pode contribuir significativamente para o diagnóstico, bem como auxiliar na compreensão das necessidades para um acompanhamento integrativo, visando a manutenção da saúde e da qualidade de vida dos indivíduos afetados.

O presente estudo objetivou ampliar o conhecimento acerca das anomalias dentárias e craniofaciais em indivíduos com AF empregando-se uma busca sistemática da literatura e análise de uma coorte proveniente de dois centros de referência brasileiros.

2 REVISÃO DE LITERATURA

2.1 Anemia de Fanconi

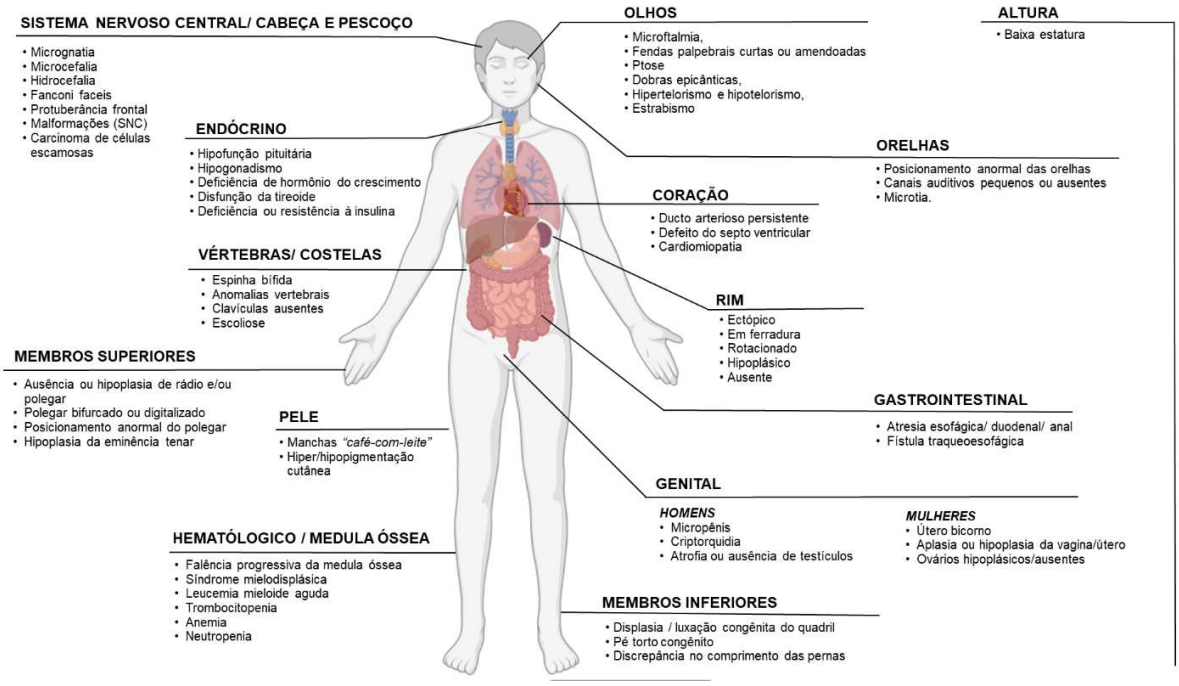
Em 1927, Guido Fanconi, um pediatra suíço documentou um caso familiar em que três meninos com idades entre 5 e 7 anos exibiam hipogonadismo, pigmentação da pele. pancitopenia e anomalias congênitas (Fanconi, 1927). AF ocorre devido à perda da função de ao menos um dos 22 genes envolvidos na via de reparo do DNA FA/BRCA (Peake; Noguchi, 2022). Essa via coordena processos e proteínas que auxiliam na reparação de lesões no DNA, incluindo ligações cruzadas entre cadeias de DNA e quebras de fita dupla. Tais danos ao DNA podem ter origem endógena ou exógena, variando desde produtos metabólicos, agentes terapêuticos à carcinógenos ambientais (Ceccaldi; Sarangi; D'Andrea, 2016; Kottemann; Smogorzewska, 2013; Oostra et al , 2012; Peake; Noguchi, 2022).

Quando não são devidamente reparadas, essas lesões podem resultar em instabilidade genômica, um traço característico do câncer, fazendo com que os indivíduos com AF apresentam um risco elevado de desenvolvimento de neoplasias malignas, principalmente Leucemia Mielóide Aguda (LMA) e tumores sólidos, como o Carcinoma de Células Escamosas de Cabeça e Pescoço (CCECP) especialmente o Carcinoma de Células Escamosas Oral (CCEO) (Alter et al ,2018; Auerbach, 2009; Dufor; Peake; Noguchi, 2022, Pierri, 2022).

2.2 Alterações congênitas

Aproximadamente dois terços dos indivíduos afetados apresentam pelo menos uma anormalidade física congênita (Shimamura; Alter, 2010). Tais anormalidades já são bem estabelecidas na literatura (Alter; Giri, 2016; Auerbach, 2009; Kerviler et al., 2000; Fiesco-Roa et al., 2019; Moreno et al., 2021). (FIGURA 1)

Figura 1 – Espectro fenotípico, alterações congênitas e caracterísitcas clínicas comumente associadas à Anemia de Fanconi



Legenda: Espectro fenotípico, alterações congênitas e características clínicas comumente associadas à Anemia de Fanconi. segundo o Registro Internacional de Anemia de Fanconi (IFAR) (Auerbach 2009).
Abreviações: SNC – Sistema Nervoso Central
Fonte: Elaborado pela autora, 2024.

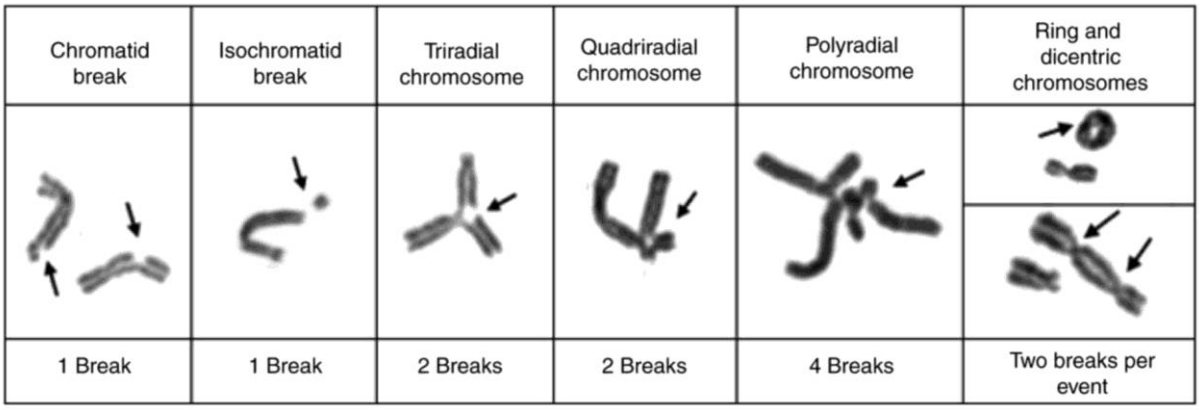
No entanto, apesar de a AF ser essencialmente caracterizada a partir desse padrão fenotípico heterogêneo, algumas dessas características podem ser sutis ou ausentes em muitos pacientes, consequentemente, o diagnóstico baseado apenas a partir de avaliações clínicas tende a não ser confiável. Portanto, a suspeita clínica deve ser idealmente confirmada por exames laboratoriais. (Alter; Giri, 2016; Amenábar et al., 2019; Auerbach, 2009; Fiesco-Roa et al., 2019).

2.3 Diagnóstico

A possibilidade de diagnóstico de AF deve ser considerada em casos de insuficiência da medula óssea (IMO) associada ou não à malformações clássicas adicionais, bem como em crianças e adultos com câncer exibindo resposta incomum a agentes quimio ou radioterápicos, em adultos relativamente jovens apresentando carcinomas em boca, esôfago ou região anogenital ou em indivíduos que apresentam quebras cromossômicas induzidas devido à exposição à agentes de ligação cruzada de DNA (Alter 2003, 2005; Dufour; Pierri, 2022)

A identificação da AF como uma condição de instabilidade cromossômica teve origem na observação de aberrações cromossômicas que surgiam naturalmente em preparações citogenéticas convencionais. Entretanto, tal método não era confiável para o uso em diagnósticos devido à significativa disparidade nos resultados. (Oostra et al., 2012). Estudos posteriores demonstraram que as células dos indivíduos com AF exibiam extrema sensibilidade aos agentes de ligação cruzada mitomicina C (MMC) e diepoxibutano (DEB) (Auerbach; Wolman,1976; Sasaki; Tonomura, 1973) que passaram a ser rotineiramente utilizados para o diagnóstico da AF. Considerando que as células dos indivíduos com AF tendem a presentar um elevado número de quebras cromossômicas, bem como a presença de figuras radiais e maior proporção de células aberrantes quando expostas à esses agentes, tal procedimento se tornou o padrão ouro para o estabelecimento do diagnóstico. (Fargo et al , 2014). (FIGURA 2)

Figura 2 – Eventos cromossômicos aberrantes após exposição das células à MMC ou DEB.



Legenda: Eventos cromossômicos aberrantes considerados para a quantificação de quebras cromossômicas. Testes de fragilidade de pacientes realizados no Instituto de Genética Humana da Pontifícia Universidade Javeriana.
Fonte: MORENO et al., 2021, p. 7.

2.4 Alterações dentárias

Enquanto malformações congênitas e anormalidades hematológicas são bem reconhecidas como parte do espectro fenotípico da AF (Altintas et al., 2023; Auerbach, 2009; Dufour; Olson, 2023; Pierri, 2022), a variedade de manifestações que afetam o sistema estomatognático desses indivíduos são menos caracterizadas (Açikgöz et al., 2005; Araújo et al., 2007; Goswami; Bhushan; Goswami, 2016; Kaimenyi; Meme, 1988; Opinya; Miranda et al., 2020; Pavlič et al., 2017). Caracterizar e definir a

etiologia das anomalias dentárias ou craniofaciais em indivíduos com doenças genéticas como AF representa um grande desafio, particularmente considerando os complexos mecanismos genéticos e moleculares inerentes à síndrome bem como a possível influência de fatores locais e sistêmicos.

Por vezes, o diagnóstico de pacientes com AF ocorre apenas após a constatação de anormalidades hematológicas mesmo naqueles indivíduos que exibem malformações congênitas características. (Auerbach, 2009). Esse atraso no diagnóstico pode ser atribuído à falta de conhecimento médico sobre o amplo espectro fenotípico da AF e portanto, a ampliação dos critérios de avaliação pode favorecer o diagnóstico em estágios precoces. (Alter; Giri, 2016; Fiesco - Roa et al , 2019).

Uma forma de alcançar esse objetivo se dá a partir da ampliação dos critérios avaliativos durante o exame do sistema estomatognático principalmente considerando que avaliações clínicas odontológicas precoces e regulares já são práticas padrão para a manutenção de sua saúde bucal e qualidade de vida geral desses indivíduos. A relevância clínica da avaliação regular da saúde bucal em indivíduos com AF é justificada pelo risco elevado de desenvolvimento de câncer oral, alterações da mucosa, incluindo as desordens orais potencialmente malignas (DOPM) (Alter, 2017; Kutler et al., 2003; Santana et al., 2024), bem como ao estado dentário e periodontal precário frequentemente atribuídos à insuficiência hematológica ou higiene oral inadequada (Araújo et al., 2007; Lyko et al., 2016). Ampliar e estabelecer uma busca padronizada das características dentárias e craniofaciais pode auxiliar no reconhecimento do amplo espectro de fenótipos associados à síndrome. (FIGURA 3).

Além disso, o fenótipo dentário serve como uma valiosa ferramenta diagnóstica para diversas doenças raras (Dupre et al., 2024; Kunz et al., 2020; Lubinsky; Kantaputra, 2016, Lutz et al., 2020; Prado et al., 2023). Estudos prévios relataram que indivíduos com AF apresentam alterações dentárias relacionadas à forma, número, tamanho, posição bem como anormalidades radiculares. (Altay et al., 1997; Açikgöz et al., 2005; Araújo et al., 2007; Tekcicek et al., 2007). Alterações dentárias podem ser observadas na população geral, possivelmente influenciadas por fatores genéticos e ambientais (Laganà et al., 2017; Souza-Silva et al., 2018; Varela; Arrieta; Ventureira, 2009). Na população acometida pela AF, a ocorrência dessas alterações pode ser esporádica ou associada a anormalidades craniofaciais, alterações endócrinas bem como devido ao uso de medicamentos e/ou regimes de condicionamento para o transplante de células-tronco hematopoéticas (TCTH) (Van

Gennip et al., 2023; Yalman et al., 2001).

2.5 Alterações craniofaciais

Dentre as alterações craniofaciais destaca-se a microcefalia (MIC), descrita como um tamanho da cabeça menor que dois desvios-padrão (DP) da média para uma determinada idade e gênero. As causas da MIC podem variar de fatores genéticos a influências ambientais (PirozzI; Nelson; Mirzaa, 2018). A microcefalia leva a anormalidades distintas na forma do crânio e da face devido a um desequilíbrio nos padrões de crescimento, sendo por vezes, associada a dismorfismo craniofacial e fendas palatinas. (Von Der Hagen et al., 2014).

Além disso, a microcefalia aumenta o risco de defeitos de esmalte e alterações na sequência usual de erupção dentária. De acordo com (GOMES et al., 2023), uma proporção significativa de crianças com microcefalia experimenta mudanças tanto na sequência (93,5%) quanto no tempo (96,9%) da erupção do dente decíduo, tornando-as 51,6 vezes mais propensas a desenvolver defeitos de esmalte. Considerando que a microcefalia é uma característica marcante dos indivíduos com AF, é importante ressaltar que quando em associação com outros parâmetros faciais, como micrognatia e face alongada, pode auxiliar no diagnóstico da AF (Avila et al., 2014; Fiesco-Roa et al., 2019)

A micrognatia pode ser definida como uma mandíbula anormalmente pequena e, apesar de ocorrer esporadicamente, está frequentemente associada a diferentes síndromes, especialmente quando acompanhada de alterações esqueléticas, defeitos do sistema nervoso central, dismorfismo facial (incluindo defeitos orais e dentários) e problemas gerais de crescimento, assim como observado em indivíduos com AF.(Chen et al., 2019; Society for Maternal-Fetal Medicine et al., 2019;). (FIGURA 3)

2.6 Alterações endócrinas

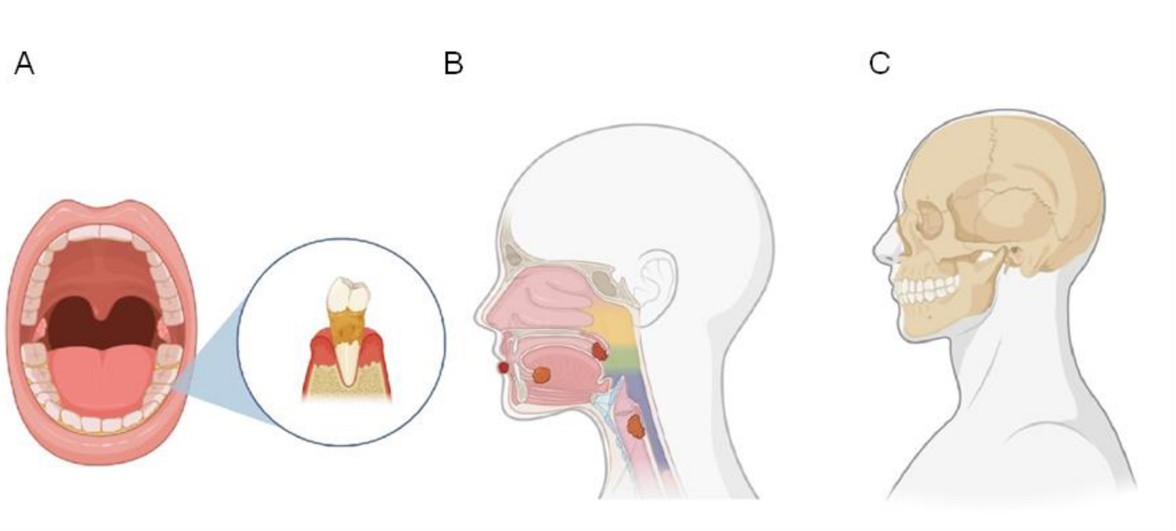
Cerca de, 80% das crianças e adultos com AF apresentam ao menos uma anormalidade endócrina podendo apresentar hipotireoidismo primário, volume médio da hipófise reduzido, deficiência clássica de hormônio do crescimento (DHC) ou disfunção hipotalâmica levando à DHC "parcial" (Aksu et al., 2020; Auerbach, 2009; Giri et al. , 2007; Johnson-Tesch et al., 2017; Petryk et al., 2015). A DHC também está

associada a importantes características como mandíbula curta, maturidade dentária ligeiramente atrasada, maior prevalência de microdontia e hipodontia, e atraso na idade óssea, que por sua vez pode ocasionar apinhamento dentário devido a déficit de espaço e má oclusão (Davidopoulou; Chatzigianni 2017; Rose et al., 2012; Torlińska-Walkowiak et al., 2023; Torlińska-Walkowiak et al., 2022; Wise; Frazier-Bowers; D'Souza, 2002).

2.7 Medicações antineoplásicas e transplante de células tronco hematopoiéticas

As medicações antineoplásicas e outros medicamentos utilizados durante o TCTH, que é atualmente o único tratamento curativo para a IMO em indivíduos com AF (Cancio et al., 2024) apresentam o potencial de afetar o desenvolvimento dentário, eventualmente resultando em agenesia dentária, alterações no tamanho dos dentes e das raízes e defeitos de esmalte (Dahllöf, 2008; Fernandes et al., 2015; Vaughan et al., 2005). Embora o histórico de TCTH tenha sido documentado em alguns relatos de pacientes com AF (Falci et al., 2011; Mahmoud et al., 2024; Miranda et al , 2020), as informações fornecidas são limitadas a respeito da sua potencial influência no desenvolvimento dentário e craniofacial desses indivíduos.

Figura 3 – Alterações comumente reportadas em região de cabeça e pescoço em indivíduos com AF



Legenda: A – Condição dentária e periodontal precária comumente associada à insuficiência hematológica ou à higiene oral inadequada. B – Propensão ao desenvolvimento de carcinoma de células escamosas em região de cabeça e pescoço, especialmente em cavidade oral. C – Alterações craniofaciais.
Fonte: Elaborado pela autora, 2024.

As doenças genéticas são individualmente raras, mas, coletivamente, afetam uma parcela substancial da população (LUO et al., 2019; SOBRINHO et al., 2022). Atualmente, existem mais de 10.867 doenças raras, as quais, coletivamente, afetam de 3,5 a 5,9% da população mundial, ou seja, cerca de 262,9 a 446,2 milhões de indivíduos. (Haendel et al., 2020; Wakap et al., 2020)

Dessa forma, diagnósticos precisos e precoces de doenças raras têm implicações significativas tanto para o paciente e sua família quanto para os sistemas de saúde e são essenciais para garantir o acesso a cuidados e tratamentos adequados. (Aymé et al., 2008) Visando o atendimento a essa demanda em 2014, o Ministério da Saúde instituiu a Política Nacional de Atenção Integral às Pessoas com Doenças Raras. (https://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html)

Através dessa política, o Sistema Único de Saúde (SUS) proporciona atendimento para a prevenção, diagnóstico, tratamento e reabilitação de pessoas com doenças raras. Esse atendimento é feito através de avaliações individualizadas conduzidas por equipes multidisciplinares em vários serviços de saúde em todo o país, visando reduzir a mortalidade e morbimortalidade, minimizar complicações e melhorar a qualidade de vida dos indivíduos afetados.

A colaboração dos cirurgiões-dentistas nessa equipe é essencial, especialmente considerando que anormalidades orofaciais e dentárias são características significativas de diversas síndromes (Martelli; Júnior, 2020) e por vezes podem ser as primeiras características a gerar suspeitas sobre a necessidade de avaliações mais extensas. Mas para tanto, é imperativo estabelecer um sistema de atendimento coordenado, fundamentado em evidências científicas robustas e comprovadas, além de assegurar a participação de profissionais deviamente qualificados.

A investigação de anomalias dentárias e craniofaciais em indivíduos com AF pode contribuir significativamente para o diagnóstico, melhorar a compreensão das necessidades de cuidados com a saúde bucal e subsidiar a inclusão desses parâmetros em avaliações subsequentes para garantir categorização e nomenclatura precisas. O objetivo do presente estudo foi duplo; realizar uma revisão sistemática da literatura sobre anomalias dentárias em indivíduos com AF e avaliar a ocorrência de anomalias dentárias e craniofaciais nessa população dentro de uma coorte de dois centros de referência brasileiros.

3 OBJETIVOS

3.1 Objetivo geral

Realizar uma revisão sistemática da literatura sobre anomalias dentárias em indivíduos com anemia de Fanconi e avaliar a ocorrência de anomalias dentárias e craniofaciais nessa população dentro de uma coorte de dois centros de referência brasileiros.

3.2 Objetivos específicos

Analisar possíveis varíaveis clínicas associadas com as anomalias dentárias e craniofaciais.

4 METODOLOGIA EXPANDIDA

Capítulo 1: Revisão sistemática da literatura

4.1 Protocolo e registro da revisão sistemática

Esta revisão sistemática aderiu às diretrizes descritas no Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). Um protocolo foi registrado no International Prospective Register of Systematic Reviews (PROSPERO; CRD42024521989).

4.2 Delineamento do estudo

Trata-se de uma revisão sistemática, conduzida em setembro de 2023 e posteriormente atualizada em março de 2024 no PubMed, Web of Science, Ovid, Scopus, Embase e LILACS para identificar estudos observacionais avaliando anomalias dentárias e oclusais em indivíduos com AF. Também foi realizada uma busca no Google Acadêmico, limitada às primeiras 200 referências, e ordenada pelos acessos mais recentes (Haddaway et al., 2015). Para garantir a abrangência, as listas de referências dos estudos incluídos foram pesquisadas manualmente, na tentativa de recuperar artigos potencialmente relevantes que poderiam ter sido negligenciados em repositórios eletrônicos. Se necessário, foi feito contato com os autores dos artigos incluídos para obter informações adicionais. O software EndNote (Clarivate Analytics, Londres, Reino Unido) foi empregado para gerenciamento de referência.

4.2.1 Processo de triagem

As referências foram minuciosamente examinadas em duas etapas. Inicialmente, três autores (P.A.S.R., N.C.M.S. e J.A.A.A.) avaliaram independentemente títulos e resumos. Os artigos considerados potencialmente elegíveis foram submetidos à análise exaustiva do texto completo pelos autores. Na segunda etapa, os autores avaliaram os textos completos e incluíram aqueles que atendiam aos critérios de elegibilidade. Quaisquer discordâncias foram resolvidas através de discussão com um autor sênior (T.A.S.).

4.2.2 Extração de dados

Dois autores (P.A.S.R. e N.C.M.S.) extraíram os dados dos artigos selecionados, enquanto outros dois autores (J.A.A.A. e T.A.S.) verificaram independentemente as informações coletadas. O processo de extração de dados compreendeu informações sobre sobrenome do primeiro autor, ano de publicação, país de coleta de dados, número de indivíduos, sexo, idade no momento do diagnóstico da AF e diagnóstico oral, manifestações sistêmicas e bucais (i.e., anomalias craniofaciais, dentárias e oclusais), história de TCTH, informações genéticas (se disponíveis), tratamento administrado e desfechos.

4.2.3 Avaliação do risco de viés do estudo

A qualidade metodológica dos estudos foi avaliada por meio do Critical Appraisal Checklist do Joanna Briggs Institute da Universidade de Adelaide, Austrália. Foram empregados critérios de avaliação de anomalias dentárias específicos para cada tipo de estudo (relato de caso e estudos transversais) (Moola et al., 2020). Cada instrumento continha oito parâmetros e em cada parâmetro, os estudos incluídos foram categorizados em "sim" (se o estudo preencheu o critério avaliado), "não" (se o estudo não preencheu o critério avaliado), "pouco claro" (se o estudo não forneceu informações suficientes sobre se o estudo preencheu ou não os critérios) ou "não aplicável" para cada parâmetro. Eventuais discrepâncias na avaliação crítica foram resolvidas por meio de discussão com um terceiro autor (T.A.S.).

Capítulo 2: Série de casos

4.3 Estabelecimento e apuração ética

Este estudo foi realizado em dois serviços de referência brasileiros: o Hospital das Clínicas da Universidade Federal de Minas Gerais em Belo Horizonte e o Hospital de Clínicas da Universidade Federal do Paraná em Curitiba no período de 2021 a 2023. O estudo aderiu às diretrizes do Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Knottnerus; Tugwell, 2008) O estudo foi

submetido à Diretoria de Ensino, Pesquisa e Extensão do HC-UFMG (Odontologia); ao Comitê de Ética em Pesquisa (COEP) da Universidade Federal de Minas Gerais (UFMG) e Universidade Federal do Paraná (UFPR) como também à Comissão Nacional de Ética em Pesquisa (CONEP), e aprovado sob o número de parecer: 6.254.512 e CAAE: 66312622.4.1001.5149 (APÊNDICE A), conforme a Resolução 466, de 12 de dezembro de 2012. Os pacientes assinaram o termo de consentimento livre e esclarecido e seu anonimato foi resguardado de acordo com a Declaração de Helsinque.

4.4 Participantes e coleta de dados

Foram incluidos no estudo, indivíduos com AF diagnosticados de acordo com os critérios descritos nas Diretrizes de Cuidados Clínicos da Anemia de Fanconi (https://www.fanconi.org/) de 2020 em que o diagnóstico envolve testes de quebra cromossômica em linfócitos do sangue periférico usando agentes de reticulação de DNA, principalmente diepoxibutano (DEB) ou mitomicina C (MMC). Também foram considerados critérios que definem o fenótipo físico associado à AF, incluindo aqueles descritos no VACTERL-H e no PHENOS (Alter; Giri, 2016; Solomon et al., 2012).

A partir da avaliação prontuários médicos e odontológicos dos indivíduos incluídos foram obtidas informações referentes ao sexo, idade no momento do diagnóstico da AF , histórico de TCTH, informações genéticas quando disponíveis entre outras. Para a avaliação do estado de saúde bucal, foram realizados exames clínicos por dois cirurgiões-dentistas (P.A.S.R. e N.C.M.S.). Os exames radiográficos, incluindo panorâmica e/ou bitewing, foram obtidos e avaliados por um radiologista bucomaxilofacial (T.M.P.A.) e um patologista oral (T.A.S.). Anomalias dentárias (por exemplo, raiz, estrutura dentária e problemas relacionados à erupção/esfoliação) e estado de oclusão foram avaliados de acordo com o sistema de classificação proposto por de (Dure-Molla et al 2019). Foram excluídos os casos com informações clínico-demográficas incompletas, indivíduos com diagnósticos limítrofes e aqueles com radiografias de baixa qualidade.

4.5 Análise de dados

Os dados foram tabulados utilizando o software Microsoft Office Excel 2019

(software Microsoft®, Redmond, WA, EUA) e realizada análise descritiva. O Pacote Estatístico para as Ciências Sociais (SPSS; IBM, 22,0; Armonk, NY, EUA) foi utilizado para análise estatística. O teste de Mann-Whitney, o teste do qui-quadrado e o modelo linear generalizado foram empregados para comparar as variáveis independentes (variáveis clínico-demográficas) com a variável dependente (presença/ausência de anomalias dentárias e número de anomalias dentárias). A significância estatística foi estabelecida em $p<0,05$. Os gráficos foram criados utilizando a linguagem de programação R (R Core Team, Viena, Áustria) dentro do ambiente RStudio (RStudio, Boston, Massachusetts, EUA), utilizando a biblioteca ggplot2 (Wickham, 2016) e a função barplot.

5 ARTIGO

5.1 Estudo intitulado "*Building upon evidence on dental and craniofacial anomalies in Fanconi anemia: a systematic review of 158 cases and additional 46 reports"* submetido ao periódico Oral Diseases (fator de impacto: 3.8; ISSN:1601-0825; estrato A1)

5.2 Building upon evidence on dental and craniofacial anomalies in Fanconi anemia: a systematic review of 158 cases and additional 46 reports

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Abstract

Background: Fanconi anemia (FA), a rare genetic disorder, has not been comprehensively researched in terms of dental and craniofacial aspects.

Purpose: To perform a systematic review of the literature on dental and craniofacial anomalies in individuals with FA and to evaluate their occurrence within a cohort from two Brazilian referral centers.

Methods: Electronic searches were conducted across six databases, supplemented by manual scrutiny and gray literature. The case series, based on clinicoradiographic assessments, included 46 patients diagnosed with FA.

Results: A total of 19 articles describing 158 FA cases were analyzed. The estimated prevalence of dental anomalies ranged from 13.3% to 71.4%. Among these cases, 130 had dental and/or radicular abnormalities, while 56 had malocclusion and/or craniofacial anomalies. Our series revealed that 93.5% of patients exhibited dental/craniofacial anomalies, particularly root abnormalities. Males and individuals with endocrine alterations predominantly experienced eruption/exfoliation anomalies. A higher occurrence of anomalies related to tooth size was observed in individuals who underwent hematopoietic stem-cell transplantation at age ≥14 years.

Conclusion: The limited literature and the variability of dental and craniofacial anomalies in FA underscore the necessity of expanding and standardizing diagnostic criteria to effectively monitor and mitigate their impact on health and quality of life.

Keywords: dental radiography; Fanconi anemia; oral health; oral manifestations; skeleton

1. Introduction

Fanconi anemia (FA) is a rare genetic disorder characterized by autosomal recessive or X-linked transmission, affecting approximately 1 in 100,000 to 160,000 individuals (Auerbach, 1995; Auerbach, 2009). FA results from the loss of function of genes involved in the DNA repair pathway, which explains the elevated cancer susceptibility observed in affected individuals (Kutler et al., 2003; Alter, 2017; Nalepa and Clapp, 2018; Peake et al., 2022).

Approximately two-thirds of affected individuals present with at least one congenital physical abnormality (Shimamura and Alter, 2010). FA is also associated with a diverse range of characteristics classified within the VACTERL-H spectrum, which includes vertebral, anal, cardiac, tracheoesophageal fistula, esophageal atresia, renal, upper limb, and hydrocephalus abnormalities (Alter and Giri, 2016). Additional alterations are further categorized under the acronym PHENOS, which stands for microcephaly, microphthalmia, central nervous system anomalies, otological findings, and short stature (Alter and Giri, 2016). Some individuals also exhibit typical facies characterized by a triangular shape associated with microcephaly, micrognathia, middle facial hypoplasia, bilateral epicanthic folds, microphthalmia, and a broad nasal base (DE KERVILER et al., 2000; Auerbach, 2009; Moreno et al., 2021).

Despite the extensive phenotypic evaluation of individuals with FA, the scientific literature lacks comprehensive research on the dental findings associated with this condition. Due to the rarity of the condition, studies often have limited sample sizes and focus on a unique aspect of the disease, often with inadequate follow-up documentation. The clinical relevance of regular oral health assessments in individuals with FA is justified by the risk of oral cancer and mucosal alterations, including oral potentially malignant disorders (OPMD) (Kutler et al., 2003; Alter, 2017; Santana et al., 2024), as well as poor dental and periodontal status, likely attributed to hematologic failure or inadequate oral hygiene (de Araújo et al., 2007; Lyko et al., 2016). Therefore, a more thorough analysis of the dental features of individuals affected by FA is warranted.

The dental phenotype serves as a valuable diagnostic tool for several rare diseases (Lubinsky and Kantaputra, 2016; Kunz et al., 2020; Lutz et al., 2020; Prado et al., 2023; Dupre et al., 2024). Previous studies have reported that individuals with

FA exhibit alterations related to the shape, number, size, position, and radicular abnormalities (Altay et al., 1997; Açikgöz et al., 2005; de Araújo et al., 2007; Tekcicek et al., 2007). Dental alterations may be observed in the general population, possibly influenced by genetic and environmental factors (Varela et al., 2009; Laganà et al., 2017; Souza-Silva et al., 2018). Within the population affected by FA, the occurrence of these alterations may be sporadic and further associated with skeletal and craniofacial abnormalities (Auerbach, 2009), endocrine alterations (Torlińska-Walkowiak et al., 2022; Torlińska-Walkowiak et al., 2023), as well as medications and/or conditioning regimens for hematopoietic stem-cell transplantation (HSCT) (Yalman et al., 2001; van Gennip et al., 2023).

The investigation of dental and craniofacial anomalies in individuals with FA can significantly contribute to diagnosis, enhance understanding of oral health care needs, and support the inclusion of these parameters in subsequent assessments to ensure accurate categorization and nomenclature. The aim of the present study was twofold: to perform a systematic review of the literature on dental anomalies in individuals with FA and to assess the occurrence of dental and craniofacial anomalies within a cohort from two Brazilian referral centers.

2. Material and methods

2.1. Systematic review

2.1.1. Selection protocol

Searches were conducted in September 2023 and subsequently updated in March 2024 in PubMed, Web of Science, Ovid, Scopus, Embase, and LILACS to identify observational studies assessing dental and occlusal anomalies in individuals with FA. No restrictions on language or publication period were applied. The search strategies employed in each database are detailed in Supplementary File 1. A search was also conducted in Google Scholar, limited to the first 200 references and ordered by the most recent hits (Haddaway et al., 2015). To ensure comprehensiveness, the reference lists of included studies were manually searched to retrieve potentially relevant articles that could have been overlooked in electronic repositories. If necessary, contact with the authors of the included articles was made to obtain additional information. EndNote software (Clarivate Analytics, London, UK) was employed for reference management.

2.1.2. Screening process

The references were scrutinized meticulously in two stages. Initially, three authors (P.A.S.R., N.C.M.S., and J.A.A.A.) independently evaluated titles and abstracts. References considered potentially eligible underwent a comprehensive full-text analysis by the authors, and those meeting the eligibility criteria were included. Any disagreements were resolved through discussion with a senior author (T.A.S.).

2.1.3. Data extraction

Two authors (P.A.S.R. and N.C.M.S.) extracted data from the selected articles, while two other authors (J.A.A.A. and T.A.S.) independently verified the collected information. The data extraction process included information on the first author's last name, year of publication, country where data collection took place, number of individuals, sex, age at the time of FA diagnosis and oral diagnosis, systemic and oral manifestations (i.e., craniofacial, dental and occlusal anomalies), HSCT history, genetic information (if available), treatment administered, and outcomes.

2.1.4. Study risk of bias assessment

The methodological quality of the studies was assessed using the Critical Appraisal Checklist of the Joanna Briggs Institute from the University of Adelaide, Australia. Criteria specific to dental anomalies assessment for each study type (case report and cross-sectional studies) were employed (Moola et al., 2020). Each tool had eight parameters, and in each parameter, the included studies were categorized as “yes”,(if the study fulfilled the criterion assessed) “no”,(if the study did not fulfill the criterion evaluated) “unclear”, (the study did not provide enough information whether the study fulfilled or did not fulfill the criteria) or “not applicable” for each parameter. Any discrepancies in the critical appraisal were resolved through discussion with a third author (T.A.S.).

2.1.5. Protocol and registration

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). A protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024521989).

2.2. Case series

2.2.1. Setting and ethical clearance

This study was conducted from 2021 to 2023 at two Brazilian referral services: the Clinics Hospital of the Federal University of Minas Gerais in Belo Horizonte and the Clinics Hospital of the Federal University of Paraná in Curitiba. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Knottnerus & Tugwell, 2008) and received approval from an Institutional Ethics Committee (No. 66312622.4.1001.5149). Patients provided written informed consent, and their anonymity was safeguarded in compliance with the Declaration of Helsinki.

2.2.2. Participants and data collection

Individuals were diagnosed with FA according to the criteria outlined in the 2020 Fanconi Anemia Clinical Care Guidelines (https://www.fanconi.org/). Diagnosis involved testing for chromosome breakage in peripheral blood lymphocytes using DNA cross-linking agents, primarily diepoxybutane (DEB) or mitomycin C (MMC). Criteria defining the physical phenotype associated with FA, including those outlined in VACTERL-H and PHENOS, were also considered (Solomon et al., 2012; Alter and Giri, 2016).

Affected individuals underwent evaluations to collect data on sex, age at the time of FA diagnosis, and history of HSCT. For oral health status assessments, clinical examinations were conducted by two dentists (P.A.S.R. and N.C.M.S.). Radiographic exams, including panoramic and/or bitewing, were obtained and assessed by an oral and maxillofacial radiologist (T.M.P.A.) and an oral pathologist (T.A.S.). Dental anomalies (e.g., root, tooth structure, and eruption/exfoliation-related issues) and occlusal status were evaluated according to the classification system proposed by de La Dure-Molla et al. (2019). Cases with incomplete clinicodemographic information, individuals with borderline diagnoses, and those with poor-quality radiographs were excluded.

2.3. Data analysis

Data were tabulated using Microsoft Office Excel 2019 software (Microsoft® software, Redmond, WA, USA), and descriptive analysis was conducted. The Statistical Package for the Social Sciences (SPSS; IBM, 22.0; Armonk, NY, USA) was utilized for statistical analysis. The Mann-Whitney test, chi-square test, and generalized linear model were employed to compare independent variables (clinicodemographic variables) with the dependent variable (presence/absence of dental anomalies and number of dental anomalies). Statistical significance was set at $p<0.05$. Charts were created using the R programming language (R Core Team, Vienna, Austria) within the RStudio environment (RStudio, Boston, Massachusetts, USA), using the ggplot2 library (Wickham, 2016) and the barplot function.

3. Results

3.1. Systematic review

3.1.1. Study selection

The electronic searches initially identified 200 articles. After removing 86 duplicates, the remaining 114 references were scrutinized using the inclusion and exclusion criteria. Nineteen articles met the eligibility criteria (Joho and Marechaux, 1979; Opinya et al., 1988; Altay et al., 1997; Nowzari et al., 2001; Açikgöz et al., 2005; de Araújo et al., 2007; Tekcicek et al., 2007; Falci et al., 2011; Zen et al., 2011; Salinas et al., 2012; Jurca et al., 2014; Goswami et al., 2016; Wenger et al., 2016; Pavlič et al., 2017; Miranda et al., 2020; Touil et al., 2020; Ozler et al., 2022; Imen et al., 2022; Mahmoud et al., 2024). Supplementary File 2 outlies excluded articles after full-text examination, along with their respective exclusion reasons. A flowchart illustrating the article selection process is provided in Supplementary File 3.

3.1.2. Studies and characteristics of affected individuals

The included studies comprised four cross-sectional studies, two cross-sectional studies with a control group, and 13 case reports. These articles were published between 1979 and 2024. A total of 158 individuals diagnosed with FA, exhibiting dental and/or occlusal anomalies, were assessed. The studies were conducted in Brazil (n=4), Turkey (n=4), India (n=2), the USA (n=2), Mexico (n=1),

Romania (n=1), Slovenia (n=1), Switzerland (n=1), Tunisia (n=2), and Saudi Arabia (n=1).

Males (n=92; 58.2%) were the most affected, resulting in a male-to-female ratio of 1.4:1. The age distribution among individuals ranged from two weeks to 28 years. The phenotypic characteristics of FA manifested in multiple systems, consistent with the VACTERL-H and PHENOS criteria (Solomon et al., 2012; Alter and Giri, 2016), are illustrated in Figure 1.

3.1.3. Dental anomalies

Fifty-five individuals exhibited some form of anomaly in number and/or shape. The most frequent anomaly was the absence of teeth (n=23), including agenesis (n=12), hypodontia (n=7), tooth loss (n=1), congenital absence of teeth (n=2), and absence of tooth germs (n=1). The second most common anomaly was microdontia (n=16), followed by enamel pearls (n=4), abnormal tooth shape (n=3), taurodontism (n=3), supernumerary teeth (n=2), mesiondens (n=1), deformed dental anatomy (n=1), cingulate hypertropia (n=1), and dens invaginatus (n=1).

Twenty-four individuals exhibited some root anomaly. Radicular tapering (n=12) and “V” formation on root apex curvature during radicular development (n=9) were the most frequently observed characteristics. Accentuated root curvature (n=1), tapered root formation of permanent teeth (n=1), and root dilaceration (n=1) were additional reported root anomalies.

Concerning dental structure anomalies, eight individuals exhibited some form of color change: tooth color (n=4), opalescent enamel (n=2), yellow discoloration of teeth (n=1), and discolored teeth (n=1). Three individuals exhibited hypoplasia: enamel hypoplasia (n=2) and hypoplasia in unerupted teeth (n=1). One individual exhibited attrition, and another erosion. In total, 13 individuals exhibited some anomaly of dental structure.

Eight individuals exhibited eruption/exfoliation anomalies: ankylosis (n=1), presence of multiple primary teeth (n=1), impacted teeth (n=1), prolonged retention of deciduous teeth (n=1), absence of eruption of permanent teeth (n=1), retained deciduous teeth (n=1), delayed eruption of permanent teeth (n=1), and preservation of the second lower primary molar (n=1). In one study, it was impossible to define the exfoliation/eruption anomaly in place (Nowzari et al., 2001).

The most common position anomaly was rotated permanent teeth (n=21). Other

reported anomalies included dental crowding (n=3), transposition (n=2), irregular spacing of the teeth (n=1), deviation of the upper midline (n=1), lack of space in the lower dental arch (n=1), and counter-clockwise rotation (n=1). In total, 30 individuals exhibited anomalies of tooth position.

In seven studies, the affected dentition reported by the authors was the permanent dentition. In six studies, both primary and permanent dentitions were affected, and in five studies, the affected dentition was not specified (Tables 1 and 2).

3.1.4. Malocclusion and craniofacial anomalies

Thirteen individuals exhibited malocclusion: crossbite (n=2), anterior open bite (n=1), overbite (n=1), overjet (n=1), right canine in an end-to-end relation (n=1), absence of a defined occlusal plane (n=1), first molars in a class II relationship (n=1), class III skeletal pattern (n=1), class III malocclusion (n=1), open gonial angle (n=1), and maxillary deficiency (n=1).

Regarding craniofacial anomalies, the most common was microcephaly (n=27). Four individuals presented with some hypoplasia: maxillary hypoplasia (n=1), jaw hypoplasia (n=1), mandibular angle hypoplasia (n=1), and midface hypoplasia (n=1). Other anomalies present were micrognathia (n=4), triangular face (n=4), long face (n=1), facial asymmetry/dystrophy (n=2), craniofacial dysmorphism (n=1), slight skeletal discrepancy (n=1), hypo-divergent growth pattern (n=1), cleft palate (n=1), narrow palate (n=1), and palate with keloid scar after cleft palate surgery (n=1). In total, 48 individuals exhibited some craniofacial anomaly (Tables 1 and 2; Figure 1).

3.1.5. Quality assessment of the studies

Information on identified confounding factors and strategies to deal with confounding factors was absent in two (33.3% each) of the cross-sectional studies. One (16.7%) study did not detail the subjects and the setting, as well as the outcomes measured (16.7%) (Supplementary Table 4). Regarding case reports, there were concerns about the lack of information on adverse events/unanticipated events (46%), insufficient description of the post-intervention clinical condition (54%), inadequate detailing of intervention or treatment procedures (46%), diagnostic tests/assessment methods (23%), and clinicodemographic characteristics of individuals (15.4% each) (Supplementary Table 5).

3.2. Case series

3.2.1. Clinicodemographic characteristics

A total of 24 (52.2%) women and 22 (47.8%) men were included, with a mean age of 18.7 ± 8.4 years (range: 8–42 years). Most individuals (n=36; 78.3%) had undergone HSCT, with a mean age at transplantation of 12.5 ± 8.7 years (range: 3–40 years).

Twenty-four (52.2%) patients showed no endocrine alterations, and 10 (21.7%) individuals were under investigation for endocrine diseases. Twelve (26.1%) patients (n=8 female and n=4 male) exhibited at least one alteration or were using specific medications. The following endocrine alterations were reported: hyperthyrotropinemia, Graves' disease, hypogonadotropic hypogonadism, testicular hypotrophy to age-related standards, panhypothyroidism, growth hormone deficiency, adenohypophyseal hypoplasia, agenesis of the stalk, ectopic neurohypophysis, hirsutism, elevated thyroid-stimulating hormone, and elevated follicle-stimulating hormone.

Regarding skeletal abnormalities, five (10.9%) individuals showed no alterations in upper or lower limbs, and 17 (37.0%) had at least one alteration in upper and lower limbs. For 24 (52.2%) individuals, this information was unavailable. The most frequent limb alterations were thumb anomalies (n=14; 30.4%), hypothenar eminence (n=3; 6.5%), asymmetry of lower limbs (n=2; 4.3%), and bilateral anomalies of the radius (n=2; 4.3%). Concerning vertebral alterations, nine (19.6%) individuals showed no alterations, while four (8.7%) individuals exhibited vertebral alterations, including thoracic asymmetry, pectus excavatum, scoliosis, spinal malformations, and calcified nodules in the thoracic spine.

Forty-three (93.5%) individuals exhibited dental and/or craniofacial anomalies. Nine (19.6%) individuals exhibited the characteristic Fanconi facies, while nine (19.5%) did not show it. For 28 (60.9%) individuals, information in this regard was unavailable. It is important to recognize that the evaluation of this facial pattern can rely on subjective interpretation, consequently posing challenges in developing a precise clinical definition (Avila et al., 2014).

Four individuals did not exhibit any dental anomalies; among these, one patient had just one craniofacial anomaly. Radicular anomalies (n=32) were the most frequent, followed by anomalies of tooth position (n=28) and number of teeth (n=20). Eruption/exfoliation and dental shape alterations affected 10 patients. Eleven patients

had changes in dental structure. Four and three patients exhibited anomalies of dental size and dental pulp, respectively. Craniofacial anomalies were found in 10 individuals (Figure 2A).

A total of 185 occurrences of dental and craniofacial anomalies were detected. Of these, 29.7% (n=55) affected roots and 2.2% (n=4) involved dental pulp. Twenty-two (11.9%) events of craniofacial anomalies were observed. Anomalies of dental position (n=41; 22.2%), number (n=21; 11.3%), eruption and/or exfoliation (n=15; 8.1%), structure (n=12; 6.5%), shape (n=10; 5.4%), and size (n=5; 2.7%) were observed. Among all reported tooth anomalies, only five occurred in deciduous teeth; all the remaining occurrences were related to permanent teeth (Figure 2A).

A co-occurrence analysis of these alterations was performed. Although no significant associations were found, individuals affected by alterations in the number and position of teeth, as well as root alterations, were more likely to have eruption and/or exfoliation changes. Craniofacial alterations co-occurred more frequently with eruption and/or exfoliation changes and with radicular anomalies. Despite the few cases in this series, dental pulp changes seemed to occur in association with other dental anomalies instead of in isolation (Figure 2B).

3.2.2. Anomaly in the size and shape of dental roots

Thirty-two (69.6%) patients exhibited some type of root anomaly. Root dilaceration was the most prevalent radicular anomaly, affecting 22 individuals and involving 43 teeth of distinct groups. The permanent maxillary right first molar and the permanent maxillary left second molar were the most affected teeth (Figures 3A and E). The second most prevalent radicular anomaly was short roots, occurring in nine individuals and affecting 22 teeth of different groups. The permanent maxillary right first molar and permanent maxillary left first molar were the most frequently affected teeth. Other root anomalies observed included unirradicular molars (n=4), radicular convergence (n=4) (Figure 3B), radicular divergence (n=4) (Figure 3B), root fusion (n=4), bulky roots (n=3), narrow roots (n=3) (Figure 3A), supernumerary roots (n=1), and internal root resorption (n=1).

3.2.3. Anomalies in tooth position

Twenty-eight (60.9%) patients exhibited some type of dental position anomaly. Rotation was the most prevalent alteration, affecting 25 individuals and 53 teeth. The

permanent mandibular right canine and mandibular right first premolar were the most frequently affected teeth (Figures 3B, C, E, and F). Dental crowding was present in four cases (Figure 3E). Other position anomalies included diastema (n=4), mesialized or distalized teeth (n=5) (Figure 3B), midline deviation (n=1) (Figure 4A), and spaced teeth (n=1) (Figure 4A).

3.2.4. Anomalies in the number of teeth

Twenty (43.5%) patients presented with some form of anomaly related to the number of teeth. Hypodontia was the most frequent anomaly in terms of number, affecting 12 individuals and 19 teeth. Among these, the permanent maxillary right lateral incisor and the permanent mandibular right lateral incisor were the most affected (Figures 3A-D and Figure 4D). Eight patients exhibited missing teeth (when it was impossible to determine whether the cause of tooth absence was prior extraction or agenesis). Other anomalies of tooth number included mesiodens (n=1).

3.2.5. Anomalies in eruption and exfoliation

Eruption/exfoliation irregularities were observed in 10 (21.7%) patients. Four patients exhibited a delay in deciduous exfoliation (Figures 3A-B). Among these, one case exhibited agenesis of permanent, while in three cases, there was a delay in the eruption of permanent teeth, affecting the permanent maxillary right canine, the left second premolar, the mandibular left canine, and the left second premolar. Eruption failure was observed in four individuals affecting five teeth, mostly the permanent canines.

3.2.6. Dental structure anomalies

Dental structural abnormalities were observed in 11 (23.9%) patients. Enamel hypoplasia was the most frequent structural anomaly, affecting three individuals and involving 23 teeth of distinct groups. Among these, the permanent maxillary right central incisor and the permanent maxillary left central incisor were the most affected teeth (Figure 3C). Enamel pearls were observed in eight individuals (n=16 teeth). The permanent maxillary right first molar exhibited the highest frequency of this anomaly.

3.2.7. Dental shape anomalies

Ten (21.7%) patients exhibited dental shape alterations. The barrel-shaped tooth was the most prevalent shape alteration, observed in six individuals (n=10 teeth). The permanent maxillary left lateral incisor was the most affected, followed by the permanent maxillary right lateral incisor (Figure 3B). Others included conical tooth (n=2) (Figure 3F), peg-shaped (n=1), and talon cusp (n=1) (Figure 3E).

3.2.8. Dental size anomalies

Four (8.7%) patients exhibited dental size anomalies. The most frequent anomaly of size was taurodontism, affecting four patients. Another size anomaly was microdontia (n=1).

3.2.9. Dental pulp anomalies

Alterations in the pulp were identified in three (6.5%) patients. These anomalies included pulp chamber calcification (n=1) (Figure 4B), pulp chamber obliteration (n=1), and changes in pulp chamber volume (n=2) (Figure 4B).

3.2.10. Craniofacial anomalies

Fifteen (32.6%) individuals exhibited craniofacial alterations. The most prevalent finding was elongation of the styloid process, observed in four individuals. Others included condylar flattening (n=3), mandibular sclerosis (n=3), micrognathia (n=3), subchondral cyst (n=2), bifid condyle (n=1), condyles with discrepant morphology and/or size between left and right sides (n=1), macrocrania (n=1), microcephaly (n=1), and microcondyle (n=1). In two cases, the evaluation of condylar morphology was impossible.

3.2.11. Association of dental anomalies with clinicodemographic variables

The analysis of tooth alteration with clinicodemographic variables revealed that men (eight patients and 11 occurrences) were most affected by eruption/exfoliation anomalies compared to women (two patients and four occurrences) (p=0.031). Additionally, endocrine disorders were significantly associated with anomalies of tooth eruption/exfoliation (p=0.047). The number of anomalies related to tooth size was associated with the age of HSCT (p=0.002), meaning that these alterations were only observed in patients who had undergone HSCT at age ≥14 years old. No other

significant associations were observed (Table 3).

3.3. Comparative analysis between the literature and the current case series

From the six cross-sectional studies analyzed, it was possible to determine the exact number of affected individuals in two of them, with proportions of 24/52 (46.1%) (Altay et al., 1997) and 2/15 (13.3%) (Açikgöz et al., 2005). In the present case series, 43/46 (93.5%) individuals exhibited some dental or craniofacial anomaly. In the other cross-sectional studies, the estimated percentages of affected individuals were 27.3% (Ozler et al., 2022), 38.5% (Tekcicek et al., 2007), 63.6% (de Araújo et al., 2007), and 71.4% (Zen et al., 2011).

A comparative analysis of findings from the present case series and the literature, considering the number of occurrences/types of anomalies, is provided in Supplementary File 6. Although the present sample is smaller (n=46) compared to the literature (n=158), higher frequencies of anomalies related to size, position, number, pulp, and radicular anomalies were identified in comparison to other studies. In our sample, the most frequently reported alteration was that affecting roots, while in the literature, craniofacial anomalies were the most frequently reported.

4. Discussion

While congenital malformations and hematologic abnormalities are well recognized as part of the phenotypic spectrum of FA (Auerbach, 2009; Dufour et al., 2022; Altintas et al., 2023; Olson et al., 2023), the variety of manifestations affecting the stomatognathic system of these individuals is much less characterized (Opinya et al., 1988; Açikgöz et al., 2005; de Araújo et al., 2007; Goswami et al., 2016; Pavlič et al., 2017; Miranda et al., 2020). The present systematic review of the literature has identified dental and/or craniofacial anomalies in 158 individuals with FA, with frequencies varying from 13% to 71% (Joho and Marechaux, 1979; Opinya et al., 1988; Altay et al., 1997; Nowzari et al., 2001; Açikgöz et al., 2005; de Araújo et al., 2007; Tekcicek et al., 2007; Falci et al., 2011; Zen et al., 2011; Salinas et al., 2012; Jurca et al., 2014; Goswami et al., 2016; Wenger et al., 2016; Pavlič et al., 2017; Miranda et al., 2020; Touil et al., 2020; Ozler et al., 2022; Imen et al., 2022; Mahmoud et al., 2024). In contrast, 93.5% of individuals in the present case series exhibited either a dental or craniofacial anomaly. Moreover, higher frequencies of dental anomalies related to size, position, number, pulp, and radicular were mostly identified in our sample. Craniofacial anomalies, on the other hand, were more frequent in the literature. These apparent discrepancies may be due to limited evidence, variability in study aims, and evaluation strategies, underscoring the necessity for a systematic investigation of dental and craniofacial characteristics in individuals with FA.

The most frequent anomaly found in the present sample affected the roots. These changes were accompanied by alterations in eruption and/or exfoliation, as well as in the shape, size, pulp, and craniofacial morphology. These anomalies have a multifactorial etiology, with evidence of chromosomal, polygenic, single-gene, and environmental influences (Miziara et al., 2008; Brook et al., 2014). Root abnormalities may coincide with abnormal crown features, such as size, shape, or structure, mainly because crown and root formation are sequential and closely related processes that are also co-dependent on pulp homeostasis (Suda and Moriyama, 2009; Luder, 2015; Laganà et al., 2017).

Eruption/exfoliation anomalies were observed in one-fifth of the individuals in the present sample, affecting both primary and permanent dentition. Conversely, these anomalies were observed in a small proportion (4.5%) of individuals in the assessed literature (Falci et al., 2011; Salinas et al., 2012; Goswami et al., 2016; Pavlič et al., 2017; Ozler et al., 2022). These anomalies may be associated with endocrine diseases

(Suri et al., 2004). For instance, 80% of children and adults with FA have at least one endocrine abnormality and may experience primary hypothyroidism, a smaller average pituitary volume, classical growth hormone deficiency (GHD), or hypothalamic dysfunction leading to “partial” GHD (Giri et al., 2007; Auerbach, 2009; Petryk et al., 2015; Johnson-Tesch et al., 2017; Aksu et al., 2020). GHD is associated with a short mandible, slightly delayed dental maturity, a higher prevalence of microdontia and hypodontia, and bone age delay, which may, in turn, cause teeth crowding due to a deficit of space and malocclusion (Wise et al., 2002; Rose et al., 2012; Davidopoulou et al., 2017; Torlińska-Walkowiak et al., 2022; Torlińska-Walkowiak et al., 2023). Endocrine abnormalities occurred in 26% of our sample and were associated with tooth eruption/exfoliation anomalies. However, no correlation was found between endocrine changes and craniofacial or other dental alterations. Sporadic studies in the literature report the co-occurrence of endocrine and dental/craniofacial alterations (Nowzari et al., 2001; Goswami et al., 2016; Miranda et al., 2020), but further studies are necessary to define a causal association.

Changes in the pattern of tooth eruption and dental abnormalities can significantly influence the organization of dental arches, contributing to disturbances in craniofacial development (Fernandez et al., 2018; Vucic et al., 2019; Wagner et al., 2020). Almost one-third of FA patients from the literature exhibited craniofacial alterations, particularly microcephaly and hypoplasia of the maxilla, mandibular angle, and midface. Other important findings included micrognathia and a triangular face. In the present series, approximately 33% of individuals exhibited craniofacial alterations, with changes including condylar abnormalities, elongation of the styloid process, and micrognathia.

These differences highlight the necessity of expanding the evaluative criteria concerning the presence of other craniofacial alterations, particularly those in the condyle, since 40% of individuals in our sample displayed such changes, not previously reported. These morphological changes in the condyle may occur due to developmental variations, trauma, and endocrine disturbances (Kaneyama et al., 2008, Bains et al., 2023). Additionally, these alterations may be characteristic of other conditions, such as hemifacial microsomia, Treacher-Collins syndrome, and Hallermann-Steiff syndrome (Kato et al., 2021; López et al., 2022; Preudhomme et al., 2022). The mandibular condyles are primary growth centers of the mandible and integral components of the temporomandibular joints. They play roles in establishing

and maintaining jaw position and functionality, occlusion, and typical facial development (Kikuchi et al., 2003; Costello et al., 2012). Therefore, it is plausible that abnormalities in the condyle interact with other craniofacial abnormalities seen in FA individuals (De Kerviler et al., 2000; Auerbach, 2009; Moreno et al., 2021).

In the context of craniofacial anomalies in FA, microcephaly is the most commonly found condition. It is influenced by both genetic and environmental factors (Boonsawat et al., 2019) and may be linked to the general growth problems often observed in FA individuals (Breik et al., 2016; Chen et al., 2019). Notably, microcephaly has been associated with enamel defects and changes in tooth eruption (Gomes et al., 2023), which, along with other facial parameters such as micrognathia and an elongated face, can aid in the diagnosis of FA (Avila et al., 2014; Fiesco-Roa et al., 2019).

Although dental anomalies were not significantly associated with craniofacial alterations in patients from the current series, there is no consensus on this matter elsewhere. In sporadic cases, individuals with FA did not exhibit craniofacial abnormalities; instead, a significant number showed dental anomalies (Marechaux and Joho, 1979). In other cases, patients presented concomitant dental, occlusal, and craniofacial alterations (Falci et al., 2011; Miranda et al., 2020). Additionally, anomalies in tooth size, such as agenesis, alterations in size and roots, and enamel defects, were significantly associated with the age at which HSCT was performed. Antineoplastic drugs and other medications used during HSCT can indeed affect tooth development (Vaughan et al., 2005; Dahllöf, 2008; Ruyssinck et al., 2019). While the history of HSCT has been documented in a few reports (Falci et al., 2011; Miranda et al., 2020; Mahmoud et al., 2024), limited information has been provided about its potential influence on dental and craniofacial development.

The development of the skeletal system in patients with FA is significantly affected (Alter, 2016; Fiesco-Roa et al., 2019; Dufour, 2022; Peake, 2022; Moreno et al., 2021). In the current series, about 37% of individuals exhibited at least one skeletal abnormality in either the upper or lower limbs, with anomalies in both thumbs occurring in 64.7% of cases. Although a significant association of these anomalies with dental and craniofacial changes was not detected, they may impose limitations that hinder the ability to maintain oral hygiene effectively, impacting rates of dental caries and periodontal diseases in this population (de Araújo et al., 2007; Tekcicek et al., 2007).

The present study has limitations inherent to the reviewed literature, including

gaps in knowledge, potential biases, and the lack of standardization of available data, such as unconventional dental numbering systems, which may affect the overall interpretation of the findings. Notably, some studies did not report dental anomalies despite their evident presence in the patients' clinical images. However, we provide a comprehensive analysis of dental and craniofacial findings in a representative sample from two Brazilian reference centers, utilizing standardized instruments to report the data. Future larger international multicenter studies would provide more robust evidence, improving our understanding of dental and craniofacial characteristics in FA.

The heterogeneity of data in the literature regarding which clinical information was sought and methods employed for investigation underscores the importance of gaining a better understanding of the broad spectrum of phenotypes in the FA population. According to the first comprehensive nosology in Dentistry (de La Dure-Molla et al., 2019), 408 entities are included within the classification of genetically determined dental disorders, often associated with dental agenesis, anomalies in tooth eruption, dental size and shape, as well as occlusal and craniofacial anomalies. Noteworthy, dental alterations are observed in the general population, possibly influenced by genetic and environmental factors (Varela et al., 2009; Laganà et al., 2017; Souza-Silva et al., 2018). For example, dental agenesis has a prevalence of 6.4% (Khalaf et al., 2014) and may occur sporadically or be linked to other dental (Al-Shahrani et al., 2014) and craniofacial anomalies (Oeschger et al., 2020; Alamoudi et al., 2024). This emphasizes the importance for dentists and oral and maxillofacial surgeons to be aware of these alterations, whether associated with syndromes or not, and to be capable of predicting potential oral and systemic complications that may arise from different clinical phenotypes (Bartzela et al., 2017; Luo et al., 2019; Arriagada-Vargas et al., 2022).

5. Conclusion

This study reported the diverse range of dental and craniofacial anomalies observed in FA patients. Our systematic review describes such anomalies in 158 individuals with FA, with a prevalence notably high in our 46 cases compared to the literature. Recognizing this wide spectrum of anomalies commonly found in FA patients, along with their multisystemic nature, is crucial for proper management. FA necessitates systematic monitoring by a multidisciplinary team, particularly given the potential impact of these alterations on overall health and quality of life.

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Figure 1. Distribution of systemic and oral manifestations in individuals with Fanconi anemia based on studies retrieved in the literature review**.**

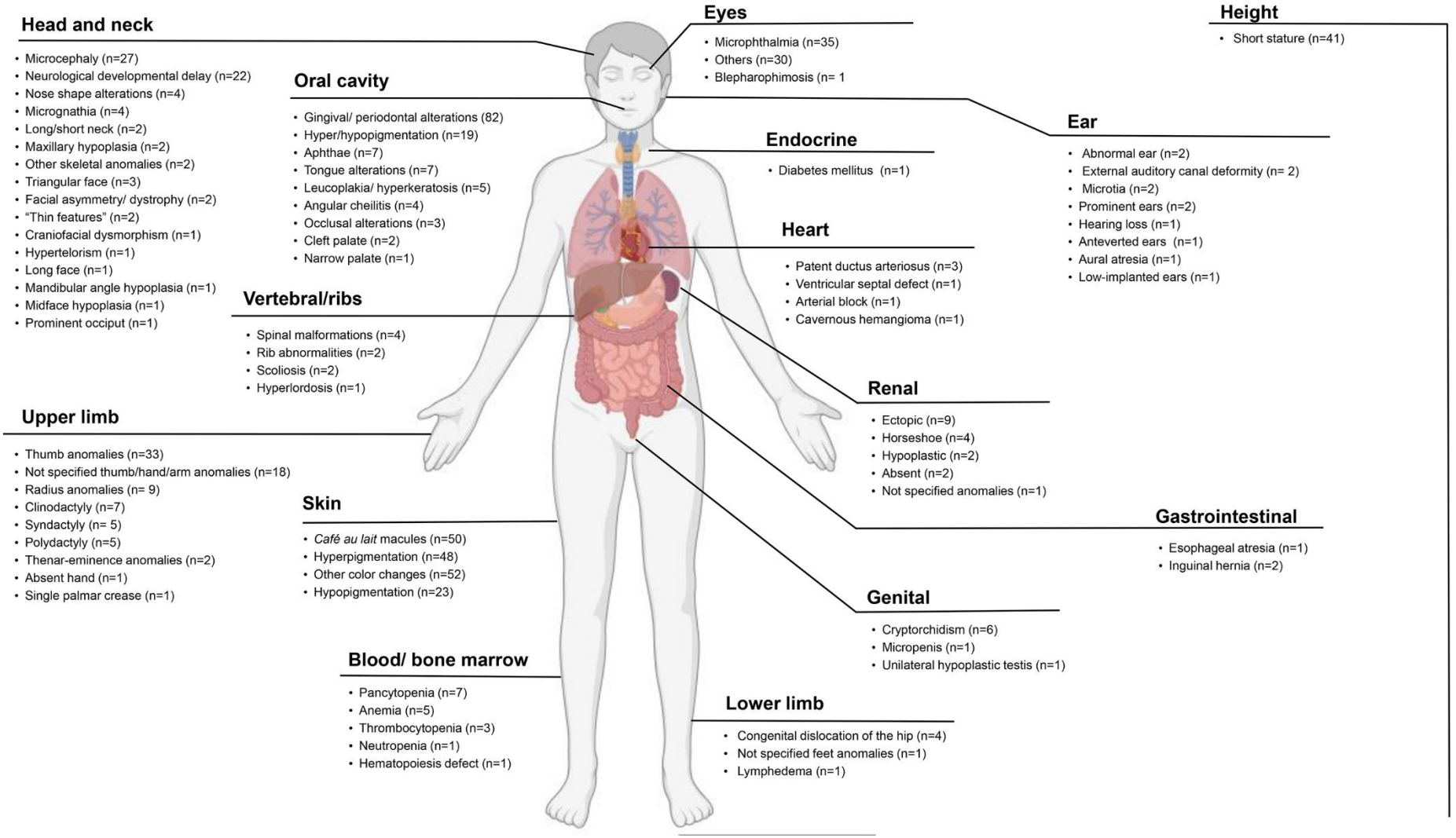


Figure 2. Distribution of dental and craniofacial anomalies among individuals with Fanconi anemia in our case series: (A) frequency and (B) co-occurrence analysis.

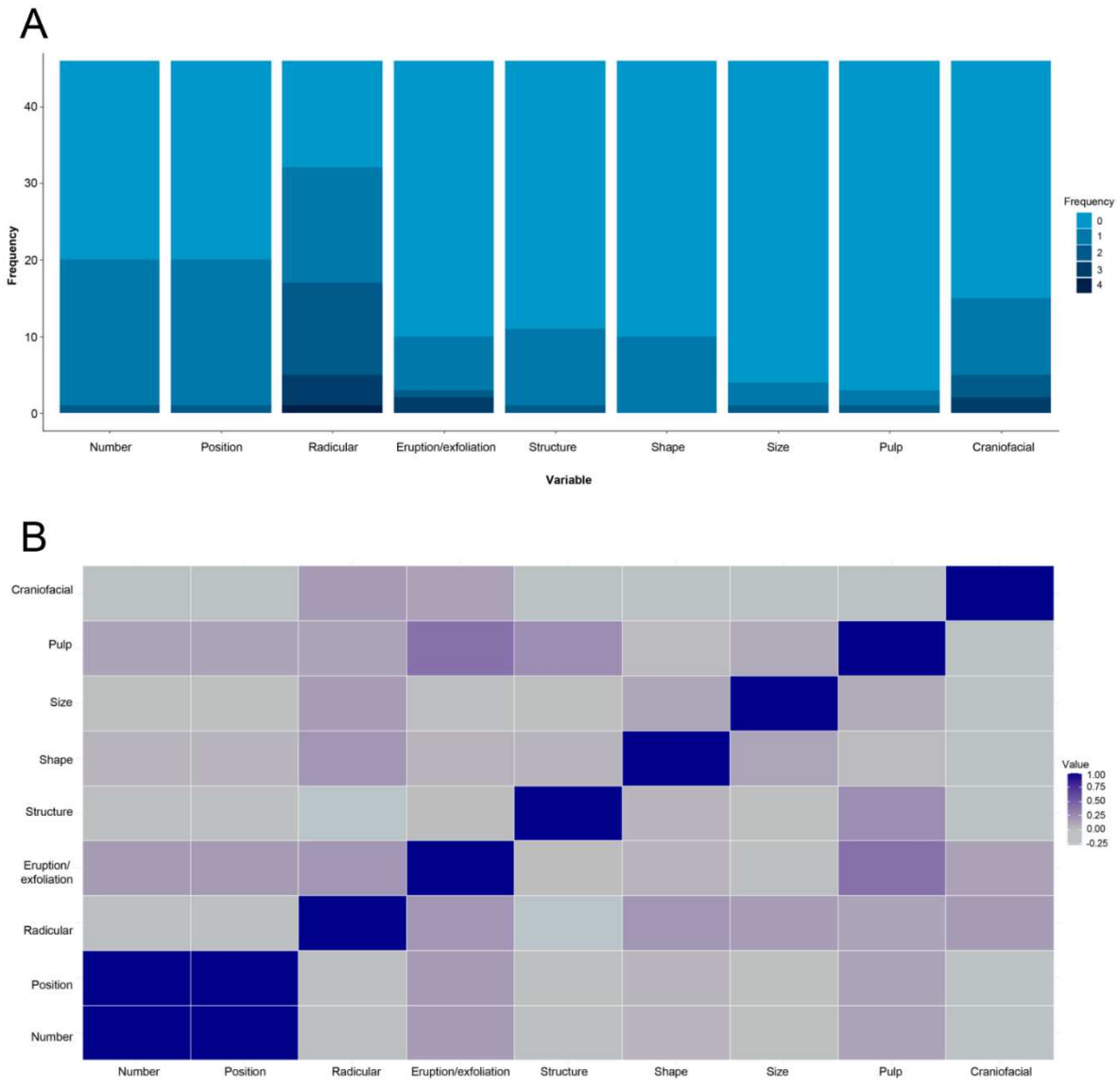
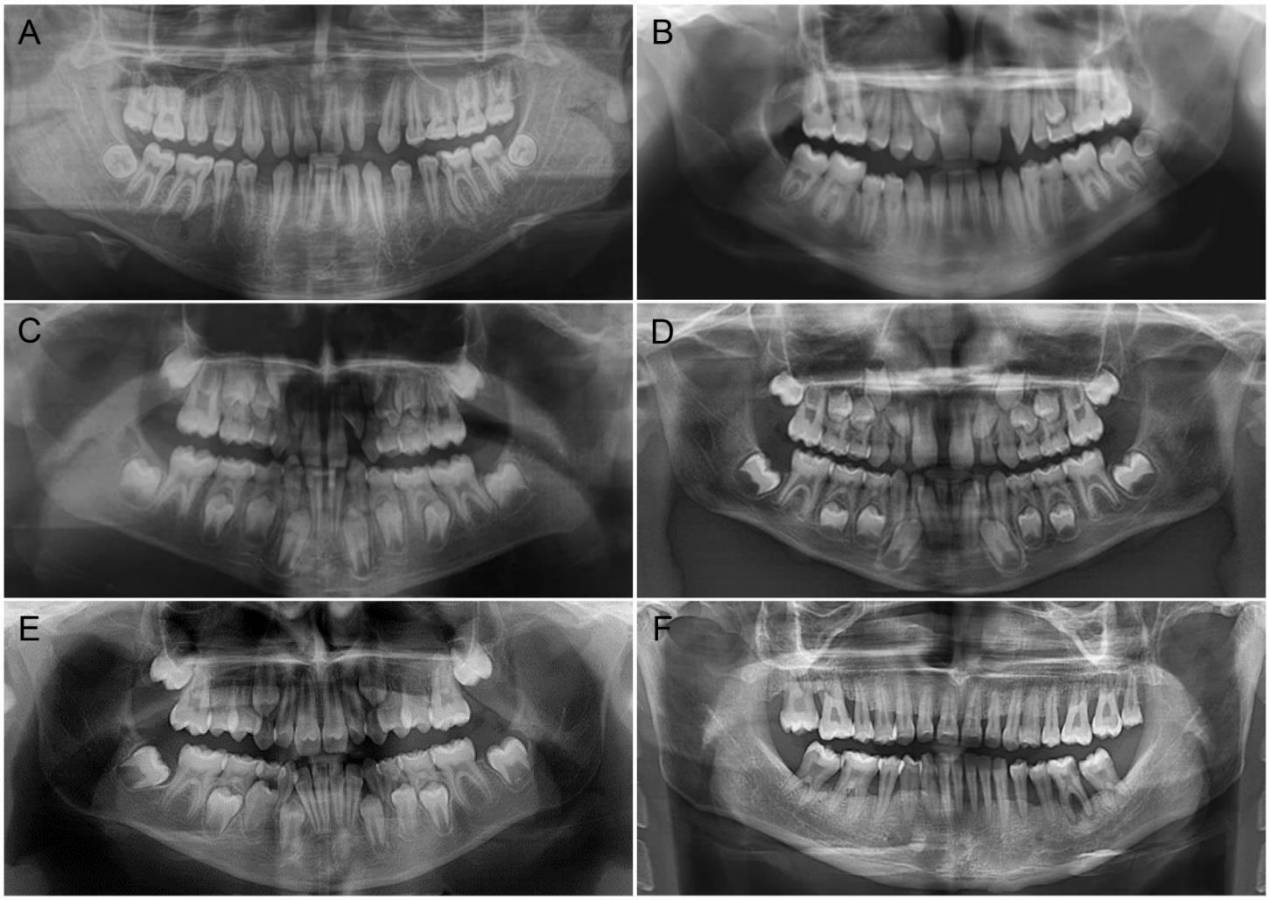


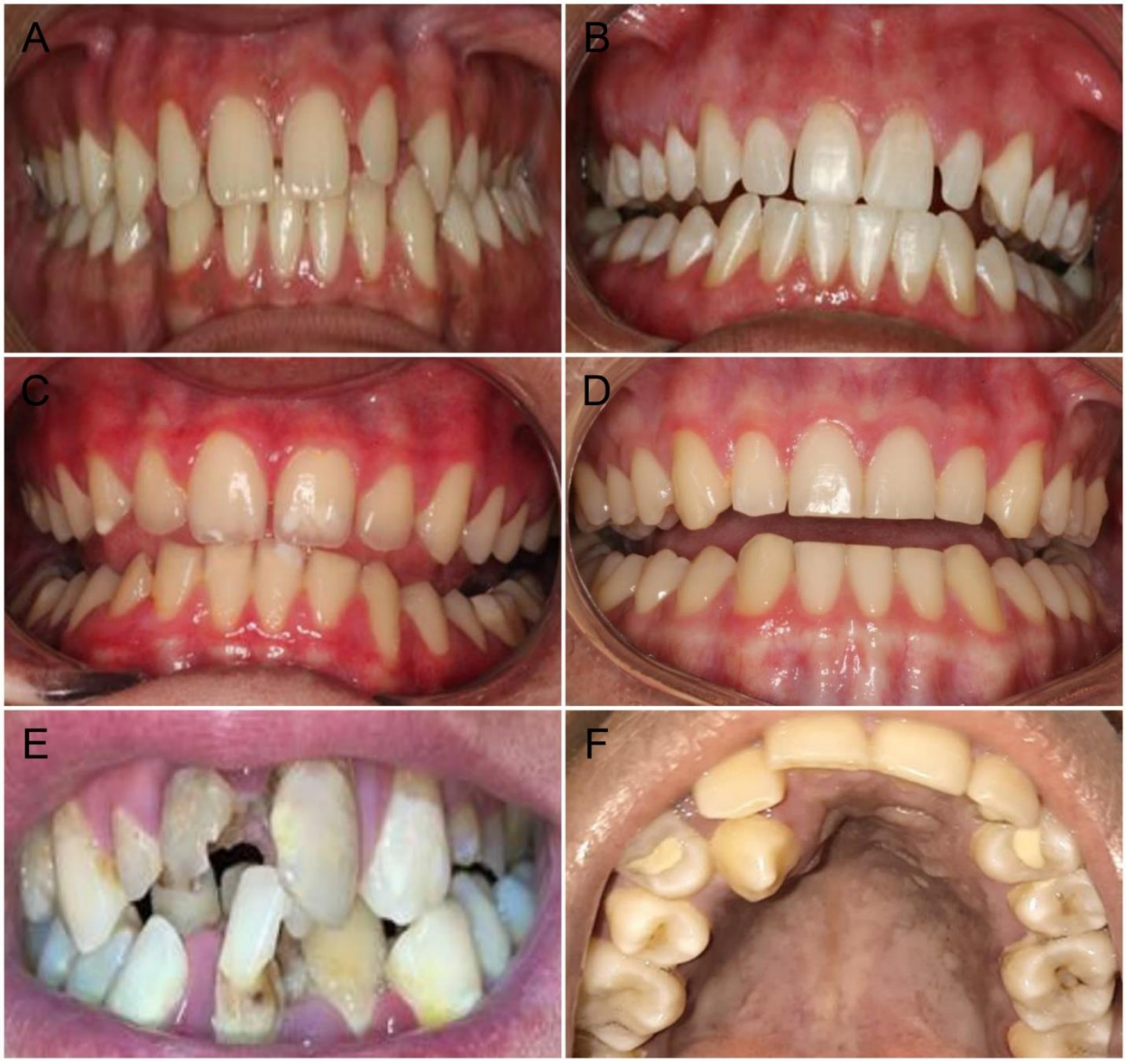
Figure 3. Radiographic findings of individuals with Fanconi anemia



(A) A 15-year-old male patient exhibits agenesis of the maxillary left second premolar, narrow roots of the first right and left mandibular molars, and the right mandibular second molar. Root dilaceration is observed on the mandibular right first premolar, along with retention of the maxillary left second deciduous molar. Dental spacing and midline deviation are in place. **(B)** A 16-year-old male patient exhibits hypodontia involving both maxillary lateral incisors. Pulp chamber calcification is observed in maxillary right and left second premolars, mandibular left and right first and second premolars, and mandibular right second molar. The right mandibular second molar displays a large pulp chamber. Root divergence is noted in mandibular incisors, while root convergence is observed in the mandibular second molar. Delayed eruption is observed in maxillary canines and maxillary second premolar. Tooth malposition includes rotation of the maxillary right canine, infra-occluded mandibular first and second right premolars, and medialization of the maxillary right canine. An enamel pearl is also observed on the right mandibular first molar, along with a retained right maxillary deciduous canine. **(C)** A 9-year-old male patient presents with a conical-shaped maxillary right lateral incisor. Agenesis of both mandibular lateral incisors is observed, along with tooth malposition characterized by rotation of the maxillary left lateral incisor. **(D)** An 8-year-old male patient exhibits agenesis of both mandibular central incisors. **(E)** An 8-year-old male patient exhibits a talon cusp observed on the maxillary right and left central incisors, along with enamel pearls on the four first molars. Root dilaceration is noted in the maxillary first molars, and tooth malposition is evident with rotation observed in the maxillary left lateral incisor and the mandibular

first and second right premolars. **(F)** A 20-year-old female patient presents with enamel pearls on the first and second right mandibular molars and the second left mandibular molar. Enamel hypoplasia is noted from canine to canine on the maxillary teeth, and tooth malposition is evident with rotation observed in the mandibular left and right premolars.

Figure 4. Dental anomalies observed in individuals with Fanconi anemia



(A) A 15-year-old male patient exhibits dental spacing and midline deviation. **(B)** A 26-year-old female shows tooth shape anomalies, notably barrel-shaped morphology in the maxillary right and left lateral incisors. **(C)** A 13-year-old male patient exhibits anomaly in the structure of mineralized tissues of teeth, notably enamel hypoplasia of the maxillary right canine, right and left central incisors, left lateral incisor, and mandibular left central incisor. **(D)** A 15-year-old male patient exhibits dental agenesis of the mandibular right lateral incisor. **(E)** A 25-year-old female patient exhibits tooth malalignment characterized by dental crowding and tooth decay. **(F)** A 23-year-old male patient presents with tooth misalignment, notably the palatal position of the right maxillary canine and right lateral incisor.

Table 1. Data on the clinical characteristics of individuals with Fanconi anemia extracted from six cross-sectional studies retrieved in the literature.

Study	Sample size	Age (range)	Sex	Dental anomalies in terms of number and shape (*n*)	Radicular anomalies (*n*)	Dental structure anomalies (*n*)	Eruption/exfoliation anomalies (*n*)	Dental position anomalies (*n*)	Occlusion anomaly (*n*)	Affected dentition	Craniofacial anomalies (*n*)
Altay et al., 1997; Turkey	52	1.8–12 years	30 M; 22 F	NI	NI	NI	NI	NI	NI	NA	Microcephaly: 22; cleft palate: 1; maxillary hypoplasia: 1
Açikgöz et al., 2005; Turkey	15	6–24 years	11 M; 4 F	Congenitally missing teeth: 1; supernumerary teeth: 1	NI	NI	NI	NI	NI	P	NI
Tekcicek et al., 2007; Turkey	26	2–18 years	17 M; 9 F	Microdontia: 10/26; hypodontia: 6/23; supernumerary teeth: 1/23	NI	NI	NI	Transposition: 2/23	NI	D and P	NI
de Araújo et al., 2007; Brazil	33	2–28 years	15 M; 18 F	Agenesis: 9; abnormal shape of the teeth: 3; enamel pearls: 4; taurodontism: 1	Radicular tapering: 12; “V” formation on root apex during radicular development: 9	Teeth color alteration: 4; opalescent enamel: 2	NI	Rotated permanent teeth: 21	NI	P	NI
Zen et al., 2011; Brazil	7	2 weeks–6 years	3 M; 4 F	NI	NI	NI	NI	NI	NI	NA	Microcephaly: 2; triangular face: 2; micrognathia: 1
Ozler et al., 2022; Turkey	11	4–17 years	6 M; 5 F	Microdontia: 3; taurodontism: 2; hypodontia: 1; cingulum hypertropia: 1	NI	Hypoplasia in unerupted teeth: 1	Ankylosis: 1	NI	NI	D and P	NI

Note: D, deciduous; F, female; M, male; NA, not applied; NI, not informed; P, permanent.

Table 2. Data on clinical characteristics of individuals with Fanconi anemia extracted from 12 case reports retrieved in the literature

Study	Sample size	Age	Sex	Dental number and shape anomalies	Radicular anomalies	Dental structure anomalies	Eruption/exfoliation anomalies	Dental position anomalies	Occlusion anomaly	Affected dentition	Craniofacial anomalies
Joho and Marechaux, 1979; Switzerland	1	19 yrs	F	Microdontia and agenesis	NI	Attrition, yellow discoloration of the teeth, and enamel hypoplasia	NI	Irregular spacing of the teeth and deviation of the upper midline	Right canines in an end-to-end relation and first molars were in Angle class II relationship	P	NI
Opinya et al., 1988; India	1	24 yrs	M	Missing teeth	NI	NI	NI	NI	NI	P	NI
Nowzari et al., 2001; USA	1	11 yrs	M	NI	NI	NI	NI	NI	NI	NI	Microcephaly
Falci et al., 2011; Brazil	1	18 yrs	M	Agenesis of several teeth, microdontia, and deformed anatomy of maxillary right first molar	Accentuated root curvature	NI	Primary teeth and impacted teeth	Counter-clock wise tooth and dental crowding	Bilateral crossbite, anterior open bite, absence of a defined occlusal plane and open gonial angle	D and P	NI
Salinas et al., 2012; Mexico	1	16 yrs	F	NI	NI	NI	Prolonged retention of deciduous teeth and absence of permanent teeth eruption	NI	NI	D and P	Micrognathia and microcephaly
Jurca et al., 2014; Romania	1	16 yrs	M	NI	NI	NI	NI	NI	NI	NI	Palate with keloid scar after cleft palate surgery, craniofacial dysmorphism, microcephaly, and long face
Goswami et al., 2016; India	1	5 yrs	M	*Mesiodens*	NI	NI	Retained deciduous teeth and delayed eruption of permanent teeth	NI	NI	D and P	NI
Pavlič et al., 2017; Slovenia	1	12 yrs	F	Absence of tooth germs	NI	NI	Preserved second lower primary molar	Lower dental arch lack of space	NI	D and P	NI
Wenger et al., 2016; USA	1	2 mo	M	NI	NI	NI	NI	NI	NI	NA	Micrognathia and facial asymmetry
Touil et al., 2020; Tunisia	1	10 yrs	M	NI	NI	Discolored teeth	NI	NI	NI	P	NI
Miranda et al., 2020; Brazil	1	8 yrs	F	Dental agenesis and microdontia	Tapered root formation of permanent teeth	NI	NI	Dental crowding	Crossbite, overbite, overjet, class III skeletal pattern, class III malocclusion, and maxillary deficiency	P	Hypodivergent growth pattern and slight skeletal discrepancy

	1	5 yrs	M	NI	NI	NI	NI	NI	NI	NA	Triangular face, thin features
Imen et al. 2022	1	12 yrs	M	NI	NI	NI	NI	NI	Crossbite	NA	Triangular face, thin features, facial dystrophy, micrognathia, narrow palate
Mahmoud et al., 2024; Saudi Arabia	1	15 yrs	M	Congenital absence of teeth and *dens envaginatus*	Root dilaceration	Enamel hypoplasia and erosion	NI	NI	NI	P	Midface hypoplasia, jaw hypoplasia, and mandibular angle hypoplasia

Note: D, deciduous; F, female; M, male; mo, months; NA, not applied; NI, not informed; P, permanent; yrs, years.

Table 3. Association of clinicodemographic variables and dental anomalies in individuals with Fanconi anemia (*n*=46)

	Type of dental anomaly (number of occurrences)						
	Number	**Position**	**Size**	**Structure**	**Root size and shape**	**Eruption/exfoliation**	**Pulp**
Sex							
Male – mean; median (range)	0.65; 1.00 (0–2)	1.00; 1.00 (0–4)	0.10; 0.00 (0–1)	0.25; 0.00 (0–1)	1.35; 1.00 (0–3)	0.50; 0.00 (0–3)	0.15; 0.00 (0–2)
Female – mean; median (range)	0.31; 0.00 (0–1)	0.88; 1.00 (0–3)	0.06; 0.00 (0–1)	0.31; 0.00 (0–1)	1.13; 1.00 (0–4)	0.25; 0.00 (0–3)	0.06; 0.00 (0–1)
p value*	0.173	1.00; 0.709	1.000	0.879	0.276	**0.031**	0.478
HSCT							
Yes – mean; median (range)	0.50; 0.00 (0–2)	0.94; 1.00 (0–4)	0.08; 0.00 (0–1)	0.28; 0.00 (0–1)	1.25; 1.00 (0–4)	0.39; 0.00 (0–3)	0.11; 0.00 (0–2)
No – mean; median (range)	0.30; 0.00 (0–1)	0.70; 0.50 (0–3)	0.20; 0.00 (0–2)	0.20; 0.00 (0–2)	1.00; 1.00 (0–2)	0.10; 0.00 (0–1)	0.00; 0.00 (0–0)
p value*	0.449	0.446	0.672	0.410	0.648	0.353	0.585
Age at HSCT							
Coefficient β (SE)	0.01 (0.01)	-0.01 (0.01)	0.10 (0.03)	0.01 (0.02)	-0.01 (0.01)	-0.01 (0.03)	0.03 (0.04)
p value**	0.092	0.248	**0.002**	0.433	0.318	0.654	0.434
Craniofacial anomalies							
Present – mean; median (range)	0.40; 0.00 (0–1)	1.13; 1.00 (0–3)	0.00; 0.00 (0–0)	0.07; 0.00 (0–1)	1.47; 1.00 (0–4)	0.53; 0.00 (0–3)	0.00; 0.00 (0–0)
Absent – mean; median (range)	0.48; 0.00 (0–2)	0.77; 1.00 (0–4)	0.16; 0.00 (0–2)	0.35; 0.00 (0–2)	1.06; 1.00 (0–3)	0.23; 0.00 (0–3)	0.13; 0.00 (0–2)
p value*	0.775	0.314	0.288	0.069	0.191	0.194	0.541
Fanconi anemia facies							
Present – mean; median (range)	0.67; 1.00 (0–2)	1.11; 1.00 (0–3)	0.22; 0.00 (0–2)	0.11; 0.00 (0–1)	1.44; 2.00 (0–4)	0.67; 0.00 (0–3)	0.22; 0.00 (0–2)

Absent – mean; median (range)	0.33; 0.00 (0–1)	0.33; 0.00 (0–2)	0.00; 0.00 (0–0)	0.22; 0.00 (0–1)	1.33; 1.00 (0–3)	0.44; 0.00 (0–2)	0.11; 0.00 (0–1)
p value*	0.456	0.089	1.000	1.000	0.889	1.000	1.000
Skeletal anomalies of upper and lower limbs							
Present – mean; median (range)	0.35; 0.00 (0–1)	0.76; 0.00 (0–3)	0.12; 0.00 (0–2)	0.35; 0.00 (0–1)	1.24; 1.00 (0–4)	0.29; 0.00 (0–3)	0.12; 0.00 (0–2)
Absent – mean; median (range)	0.80; 1.00 (0–2)	0.40; 0.00 (0–1)	0.00; 0.00 (0–0)	0.00; 0.00 (0–0)	1.20; 1.00 (0–3)	1.00; 0.00 (0–3)	0.20; 0.00 (0–1)
p value*	0.199	0.712	1.000	0.266	1.000	0.367	0.411
Vertebral anomalies							
Present – mean; median (range)	0.50; 0.50 (0–1)	0.75; 0.00 (0–3)	0.00; 0.00 (0–0)	0.50; 0.50 (0–1)	2.50; 2.50 (1–4)	1.00; 0.50 (0–3)	0.50; 0.00 (0–2)
Absent – mean; median (range)	0.50; 0.00 (0–2)	0.71; 0.50 (0–3)	0.14; 0.00 (0–2)	0.07; 0.00 (0–1)	1.07; 1.00 (0–3)	0.43; 0.00 (0–3)	0.07; 0.00 (0–1)
p value*	1.000	0.632	1.000	0.108	0.060	0.456	0.222
Endocrine abnormalities							
Present – mean; median (range)	0.33; 0.00 (0–1)	0.83; 1.00 (0–3)	0.17; 0.00 (0–2)	0.42; 0.00 (0–2)	1.08; 1.00 (0–2)	0.83; 0.00 (0–3)	0.17; 0.00 (0–2)
Absent – mean; median (range)	0.42; 0.00 (0–2)	0.88; 0.50 (0–4)	0.13; 0.00 (0–1)	0.17; 0.00 (0–1)	1.33; 1.00 (0–4)	0.17; 0.00 (0–1)	0.08; 0.00 (0–1)
p value*	0.914	0.714	1.000	0.311	0.666	**0.047**	0.691

Note: HSCT, hematopoietic stem-cell transplantation; SE, standard error.
*Mann-Whitney test.
**Generalized linear model. Bold indicates statistically significance at $p<0.05$.

Supplementary Files

Building upon evidence on dental and craniofacial anomalies in Fanconi anemia: systematic review of 158 cases and additional 46 reports

Table of contents

Supplementary File 1. Search strategies employed to identify articles in electronic databases

PubMed, Web of Science, and Ovid	Fanconi anemia OR Fanconi pancytopenia OR Fanconi panmyelopathy OR Fanconi hypoplastic anemia AND tooth abnormalities OR tooth abnormality OR tooth anomaly OR tooth anomalies OR teeth abnormalities OR teeth abnormality OR teeth anomalies OR teeth anomaly OR dental abnormalities OR dental abnormality OR dental anomalies OR dental anomaly OR dental aberration OR anodontia OR hypodontia OR oligodontia OR supernumerary teeth OR microdontia OR macrodontia OR unerupted tooth OR unerupted teeth OR conoid teeth OR conoid tooth OR delayed tooth eruption OR dens in dens OR dens in den OR twinning OR root laceration OR supernumerary root OR transposition OR transmigration OR gyroversion OR ectopic eruption OR taurodontism OR root deformities OR impacted tooth OR impacted teeth OR tooth dilaceration OR teeth dilaceration OR crown dilaceration OR hypercementosis OR pulp stone OR obliterated pulp chamber OR short root OR narrow root OR tooth agenesis OR malocclusion OR orthodontic OR Angle class I OR Angle class II OR Angle class III OR crowding OR crossbite OR cross-bite OR cross bite OR prognathism OR overbite OR over-bite OR over bite OR openbite OR open-bite OR open bite OR retrognathism OR cephalometry OR cephalometric OR lateral radiography OR lateral radiograph
Scopus	“Fanconi anemia” OR “Fanconi pancytopenia” OR “Fanconi hypoplastic anemia” AND “tooth abnormalities” OR “tooth abnormality” OR “tooth anomaly” OR “tooth anomalies” OR “teeth abnormalities” OR “teeth abnormality” OR “teeth anomalies” OR “teeth anomaly” OR “dental abnormalities” OR “dental abnormality” OR

	“dental anomalies” OR “dental anomaly” OR “dental aberration” OR anodontia OR hypodontia OR oligodontia OR “supernumerary teeth” OR microdontia OR macrodontia OR “unerupted tooth” OR “unerupted teeth” OR “conoid teeth” OR “conoid tooth” OR “delayed tooth eruption” OR “dens in dens” OR “dens in den” OR twinning OR “root laceration” OR “supernumerary root” OR transposition OR transmigration OR “ectopic eruption” OR taurodontism OR “root deformities” OR “impacted tooth” OR “impacted teeth” OR “tooth dilaceration” OR “teeth dilaceration” OR “crown dilaceration” OR hypercementosis OR “pulp stone” OR “obliterated pulp chamber” OR “short root” OR “narrow root” OR “tooth agenesis” OR malocclusion OR orthodontic OR “Angle class” OR crowding OR crossbite OR cross-bite OR “cross bite” OR prognathism OR overbite OR over-bite OR “over bite” OR openbite OR open-bite OR “open bite” OR retrognathism OR cephalometry OR cephalometric OR “lateral radiography” OR “lateral radiograph”
Embase	“Fanconi anemia” OR “Fanconi pancytopenia” OR “Fanconi panmyelopathy” OR “Fanconi hypoplastic anemia” AND “tooth abnormalities” OR “tooth abnormality” OR “tooth anomaly” OR “tooth anomalies” OR “teeth abnormalities” OR “teeth abnormality” OR “teeth anomalies” OR “teeth anomaly” OR “dental abnormalities” OR “dental abnormality” OR “dental anomalies” OR “dental anomaly” OR “dental aberration” OR anodontia OR hypodontia OR oligodontia OR “supernumerary teeth” OR microdontia OR macrodontia OR “unerupted tooth” OR “unerupted teeth” OR “conoid teeth” OR “conoid tooth” OR “delayed tooth eruption” OR “dens in dens” OR “dens in den” OR twinning OR “root

	laceration” OR “supernumerary root” OR transposition OR transmigration OR gyroversion OR “ectopic eruption” OR taurodontism OR “root deformities” OR “impacted tooth” OR “impacted teeth” OR “tooth dilaceration” OR “teeth dilaceration” OR “crown dilaceration” OR hypercementosis OR “pulp stone” OR “obliterated pulp chamber” OR “short root” OR “narrow root” OR “tooth agenesis” OR malocclusion OR orthodontic OR “Angle class I” OR “Angle class II” OR “Angle class III” OR crowding OR crossbite OR cross-bite OR “cross bite” OR prognathism OR overbite OR over-bite OR “over bite” OR openbite OR open-bite OR “open bite” OR retrognathism OR cephalometry OR cephalometric OR “lateral radiography” OR “lateral radiograph”
LILACS	Fanconi anemia AND malocclusion OR orthodontic OR dental anomaly OR dental anomalies OR dental abnormality OR dental abnormalities

Supplementary File 2. Articles excluded after reading the full text with reasons for exclusion

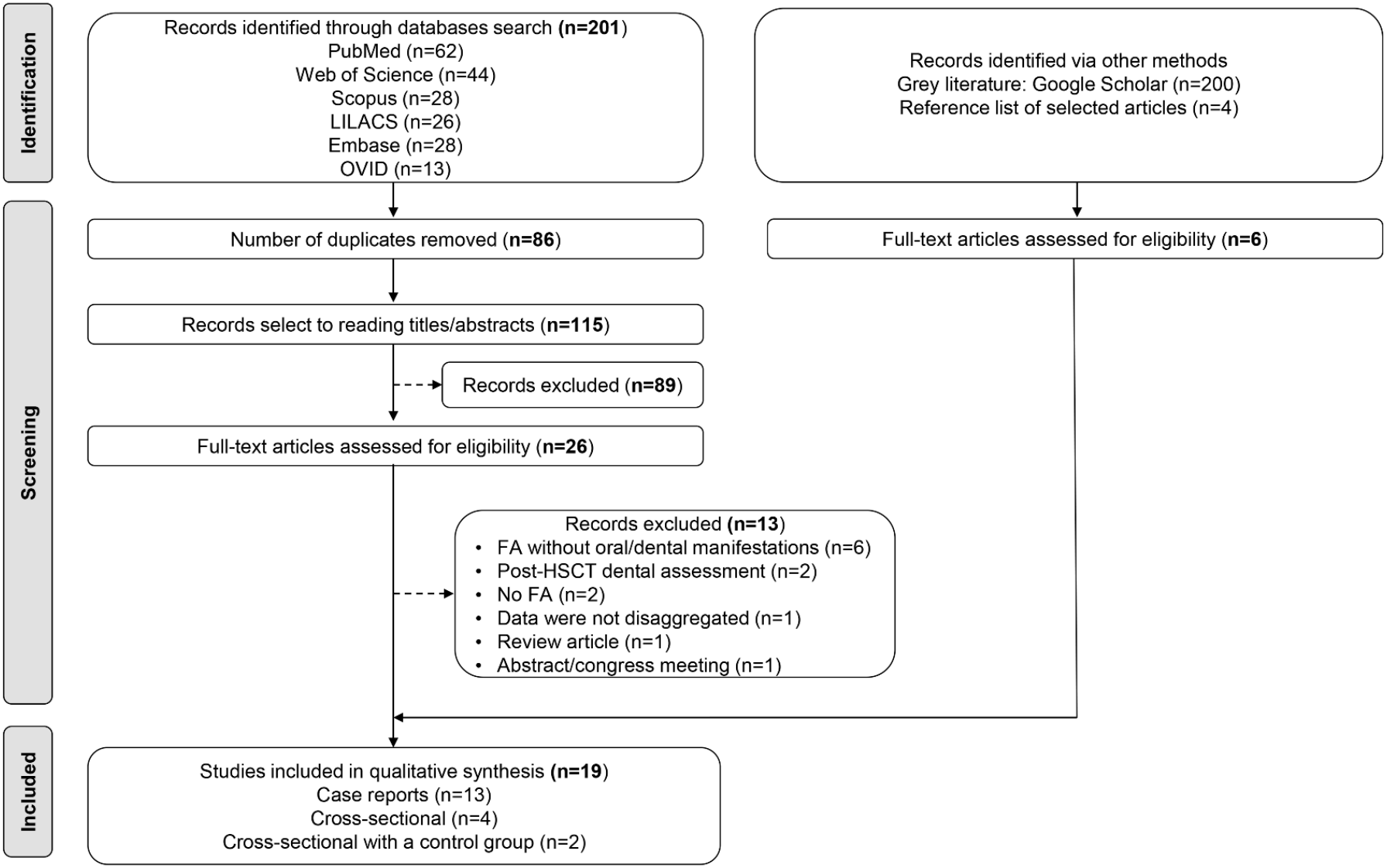
Articles	Reasons for exclusion
1. Lustig JP, Lugassy G, Neder A, Sigler E. Head and neck carcinoma in Fanconi's anaemia--report of a case and review of the literature. Eur J Cancer B Oral Oncol. 1995;31B(1):68-72	FA without oral/dental manifestation
2. Yalman N, Sepet E, Aren G, Mete Z, Külekçi G, Anak S. The effect of bone marrow transplantation on systemic and oral health in Fanconi's aplastic anemia. J Clin Pediatr Dent. 2001;25(4):329-332	Post-HSCT dental assessment
3. Açikgöz G, Açikgöz A, Keskiner I, Türk T, Otan F. Aggressive periodontitis with supernumerary teeth: a retrospective study. J Periodontol. 2004;75(11):1458-60	FA without oral/dental manifestation
4. Gomes MF, Teixeira RT, Plens G, Silva MM, Pontes EM, da Rocha JC. Naso-orbicular tissue necrosis by Streptococcus parasanguis in a patient with Fanconi anemia: clinical and laboratory aspects. Quintessence Int. 2004;35(7):572-576	FA without oral/dental manifestation
5. Koubik AC, Franca BH, Ribas Mde O, de Araújo MR, Mattioli TM, de Lima AA. Comparative study of chronological, bone, and dental age in Fanconi's anemia. J Pediatr Hematol Oncol. 2006;28(4):260-262	FA without oral/dental manifestation
6. D'Souza F, Usha MK, Subba Rao SD. Fanconi's anemia in monozygotic twins. Indian J Pediatr. 2007;74(9):859-861	FA without oral/dental manifestation

7. Saleh A, Stephen LX. Oral manifestations of Fanconi's anaemia: a case report. SADJ. 2008;63(1):28-31	FA without oral/dental manifestation
8. Avila LF, Denis Martins W, Cândido L, Ignácio SA, Bonfim CM, de Oliveira Ribas M. A study of facial pattern in patients with fanconi anemia. Cleft Palate Craniofac J. 2014;51(1):83-89	Data were not disaggregated
9. Fernandes KS, Paulo Sérgio da Silva Santos, Coracin FL, Dulley F, Rubira-Bullen IRF, Gallottini M. Oral health and dental abnormalities in children submitted to HSCT dental abnormalities after HSCT. International Journal of Clinical Dentistry. 2015; 8(1):73-81	Post-HSCT dental assessment
10. Silva AP, Rosa RF, Trevisan P, Dorneles JC, Mesquita CS, Mattos VF, Paskulin GA, Zen PR. Clinical and cytogenetic features of a Brazilian sample of patients with phenotype of oculo-auriculo-vertebral spectrum: a cross-sectional study. Sao Paulo Med J. 2015;133(3):191-198	No FA
11. Chhabra P, Trehan A, Bansal D, Jain R, Bhatia P, Varma N. Clinical profile of inherited bone marrow failure syndromes (IBMFS) in children: a tertiary care experience over 5 years. 2019;4(2):S44	Abstract/congress meeting
12. Kesici S, Ünal Ş, Kuşkonmaz B, Aytaç S, Çetin M, Gümrük F. Fanconi anemia: a single center experience of a large cohort. Turk J Pediatr. 2019;61(4):477-484	No FA

13.	Ambarkova V. Oral and dental manifestations of Fanconi anemia. Galician Med J. 2021;28(3):E202132		Review article

Note: FA, Fanconi anemia; HSCT, hematopoietic stem cell transplantation.

Supplementary File 3. Flowchart illustrating the search process



Supplementary File 4. Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies

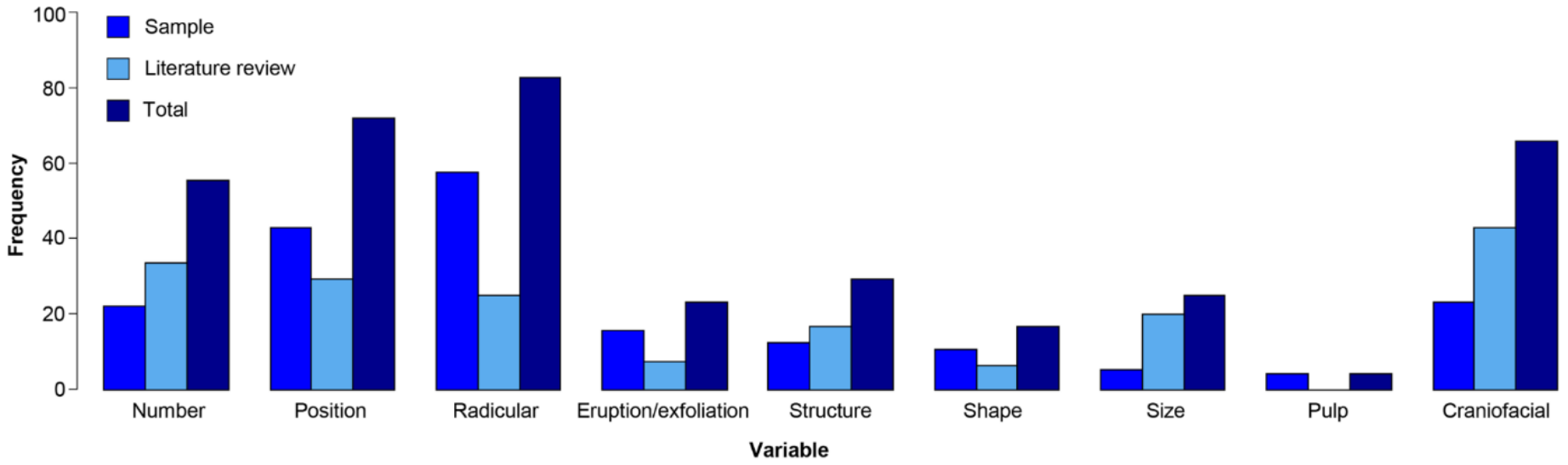
Author(s) (year of publication)	**Items**							
	Were the criteria for inclusion in the sample clearly defined?	*Were the study subjects and the setting described in detail?*	*Was the exposure measured in a valid and reliable way?*	*Were objective, standard criteria used for measurement of the condition?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the outcomes measured in a valid and reliable way?*	*Was appropriate statistical analysis used?*
Altay et al. (1997)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Açikgöz et al. (2005)	Yes	No	Yes	Yes	No	No	No	Yes
de Araújo et al. (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tekcicek et al. (2007)	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Zen et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ozler et al. (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Supplementary File 5. Joanna Briggs Institute (JBI) critical appraisal checklist for case reports

Author(s) (year of publication)	Items							
	Were patient's demographic characteristics clearly described??	*Was the patient's history clearly described and presented as a timeline?*	*Was the current clinical condition of the patient on presentation clearly described?*	*Were diagnostic tests or assessment methods and the results clearly described?*	*Was the intervention(s) or treatment procedure(s) clearly described?*	*Was the post-intervention clinical condition clearly described?*	*Were adverse events (harms) or unanticipated events identified and described?*	*Does the case report provide takeaway lessons?*
Joho and Marechaux (1979)	Yes	Yes	Yes	Yes	No	No	No	Yes
Opinya et al. (1987)	Yes	Yes	Yes	No	No	No	No	Yes
Nowzari et al. (2001)	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Falci et al. (2011)	Yes	Yes	Yes	No	No	No	No	Yes
Salinas et al. (2012)	No	Yes	Yes	Yes	No	No	No	Yes
Jurca et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Goswami et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wegner et al. (2016)	Yes	No	Yes	Yes	No	No	No	Yes
Pavlič et al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miranda et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Touil et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

(2020)								
Imen et al. (2022)	Yes	No	Yes	No	No	No	Yes	Yes
Mahmoud et al. (2024)	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Supplementary File 6. Comparative analysis of the number of occurrences of dental and craniofacial anomalies in the cases from the literature and the current sample



References

Açikgöz A, Ozden FO, Fisgin T, Açikgöz G, Duru F, Yarali N, Albayrak D. Oral and dental findings in Fanconi's anemia. Pediatr Hematol Oncol. 2005;22(6):531-539. doi: 10.1080/08880010591002413.

Aksu T, Gümrük F, Bayhan T, Coşkun Ç, Oğuz KK, Unal S. Central nervous system lesions in Fanconi anemia: experience from a research center for Fanconi anemia patients. Pediatr Blood Cancer. 2020;67(12):e28722. doi: 10.1002/pbc.28722.

Alamoudi R, Kanavakis G, Oeschger ES, Halazonetis D, Gkantidis N. Occlusal characteristics in modern humans with tooth agenesis. Sci Rep. 2024;14(1):5840. doi: 10.1038/s41598-024-56449-9.

Al-Shahrani I, Dirks W, Jepson N, Khalaf K. 3D-Geomorphometrics tooth shape analysis in hypodontia. Front Physiol. 2014;5:154. doi: 10.3389/fphys.2014.00154.

Altay C, Alikaşifoglu M, Kara A, Tunçbilek E, Ozbek N, Schroeder-Kurth TM. Analysis of 65 Turkish patients with congenital aplastic anemia (Fanconi anemia and non-Fanconi anemia): Hacettepe experience. Clin Genet. 1997;51(5):296-302. doi: 10.1111/j.1399-0004.1997.tb02477.

Alter BP, Giri N. Thinking of VACTERL-H? Rule out Fanconi anemia according to PHENOS. Am J Med Genet A. 2016;170(6):1520-1524. doi: 10.1002/ajmg.a.37637.

Alter BP. Inherited bone marrow failure syndromes: considerations pre- and posttransplant. Blood. 2017;130(21):2257-2264. doi: 10.1182/blood-2017-05-781799.

Altintas B, Giri N, McReynolds LJ, Best A, Alter BP. Genotype-phenotype and outcome associations in patients with Fanconi anemia: the National Cancer Institute cohort. Haematologica. 2023;108(1):69-82. doi: 10.3324/haematol.2021.279981.

Arriagada-Vargas C, Abeleira-Pazos MT, Outumuro-Rial M, García-Mato E, Varela-Aneiros I, Limeres-Posse J, Diz-Dios P, Diniz-Freitas M. Rare disorders: diagnosis and therapeutic planning for patients seeking orthodontic treatment. J Clin Med. 2022;11(6):1527. doi: 10.3390/jcm11061527.

Auerbach AD. Fanconi anemia and its diagnosis. Mutat Res. 2009;668(1-2):4-10. doi: 10.1016/j.mrfmmm.2009.01.013.

Auerbach AD. Fanconi anemia. Dermatol Clin. 1995;13(1):41-9.

Avila LF, Denis Martins W, Cândido L, Ignácio SA, Bonfim CM, de Oliveira Ribas M. A study of facial pattern in patients with Fanconi anemia. Cleft Palate Craniofac J. 2014;51(1):83-89. doi: 10.1597/11-321.1.

Bains SK, Bhatia A, Kumar N, Kataria A, Balmuchu I, Srivastava S. Assessment of morphological variations of the coronoid process, condyle, and sigmoid notch as an adjunct in personal identification using orthopantomograms among the north Indian population. Cureus. 2023;15(6):e40275. doi: 10.7759/cureus.40275.

Bartzela TN, Carels C, Maltha JC. Update on 13 syndromes affecting craniofacial and dental Structures. Front Physiol. 2017;8:1038. doi: 10.3389/fphys.2017.01038.

Boonsawat P, Joset P, Steindl K, Oneda B, Gogoll L, Azzarello-Burri S, Sheth F, Datar C, Verma IC, Puri RD, Zollino M, Bachmann-Gagescu R, Niedrist D, Papik M, Figueiro-Silva J, Masood R, Zweier M, Kraemer D, Lincoln S, Rodan L; Undiagnosed Diseases Network (UDN); Passemard S, Drunat S, Verloes A, Horn AHC, Sticht H, Steinfeld R, Plecko B, Latal B, Jenni O, Asadollahi R, Rauch A. Elucidation of the phenotypic spectrum and genetic landscape in primary and secondary microcephaly. Genet Med. 2019;21(9):2043-2058. doi: 10.1038/s41436-019-0464-7.

Breik O, Tivey D, Umapathysivam K, Anderson P. Mandibular distraction osteogenesis for the management of upper airway obstruction in children with micrognathia: a systematic review. Int J Oral Maxillofac Surg. 2016;45(6):769-782. doi: 10.1016/j.ijom.2016.01.009.

Brook AH, Jernvall J, Smith RN, Hughes TE, Townsend GC. The dentition: the outcomes of morphogenesis leading to variations of tooth number, size and shape. Aust Dent J. 2014;59 Suppl 1:131-142. doi: 10.1111/adj.12160.

Chen Q, Zhao Y, Qian Y, Lu C, Shen G, Dai J. A genetic-phenotypic classification for syndromic micrognathia. J Hum Genet. 2019;64(9):875-883. doi: 10.1038/s10038-019-0630-4.

Costello BJ, Rivera RD, Shand J, Mooney M. Growth and development considerations for craniomaxillofacial surgery. Oral Maxillofac Surg Clin North Am. 2012;24(3):377-396. doi: 10.1016/j.coms.2012.05.007.

Dahllöf G. Oral and dental late effects after pediatric stem cell transplantation. Biol Blood Marrow Transplant. 2008;14(1 Suppl 1):81-83. doi: 10.1016/j.bbmt.2007.11.007.

Davidopoulou S, Chatzigianni A. Craniofacial morphology and dental maturity in children with reduced somatic growth of different aetiology and the effect of growth hormone treatment. Prog Orthod. 2017;18(1):10. doi: 10.1186/s40510-017-0164-2.

de Araújo MR, de Oliveira Ribas M, Koubik AC, Mattioli T, de Lima AA, França BH. Fanconi's anemia: clinical and radiographic oral manifestations. Oral Dis. 2007;13(3):291-295. doi: 10.1111/j.1601-0825.2006.01282.x.

De Kerviler E, Guermazi A, Zagdanski AM, Gluckman E, Frija J. The clinical and radiological features of Fanconi's anaemia. Clin Radiol. 2000;55(5):340-345. doi: 10.1053/crad.2000.0445.

de La Dure-Molla M, Fournier BP, Manzanares MC, Acevedo AC, Hennekam RC, Friedlander L, Boy-Lefèvre ML, Kerner S, Toupenay S, Garrec P, Vi-Fane B, Felizardo R, Berteretche MV, Jordan L, Ferré F, Clauss F, Jung S, de Chalendar M, Troester S, Kawczynski M, Chaloyard J; International Group of Dental Nomenclature; Manière MC, Berdal A, Bloch-Zupan A. Elements of morphology: standard terminology for the teeth and classifying genetic dental disorders. Am J Med Genet A. 2019;179(10):1913-1981. doi: 10.1002/ajmg.a.61316.

Dufour C, Pierri F. Modern management of Fanconi anemia. Hematology Am Soc Hematol Educ Program. 2022;2022(1):649-657. doi: 10.1182/hematology.2022000393.

Dupre N, Riou MC, Isaac J, Ferre F, Cormier-Daire V, Kerner S, de La Dure-Molla M, Nowwarote N, Acevedo AC, Fournier BPJ. Root resorptions induced by genetic disorders: a systematic review. Oral Dis. 2024. doi: 10.1111/odi.14942.

Falci SGM, Corrêa-Faria P, Tataounoff J, Santos CRR, Marques LS. Fanconi's anemia in dentistry: a case report and brief literature review. Rev Odonto Ciênc. 2011;26(3):272-276. doi: 10.1590/S1980-65232011000300015.

Fanconi Anemia Clinical Care Guidelines. Fanconi Anemia Research Fund. 5th ed., 2020. Available from: https://www.fanconi.org/images/uploads/other/Fanconi_Anemia_Clinical_Care_Guidelines_5thEdition_web.pdf

Fernandez CCA, Pereira CVCA, Luiz RR, Vieira AR, De Castro Costa M. Dental anomalies in different growth and skeletal malocclusion patterns. Angle Orthod. 2018;88(2):195-201. doi: 10.2319/071917-482.1.

Fiesco-Roa MO, Giri N, McReynolds LJ, Best AF, Alter BP. Genotype-phenotype associations in Fanconi anemia: A literature review. Blood Rev. 2019;37:100589. doi: 10.1016/j.blre.2019.100589.

Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. J Clin Endocrinol Metab. 2007;92(7):2624-2631. doi: 10.1210/jc.2007-0135.

Gomes PN, Azevedo ID, do Amaral BA, Arrais NMR, Lima KC. Microcephaly as a risk factor for dental alterations: a case-control study. Oral Dis. 2023;29(5):2265-2271. doi: 10.1111/odi.14199.

Goswami M, Bhushan U, Goswami M. Dental perspective of rare disease of Fanconi anemia: case report with review. Clin Med Insights Case Rep. 2016;9:25-30. doi: 10.4137/CCRep.S37931.

Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of Google Scholar in evidence reviews and its applicability to grey literature searching. PLoS One. 2015;10(9):e0138237. doi: 10.1371/journal.pone.0138237.

Imen J, Nait Malek M, Zaroui J, Chalbi M, Essari A, Chemli MA. Dental management of Fanconi anemia: two case reports. Saudi J Med. 2022; 7(7):394-399. doi: 10.36348/sjm.2022.v07i07.006.

Johnson-Tesch BA, Gawande RS, Zhang L, MacMillan ML, Nascene DR. Fanconi anemia: correlating central nervous system malformations and genetic

complementation groups. Pediatr Radiol. 2017;47(7):868-876. doi: 10.1007/s00247-017-3817-x.

Joho JP, Marechaux SC. Microdontia: a specific tooth anomaly: report of case. ASDC J Dent Child. 1979;46(6):483-486.

Jurca A, Kinga K, Bembea M, Gug C, Jurca C. Fanconi anemia with cleft palate. Rev Med Chir Soc Med Nat Iasi. 2014;118(4):1074-1077.

Kaneyama K, Segami N, Hatta T. Congenital deformities and developmental abnormalities of the mandibular condyle in the temporomandibular joint. Congenit Anom (Kyoto). 2008;48(3):118-125. doi: 10.1111/j.1741-4520.2008.00191.x.

Kato RM, Moura PP, Zechi-Ceide RM, Tonello C, Peixoto AP, Garib D. Three-dimensional comparison of mandibular morphology in young people with Treacher Collins syndrome and Pierre Robin sequence. Am J Orthod Dentofacial Orthop. 2021;160(6):835-843. doi: 10.1016/j.ajodo.2020.06.053.

Khalaf K, Miskelly J, Voge E, Macfarlane TV. Prevalence of hypodontia and associated factors: a systematic review and meta-analysis. J Orthod. 2014;41(4):299-316. doi: 10.1179/1465313314Y.0000000116.

Kikuchi K, Takeuchi S, Tanaka E, Shibaguchi T, Tanne K. Association between condylar position, joint morphology and craniofacial morphology in orthodontic patients without temporomandibular joint disorders. J Oral Rehabil. 2003;30(11):1070-1075. doi: 10.1046/j.1365-2842.2003.01194.x.

Knottnerus A, Tugwell P. STROBE--a checklist to Strengthen the Reporting of Observational Studies in Epidemiology. J Clin Epidemiol. 2008;61(4):323. doi: 10.1016/j.jclinepi.2007.11.006.

Kunz F, Kayserili H, Midro A, de Silva D, Basnayake S, Güven Y, Borys J, Schanze D, Stellzig-Eisenhauer A, Bloch-Zupan A, Zenker M. Characteristic dental pattern with hypodontia and short roots in Fraser syndrome. Am J Med Genet A. 2020;182(7):1681-1689. doi: 10.1002/ajmg.a.61610.

Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, Goberdhan A, Shah JP, Singh B. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg. 2003;129(1):106-112. doi: 10.1001/archotol.129.1.106.

Laganà G, Venza N, Borzabadi-Farahani A, Fabi F, Danesi C, Cozza P. Dental anomalies: prevalence and associations between them in a large sample of non-orthodontic subjects, a cross-sectional study. BMC Oral Health. 2017;17(1):62. doi: 10.1186/s12903-017-0352-y.

López DF, Acosta DM, Rivera DA, Mejía CM. Hemifacial microsomia: treatment alternatives-a systematic review of literature. J Clin Pediatr Dent. 2022;46(5):15-30. doi: 10.22514/jocpd.2022.003.

Lubinsky M, Kantaputra PN. Syndromes with supernumerary teeth. Am J Med Genet A. 2016;170(10):2611-2616. doi: 10.1002/ajmg.a.37763.

Luder HU. Malformations of the tooth root in humans. Front Physiol. 2015;6:307. doi: 10.3389/fphys.2015.00307.

Luo E, Liu H, Zhao Q, Shi B, Chen Q. Dental-craniofacial manifestation and treatment of rare diseases. Int J Oral Sci. 2019;11(1):9. doi: 10.1038/s41368-018-0041-y.

Lutz JC, Nicot R, Schlund M, Schaefer E, Bornert F, Fioretti F, Ferri J. Dental and maxillofacial features of Noonan Syndrome: case series of ten patients. J Craniomaxillofac Surg. 2020;48(3):242-250. doi: 10.1016/j.jcms.2020.01.011.

Lyko K, Lemes AL, Bonfim C, Torres-Pereira CC, Amenábar JM. Oral health status in children and adolescents with Fanconi anemia. Spec Care Dentist. 2016;36(2):71-74. doi: 10.1111/scd.12151.

Mahmoud M, Alqabbani SA, Bedi SR, Sharma SV. Complete mouth rehabilitation in a patient with Fanconi anaemia: a rare genetic disorder. Journal of Clinical ; Diagnostic Research. 2024;18(3):SD04-SD06. doi: 10.7860/JCDR/2024/67539.19141.

Miranda F, Garib D, de Lima Netto BA, Lucena FS, da Silva Santos PS. Orthodontic intervention in Fanconi's anemia: a case report. Spec Care Dentist. 2020;40(4):382-389. doi: 10.1111/scd.12487.

Miziara RC, Mendes-Junior CT, Wiezel CEV, Simões AL, Scuoteguazza JAC, Azoubel R. A statistical study of the association of seven dental anomalies in the Brazilian population. Int J Morphol. 2008;26(2):403-406. doi:10.4067/S0717-95022008000200025.

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global.

Moreno OM, Paredes AC, Suarez-Obando F, Rojas A. An update on Fanconi anemia: clinical, cytogenetic and molecular approaches (Review). Biomed Rep. 2021;15(3):74. doi: 10.3892/br.2021.1450.

Nalepa G, Clapp DW. Fanconi anaemia and cancer: an intricate relationship. Nat Rev Cancer. 2018;18(3):168-185. doi: 10.1038/nrc.2017.116.

Nowzari H, Jorgensen MG, Ta TT, Contreras A, Slots J. Aggressive periodontitis associated with Fanconi's anemia. A case report. J Periodontol. 2001;72(11):1601-1606. doi: 10.1902/jop.2001.72.11.1601.

Oeschger ES, Kanavakis G, Halazonetis DJ, Gkantidis N. Number of teeth is associated with facial size in humans. Sci Rep. 2020;10(1):1820. doi: 10.1038/s41598-020-58565-8.

Olson TS. Management of Fanconi anemia beyond childhood. Hematology Am Soc Hematol Educ Program. 2023;2023(1):556-562. doi: 10.1182/hematology.2023000489.

Opinya GN, Kaimenyi JT, Meme JS. Oral findings in Fanconi's anemia. A case report. J Periodontol. 1988;59(7):461-463. doi: 10.1902/jop.1988.59.7.461.

Ozler CO, Mustuloglu S, Cemaloglu M, Turgut MD, Tekcicek MU, Gumruk F, Cangul SU. Oral health status of patients with inherited bone marrow failure syndromes. Pediatr Dent J. 2022;32(3):151-159. doi: 10.1016/j.pdj.2022.06.003.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.

Pavlič A, Matoh U, Rajić V, Petelin M. Effect of repeated antimicrobial photodynamic therapy in treatment of periodontitis associated with Fanconi anemia. Photomed Laser Surg. 2017;35(1):64-68. doi: 10.1089/pho.2016.4122.

Peake JD, Noguchi E. Fanconi anemia: current insights regarding epidemiology, cancer, and DNA repair. Hum Genet. 2022;141(12):1811-1836. doi: 10.1007/s00439-022-02462-9.

Petryk A, Kanakatti Shankar R, Giri N, Hollenberg AN, Rutter MM, Nathan B, Lodish M, Alter BP, Stratakis CA, Rose SR. Endocrine disorders in Fanconi anemia: recommendations for screening and treatment. J Clin Endocrinol Metab. 2015;100(3):803-811. doi: 10.1210/jc.2014-4357.

Prado HV, Soares ECB, Carneiro NCR, Vilar ICO, Abreu LG, Borges-Oliveira AC. Dental anomalies in individuals with osteogenesis imperfecta: a systematic review and meta-analysis of prevalence and comparative studies. J Appl Oral Sci. 2023;31:e20230040. doi: 10.1590/1678-7757-2023-0040.

Preudhomme R, Veyssiere A, Ambroise B, Benateau H. Hallermann Streiff syndrome: cranio-facial manifestations systematic review and report of two cases. J Stomatol Oral Maxillofac Surg. 2022;123(4):e219-e223. doi: 10.1016/j.jormas.2021.11.002.

Ruyssinck L, Toulouse K, Bordon Cueto de Braem V, Cauwels R, Dhooge C. Impact of hematopoietic stem cell transplantation on dental development. Biol Blood Marrow Transplant. 2019;25(1):107-113. doi: 10.1016/j.bbmt.2018.08.027.

Salinas A, Escamilla C, Rivera G, Martinez HR. Picture of the month-quiz case. Fanconi anemia. Arch Pediatr Adolesc Med. 2012;166(7):657-658. doi: 10.1001/archpediatrics.2012.189b.

Santana NCM, de Sena ACVP, Rocha PADS, de Arruda JAA, Torres-Pereira CC, Abreu LG, Fournier BPJ, Warnakulasuriya S, Silva TA. Oral cancer and oral potentially malignant disorders in patients with Fanconi anemia - A systematic review. Oral Oncol. 2024;150:106699. doi: 10.1016/j.oraloncology.2024.106699.

Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev. 2010;24(3):101-122. doi: 10.1016/j.blre.2010.03.002.

Solomon BD, Bear KA, Kimonis V, de Klein A, Scott DA, Shaw-Smith C, Tibboel D, Reutter H, Giampietro PF. Clinical geneticists' views of VACTERL/VATER association. Am J Med Genet A. 2012;158A(12):3087-3100. doi: 10.1002/ajmg.a.35638.

Souza-Silva BN, Vieira WA, Bernardino ÍM, Batista MJ, Bittencourt MAV, Paranhos LR. Non-syndromic tooth agenesis patterns and their association with other dental anomalies: a retrospective study. Arch Oral Biol. 2018;96:26-32. doi: 10.1016/j.archoralbio.2018.08.014.

Suda N, Moriyama K. Human diseases associated with abnormal tooth roots. J Oral Biosci. 2009;51(4):199-204. doi:10.1016/S1349-0079(09)80004-2.

Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment. A literature review. Am J Orthod Dentofacial Orthop. 2004;126(4):432-445. doi: 10.1016/j.ajodo.2003.10.031.

Tekcicek M, Tavil B, Cakar A, Pinar A, Unal S, Gumruk F. Oral and dental findings in children with Fanconi anemia. Pediatr Dent. 2007;29(3):248-252.

Torlińska-Walkowiak N, Majewska KA, Sowińska A, Kędzia A, Opydo-Szymaczek J. Skeletal and dental age discrepancy and occlusal traits in children with growth

hormone deficiency and idiopathic short stature. Clin Oral Investig. 2022;26(10):6165-6175. doi: 10.1007/s00784-022-04566-y.

Torlińska-Walkowiak N, Majewska KA, Sowińska A, Kędzia A, Opydo-Szymaczek J. Developmental enamel defects and dental anomalies of number and size in children with growth hormone deficiency. Sci Rep. 2023;13(1):14707. doi: 10.1038/s41598-023-41892-x.

Touil D, Bouhouch R, Chebil RB, Oualha L, Douki N. Gingival bleeding in a child with Fanconi anemia: a case report and literature review. Case Rep Dent. 2020;2020:3161053. doi: 10.1155/2020/3161053.

van Gennip LLA, Bulthuis MS, Blijlevens NMA, Huysmans MDNJM, van Leeuwen SJM, Thomas RZ. Caries, periodontitis and tooth loss after haematopoietic stem cell transplantation: a systematic review. Oral Dis. 2023;29(7):2578-2591. doi: 10.1111/odi.14358.

Varela M, Arrieta P, Ventureira C. Non-syndromic concomitant hypodontia and supernumerary teeth in an orthodontic population. Eur J Orthod. 2009;31(6):632-637. doi: 10.1093/ejo/cjp046.

Vaughan MD, Rowland CC, Tong X, Srivastava DK, Hale GA, Rochester R, Kaste SC. Dental abnormalities after pediatric bone marrow transplantation. Bone Marrow Transplant. 2005;36(8):725-729. doi: 10.1038/sj.bmt.1705136.

Vucic S, Dhamo B, Jaddoe VWV, Wolvius EB, Ongkosuwito EM. Dental development and craniofacial morphology in school-age children. Am J Orthod Dentofacial Orthop. 2019;156(2):229-237.e4. doi: 10.1016/j.ajodo.2018.09.014.

Wagner VP, Arrué T, Hilgert E, Arús NA, da Silveira HLD, Martins MD, Rodrigues JA. Prevalence and distribution of dental anomalies in a paediatric population based on panoramic radiographs analysis. Eur J Paediatr Dent. 2020;21(4):292-298. doi: 10.23804/ejpd.2020.21.04.7.

Wenger TL, Earl D, Chow P, Sanchez-Lara PA. Role of pediatric geneticists in craniofacial teams: the identification of craniofacial conditions with cancer predisposition. J Pediatr. 2016;175:216-223.e1. doi: 10.1016/j.jpeds.2016.04.061.

Wickham H. ggplot2: elegant graphics for data analysis. Springer-Verlag New York, 2016. Available from: https://ggplot2.tidyverse.org.

Wise GE, Frazier-Bowers S, D'Souza RN. Cellular, molecular, and genetic determinants of tooth eruption. Crit Rev Oral Biol Med. 2002;13(4):323-334. doi: 10.1177/154411130201300403.

Yalman N, Sepet E, Aren G, Mete Z, Külekçi G, Anak S. The effect of bone marrow transplantation on systemic and oral health in Fanconi's aplastic anemia. J Clin Pediatr Dent. 2001;25(4):329-332.

Zen PRG, Moraes FN de, Rosa RFM, Graziadio C, Paskulin GA. Características clínicas de pacientes com anemia de Fanconi. Rev Paul Pediatr. 2011;29(3):392-399. doi: 10.1590/S0103-05822011000300.

6 CONSIDERAÇÕES FINAIS

Este estudo relatou a diversidade de anomalias dentárias e craniofaciais observadas em pacientes com FA. O reconhecimento desse amplo espectro de anomalias comumente encontradas em pacientes com FA, juntamente com sua natureza multissistêmica, é crucial para o manejo adequado. A FA necessita de acompanhamento sistemático por equipe multidisciplinar, principalmente devido ao potencial impacto dessas alterações na saúde geral e na qualidade de vida.

REFERÊNCIAS

AÇIKGÖZ, Aydan et al. Oral and dental findings in Fanconi's anemia. **Pediatric hematology and oncology**, v. 22, n. 6, p. 531-539, 2005.

AKSU, Tekin et al. Central nervous system lesions in Fanconi anemia: Experience from a research center for Fanconi anemia patients. **Pediatric Blood & Cancer**, v. 67, n. 12, p. e28722, 2020.

ALTAY, Çiğjdem et al. Analysis of 65 Turkish patients with congenital aplastic anemia (Fanconi anemia and non-Fanconi anemia): Hacettepe experience. **Clinical genetics**, v. 51, n. 5, p. 296-302, 1997.

ALTER, Blanche P. Cancer in Fanconi anemia, 1927–2001. **Cancer**, v. 97, n. 2, p. 425-440, 2003.

ALTER, Blanche P.; GIRI, Neelam. Thinking of VACTERL-H? Rule out Fanconi Anemia according to PHENOS. **American journal of medical genetics Part A**, v. 170, n. 6, p. 1520-1524, 2016.

ALTER, Blanche P. Inherited bone marrow failure syndromes: considerations pre- and posttransplant. Hematology 2014, **the American Society of Hematology Education Program Book**, v. 2017, n. 1, p. 88-95, 2017.

ALTER, Blanche P. et al. Cancer in the National Cancer Institute inherited bone marrow failure syndrome cohort after fifteen years of follow-up. **Haematologica**, v. 103, n. 1, p. 30, 2018.

ALTER, Blanche P. Fanconi's anemia, transplantation, and cancer. **Pediatric transplantation**, v. 9, p. 81-86, 2005.

ALTINTAS, Burak et al. Genotype-phenotype and outcome associations in patients with Fanconi anemia: the National Cancer Institute cohort. **Haematologica**, v. 108, n. 1, p. 69, 2023.

AMENÁBAR, José M. et al. Two enemies, one fight: an update of oral cancer in patients with Fanconi anemia. **Cancer**, v. 125, n. 22, p. 3936-3946, 2019.

AUERBACH, Arleen D. Fanconi anemia and its diagnosis. **Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis**, v. 668, n. 1-2, p. 4-10, 2009.

AUERBACH, Arleen D.; WOLMAN, Sandra R. Susceptibility of Fanconi's anaemia fibroblasts to chromosome damage by carcinogens. **Nature**, v. 261, n. 5560, p. 494-496, 1976.

AUERBACH, Arleen D. Fanconi anemia. **Dermatologic clinics**, v. 13, n. 1, p. 41-49, 1995.

DE CASTRO AVILA, Lucia Fátima et al. A study of facial pattern in patients with

fanconi anemia. **The Cleft Palate-Craniofacial Journal**, v. 51, n. 1, p. 83-89, 2014.

CANCIO, Maria et al. Predictors of outcomes in hematopoietic cell transplantation for Fanconi anemia. **Bone Marrow Transplantation**, v. 59, n. 1, p. 34-40, 2024.

CECCALDI, Raphael; SARANGI, Prabha; D'ANDREA, Alan D. The Fanconi anaemia pathway: new players and new functions. **Nature reviews Molecular cell biology**, v. 17, n. 6, p. 337-349, 2016.

CHEN, Qiming et al. A genetic-phenotypic classification for syndromic micrognathia. **Journal of Human Genetics**, v. 64, n. 9, p. 875-883, 2019.

DAHLLÖF, Göran. Oral and dental late effects after pediatric stem cell transplantation. **Biology of Blood and Marrow Transplantation**, v. 14, n. 1, p. 81-83, 2008.

DAVIDOPOULOU, Sotiria; CHATZIGIANNI, Athina. Craniofacial morphology and dental maturity in children with reduced somatic growth of different aetiology and the effect of growth hormone treatment. **Progress in orthodontics**, v. 18, n. 1, p. 10, 2017.

DE ARAÚJO, M. R. et al. Fanconi's anemia: clinical and radiographic oral manifestations. **Oral Diseases**, v. 13, n. 3, p. 291-295, 2007.

DE KERVILER, E. et al. The Clinical and Radiological Features of Fanconi's Anaemia: Pictorial Review. **Clinical radiology**, v. 55, n. 5, p. 340-345, 2000.

DE LA DURE-MOLLA, Muriel et al. Elements of morphology: Standard terminology for the teeth and classifying genetic dental disorders. **American Journal of Medical Genetics** Part A, v. 179, n. 10, p. 1913-1981, 2019.

DUFOUR, Carlo; PIERRI, Filomena. Modern management of Fanconi anemia. **Hematology**, v. 2022, n. 1, p. 649-657, 2022.
DUPRE, Nicolas et al. Root resorptions induced by genetic disorders: A systematic review. **Oral Diseases**, 2024.

FALCI, Saulo Gabriel Moreira et al. Anemia de Fanconi em odontologia: relato de caso e breve revisão da literatura. **Revista Odonto Ciência**, v. 26, p. 272-276, 2011.

FANCONI ANEMIA RESEARCH FUND. Fanconi Anemia Clinical Care Guidelines. 5. ed. 2020. Disponível em: <https://www.fanconi.org/images/uploads/other/Fanconi_Anemia_Clinical_Care_Guidelines_5thEdition_web.pdf>. Acesso em: 2022.

FANCONI, Guido. Familiare infantile perniciosaartige Anamia (pernicioses Blutbild und Konstitution). **Jahb Kinderheikd**, v. 117, p. 257-280, 1927.

FARGO, John H. et al. Comparison of chromosome breakage in non-mosaic and mosaic patients with Fanconi anemia, relatives, and patients with other inherited bone marrow failure syndromes. **Cytogenetic and genome research**, v. 144, n. 1,

p. 15-27, 2014.

FERNANDES, Karin S. et al. Oral health and dental abnormalities in children submitted to HSCT dental abnormalities after HSCT. **International Journal of Clinical Dentistry**, p. 73, 2015.

FIESCO-ROA, Moisés O. et al. Genotype-phenotype associations in Fanconi anemia: a literature review. **Blood reviews**, v. 37, p. 100589, 2019.

GIRI, Neelam et al. Endocrine abnormalities in patients with Fanconi anemia. **The Journal of Clinical Endocrinology & Metabolism**, v. 92, n. 7, p. 2624-2631, 2007.

GOMES, Patrícia Nóbrega et al. Microcephaly as a risk factor for dental alterations: A case-control study. **Oral Diseases**, v. 29, n. 5, p. 2265-2271, 2023.

GOSWAMI, Mridula; BHUSHAN, Urvashi; GOSWAMI, Manoj. Dental perspective of rare disease of Fanconi anemia: case report with review. **Clinical Medicine Insights: Case Reports**, v. 9, p. CCRep. S37931, 2016.

HADDAWAY, Neal Robert et al. The role of Google Scholar in evidence reviews and its applicability to grey literature searching. **PloS one**, v. 10, n. 9, p. e0138237, 2015.
HAENDEL, Melissa et al. How many rare diseases are there? **Nature reviews drug discovery**, v. 19, n. 2, p. 77-78, 2020.

JOHNSON-TESCH, Benjamin A. et al. Fanconi anemia: correlating central nervous system malformations and genetic complementation groups. **Pediatric radiology**, v. 47, p. 868-876, 2017.

KOTTEMANN, Molly C.; SMOGORZEWSKA, Agata. Fanconi anaemia and the repair of Watson and Crick DNA crosslinks. **Nature**, v. 493, n. 7432, p. 356-363, 2013.

KNOTTNERUS, Andre; TUGWELL, Peter. STROBE--a checklist to Strengthen the Reporting of Observational Studies in Epidemiology. **Journal of clinical epidemiology**, v. 61, n. 4, p. 323, 2008.

KUNZ, Felix et al. Characteristic dental pattern with hypodontia and short roots in Fraser syndrome. **American Journal of Medical Genetics** Part A, v. 182, n. 7, p. 1681-1689, 2020.

KUTLER, David I. et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. **Archives of otolaryngology–head & neck surgery**, v. 129, n. 1, p. 106-112, 2003.

LAGANÀ, G. et al. Dental anomalies: prevalence and associations between them in a large sample of non-orthodontic subjects, a cross-sectional study. **BMC oral health**, v. 17, p. 1-7, 2017.

LUBINSKY, Mark; KANTAPUTRA, Piranit Nik. Syndromes with supernumerary teeth. **American Journal of Medical Genetics Part A**, v. 170, n. 10, p. 2611-2616, 2016.
LUO, En et al. Dental-craniofacial manifestation and treatment of rare diseases.

International journal of oral science, v. 11, n. 1, p. 9, 2019.

LUTZ, Jean-Christophe et al. Dental and maxillofacial features of Noonan syndrome: case series of ten patients. **Journal of Cranio-Maxillofacial Surgery**, v. 48, n. 3, p. 242-250, 2020.

LYKO, Karine et al. Oral health status in children and adolescents with Fanconi anemia. **Special Care in Dentistry,** v. 36, n. 2, p. 71-74, 2016.

MAHMOUD, MAHA et al. Complete Mouth Rehabilitation in a Patient with Fanconi Anaemia: A Rare Genetic Disorder. **Journal of Clinical & Diagnostic Research**, v. 18, n. 3, 2024.

MARTELLI, Daniella Reis Barbosa; JÚNIOR, Hercílio Martelli. Undiagnosed and rare diseases: current challenges, perspectives and contribution of oral cavity examination. **Oral surgery, oral medicine, oral pathology and oral radiology**, v. 130, n. 2, p. 227-228, 2020.

MINISTÉRIO DA SAUDE. PORTARIA Nº 199, DE 30 DE JANEIRO DE 2014. **Política Nacional de Atenção Integral às Pessoas com Doenças Raras - PNAIPDR** Disponível em: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html

MIRANDA, Felicia et al. Orthodontic intervention in Fanconi's anemia: A case report. **Special Care in Dentistry**, v. 40, n. 4, p. 382-389, 2020.

MOOLA, SZCEKRE et al. Systematic reviews of etiology and risk. In: **Joanna Briggs Institute reviewer's manual**. Adelaide, Australia: The Joanna Briggs Institute, 2017. p. 217-69.

MORENO, Olga María et al. An update on Fanconi anemia: Clinical, cytogenetic and molecular approaches. **Biomedical reports**, v. 15, n. 3, p. 1-10, 2021.

NGUENGANG WAKAP, Stéphanie et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. **European journal of human genetics**, v. 28, n. 2, p. 165-173, 2020.

OLSON, Timothy S. Management of Fanconi anemia beyond childhood. **Hematology**, v. 2023, n. 1, p. 556-562, 2023.
OOSTRA, Anneke B. et al. Diagnosis of fanconi anemia: chromosomal breakage analysis. **Anemia**, v. 2012, 2012.

OPINYA, Gladys N.; KAIMENYI, Jacob T.; MEME, Julius S. Oral findings in Fanconi's anemia: a case report. **Journal of Periodontology**, v. 59, n. 7, p. 461-463, 1988.

ORPHANET. Orphanet: The portal for rare diseases and orphan drugs. Disponível em: (http://www.orphadata.org/cgi-bin/epidemio.html)

PEAKE, Jasmine D.; NOGUCHI, Eishi. Fanconi anemia: current insights regarding

epidemiology, cancer, and DNA repair. **Human Genetics**, v. 141, n. 12, p. 1811-1836, 2022.

PAGE, Matthew J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. **Bmj**, v. 372, 2021.

PAVLIČ, Alenka et al. Effect of repeated antimicrobial photodynamic therapy in treatment of periodontitis associated with Fanconi anemia. Photomedicine and Laser Surgery, v. 35, n. 1, p. 64-68, 2017.

PEFFAULT DE LATOUR, Régis et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. **Blood, The Journal of the American Society of Hematology**, v. 122, n. 26, p. 4279-4286, 2013.

PETRYK, Anna et al. Endocrine disorders in Fanconi anemia: recommendations for screening and treatment. **The Journal of Clinical Endocrinology & Metabolism**, v. 100, n. 3, p. 803-811, 2015.

PIROZZI, Filomena; NELSON, Branden; MIRZAA, Ghayda. From microcephaly to megalencephaly: determinants of brain size. **Dialogues in clinical neuroscience**, v. 20, n. 4, p. 267-282, 2018.

PRADO, Heloisa Vieira et al. Dental anomalies in individuals with osteogenesis imperfecta: a systematic review and meta-analysis of prevalence and comparative studies. **Journal of Applied Oral Science**, v. 31, p. e20230040, 2023.

RICHTER, Trevor et al. Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group. **Value in health**, v. 18, n. 6, p. 906-914, 2015.

ROSE, Susan R. et al. Endocrine phenotype of children and adults with Fanconi anemia. **Pediatric blood & cancer**, v. 59, n. 4, p. 690-696, 2012.

SANTANA, Nayara Conceição Marcos et al. Oral cancer and oral potentially malignant disorders in patients with Fanconi anemia–A systematic review. **Oral Oncology**, v. 150, p. 106699, 2024.

SASAKI, Masao S.; TONOMURA, Akira. A high susceptibility of Fanconi's anemia to chromosome breakage by DNA cross-linking agents. **Cancer research**, v. 33, n. 8, p. 1829-1836, 1973.

SHIMAMURA, Akiko; ALTER, Blanche P. Pathophysiology and management of inherited bone marrow failure syndromes. **Blood reviews**, v. 24, n. 3, p. 101-122, 2010.

SOBRINHO, Lívia Maria Ferreira et al. The role of dental phenotypes in the diagnosis of rare diseases: Multiprofessional experience. **Oral Surgery** (1752-2471), v. 15, n. 4, 2022.

SOCIETY FOR MATERNAL-FETAL MEDICINE et al. Micrognathia. American journal

of obstetrics and gynecology, v. 221, n. 5, p. B13-B15, 2019.

SOLOMON, Benjamin D. et al. Clinical geneticists' views of VACTERL/VATER association. **American Journal of Medical Genetics Part A**, v. 158, n. 12, p. 3087-3100, 2012.

SOUZA-SILVA, Bianca Núbia et al. Non-syndromic tooth agenesis patterns and their association with other dental anomalies: A retrospective study. **Archives of Oral Biology**, v. 96, p. 26-32, 2018.

TEKCICEK, Meryem et al. Oral and dental findings in children with Fanconi anemia. **Pediatric dentistry**, v. 29, n. 3, p. 248-252, 2007.

TORLIŃSKA-WALKOWIAK, Natalia et al. Skeletal and dental age discrepancy and occlusal traits in children with growth hormone deficiency and idiopathic short stature. **Clinical Oral Investigations**, v. 26, n. 10, p. 6165-6175, 2022.

TORLIŃSKA-WALKOWIAK, Natalia et al. Developmental enamel defects and dental anomalies of number and size in children with growth hormone deficiency. **Scientific Reports**, v. 13, n. 1, p. 14707, 2023.

VAN GENNIP, Lucky LA et al. Caries, periodontitis and tooth loss after haematopoietic stem cell transplantation: A systematic review. **Oral Diseases**, v. 29, n. 7, p. 2578-2591, 2023.

VARELA, Margarita; ARRIETA, Patricia; VENTUREIRA, Cesar. Non-syndromic concomitant hypodontia and supernumerary teeth in an orthodontic population. **The European Journal of Orthodontics**, v. 31, n. 6, p. 632-637, 2009.

VAUGHAN, M. D. et al. Dental abnormalities after pediatric bone marrow transplantation. **Bone marrow transplantation**, v. 36, n. 8, p. 725-729, 2005.

VON DER HAGEN, Maja et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. **Developmental Medicine & child neurology**, v. 56, n. 8, p. 732-741, 2014.

WISE, G. E.; FRAZIER-BOWERS, S.; D'SOUZA, R. N. Cellular, molecular, and genetic determinants of tooth eruption. **Critical Reviews in Oral Biology & Medicine**, v. 13, n. 4, p. 323-335, 2002.

YALMAN, N. et al. The effect of bone marrow transplantation on systemic and oral health in Fanconi's aplastic anemia. **The Journal of Clinical Pediatric Dentistry**, v. 25, n. 4, p. 329-332, 2001.

APÊNDICE A – Aprovação do Comitê de Ética em Pesquisa

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Plataforma Brasil

PARECER CONSUBSTANCIADO DA CONEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: AVALIAÇÃO CLÍNICA, MICROSCÓPICA E MOLECULAR DAS LESÕES ORAIS MALIGNAS E POTENCIALMENTE MALIGNAS NOS PACIENTES COM ANEMIA DE FANCONI - UM ESTUDO MULTICÊNTRICO

Pesquisador: Tarcília Aparecida da Silva

Área Temática: Genética Humana:
(Haverá envio para o exterior de material genético ou qualquer material biológico humano para obtenção de material genético, salvo nos casos em que houver cooperação com o Governo Brasileiro;);
(Haverá armazenamento de material biológico ou dados genéticos humanos no exterior e no País, quando de forma conveniada com instituições estrangeiras ou em instituições comerciais;);

Versão: 3

CAAE: 66312622.4.1001.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 6.254.512

Apresentação do Projeto:

As informações contidas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram obtidas dos documentos contendo as Informações Básicas sobre o Projeto de Pesquisa (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_2033791.pdf de 08/06/2023) e do Projeto Detalhado.

INTRODUÇÃO

A Anemia de Fanconi (AF) é um distúrbio de instabilidade genômica hereditária, caracterizada por anemia aplásica, pancitopenia progressiva e anomalias congênitas. Guido Fanconi relatou os primeiros casos dessa condição em 1927 em três irmãos com microcefalia, baixa estatura, hiperpigmentação cutânea, anemia macrocítica dentre outras. Atualmente a AF apresenta uma incidência de 1 em 300.000 nascidos vivos e uma prevalência de 1-9 por milhão. A proporção de casos entre homens e mulheres é de 1,2:1. Apesar do genótipo e fenótipo da AF estarem bem caracterizados, tendo sido pelo menos 22 genes identificados na via de reparo de DNA FA/BRCA,

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Telefone: (61)3315-5877 **E-mail:** conep@saude.gov.br

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Assentimento / Justificativa de Ausência	TALE12a17anosv3.pdf	11:18:43	da Silva	Aceito
Projeto Detalhado / Brochura Investigador	projetov3.pdf	08/06/2023 11:18:19	Tarcília Aparecida da Silva	Aceito
Outros	Respostaparecer.pdf	24/02/2023 16:39:05	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TALE.pdf	24/02/2023 16:37:42	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEmaiores18anos.pdf	24/02/2023 16:37:31	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEpaisresponsaveis.pdf	24/02/2023 16:37:16	Tarcília Aparecida da Silva	Aceito
Outros	Termo_de_Constituicao_de_Biorrepositorio_vf.pdf	18/12/2022 16:46:00	Tarcília Aparecida da Silva	Aceito
Projeto Detalhado / Brochura Investigador	projetoaffinal.pdf	18/12/2022 16:41:12	Tarcília Aparecida da Silva	Aceito
Outros	anuenciahc.pdf	18/12/2022 16:40:53	Tarcília Aparecida da Silva	Aceito
Folha de Rosto	folhaDeRostoassinadadiretoria.pdf	15/10/2022 08:43:52	Tarcília Aparecida da Silva	Aceito
Declaração de concordância	Pareceraprovadocpc.pdf	15/10/2022 08:42:59	Tarcília Aparecida da Silva	Aceito

Situação do Parecer:
Aprovado

BRASILIA, 29 de Agosto de 2023

Assinado por:
Laís Alves de Souza Bonilha
(Coordenador(a))

APÊNDICE B – Ficha padronizada para coleta da dados

FICHA CLÍNICA

Nome Completo: _____

N° do Prontuário: _____ N° Ficha: _____

Idade: _____ Gênero: _____ Cor: _____

Altura/ Peso: _____

Idade do Diagnóstico: _____

Método Diagnóstico: _____

Pais Consanguíneos: _____

Algum outro membro da família é portador de AF? _____

Vacinação completa? _____

Vacina HPV: _____ Histórico de infecção por HPV? _____

Histórico TMO

Data: _____

Método/ Doador (a) é membro familiar? _____

Intercorrências durante o TMO? _____

Queixas pós TMO: _____

Histórico de GVHD: Sim ( ) Não ( )

Especifique: _____

Alterações em Pele:

Caso haja alteração em pele, especifique: _____

_____

Hemograma Recente:

Avaliar histórico ou presença de:
Equimoses: Sim ( ) Não ( )
Hematomas: Sim ( ) Não ( )
Petéquias: Sim ( ) Não ( )
Infecções: Sim ( ) Não ( )
Linfadenopatias: Sim ( ) Não ( )

Histórico de Transfusão? Sim ( ) Não ( )

Caso haja histórico de transfusão, especifique: _____

_____

Medicamentos em Uso:

Alteração em membros superiores? Sim ( ) Não ( )

Caso haja alteração, especifique: (Descrever se a alteração presente é bilateral e/ou simétrica).

Alterações na Face

Exame Físico Regional
Face triangular: Sim ( ) Não ( )
Orelhas em abano: Sim ( ) Não ( )
Assimetria – Deformidade : Sim ( ) Não ( )
Desvio dos olhos: Sim ( ) Não ( )
Alteração do tamanho dos olhos: Sim ( ) Não ( )
Lesão de Pele: Sim ( ) Não ( )
Outros:

Caso haja alteração, especifique: _____

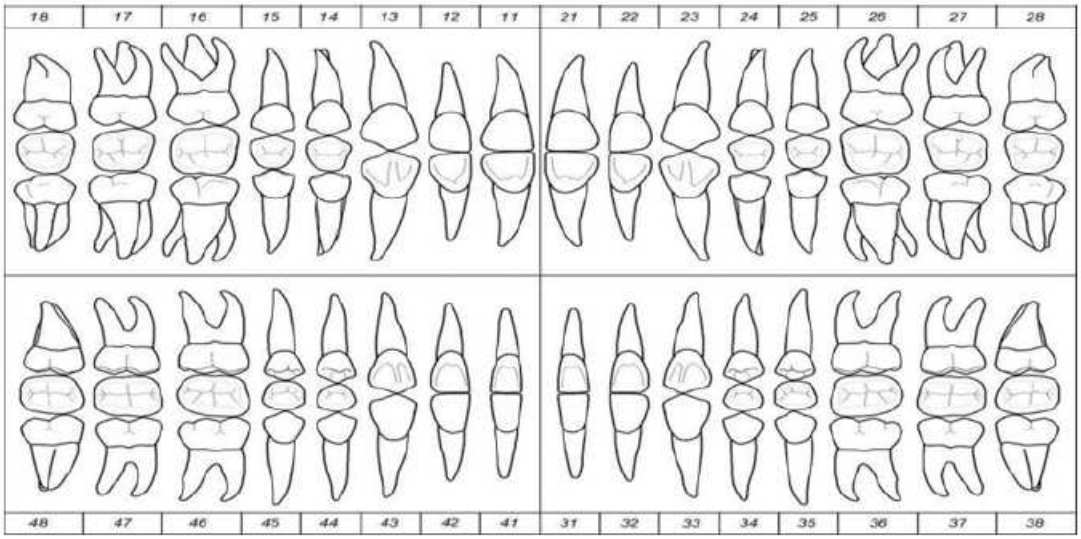
_____

Envolvimento Ganglionar

Descrição Clínica de Gânglios
Cadeia: não palpável ( ) Submandibular ( ) Cervical ( ) Submentoniano ( ) Outros ( ) (especifique)
Consistência: Normal ( ) Fibroelástico ( ) Ósseo-pétreo ( ) Mole ( ) Flutuante ( ) Cístico ( )
Sensibilidade: Normal ( ) Dolorido ( ) Discretamente dolorido ( )
Tamanho: Largura/Diâmetro/ Altura x x cm
Lateralidade: Direito ( ) Esquerdo ( ) Bilateral ( ) Mediano ( )
Número: Único ( ) Múltiplo ( ) Generalizado ( )
Aderência: Móvel ( ) Semifixo ( ) Fixo ( )
Superfície: Liso ( ) Irregular ( )

Exame Clínico intra – oral

Odontograma:



Índice de Placa Silness & Löe

0- Ausência de doença

1- Presença de placa supra gengival, estendendo-se até 1/3 da superfície exposta do dente.

2- Presença de placa bacteriana supra gengival, cobrindo mais de 1/3 e menos de 2/3 da superfície exposta.

3- Presença de placa supra gengival, cobrindo mais de 2/3 da superfície exposta do dente.

Significados:

1- ÓTIMO = 0 A 16%

2- BOM = 16 A 33%

3- MAU = 33 A 66%

4- PÉSSIMO = 66 A 100%

Dentes	Dentes	Dentes	Subtotal	Total	Percentual/significado
18,17,16,15,14	13,12,11,21,22,23	24,25,26,27,28			
Dentes	Dentes	Dentes	Subtotal		
48,47,46,45,44	43,42,41,31,32,33	34,35,36,37,38			

Periograma:

Dente	Profundidade de sondagem				Nível de Inserção Clínico				Sangramento à Sondagem			
	D	V	M	L	D	V	M	L	D	V	M	L
18												
17												
16												
15												
14												
13												
12												
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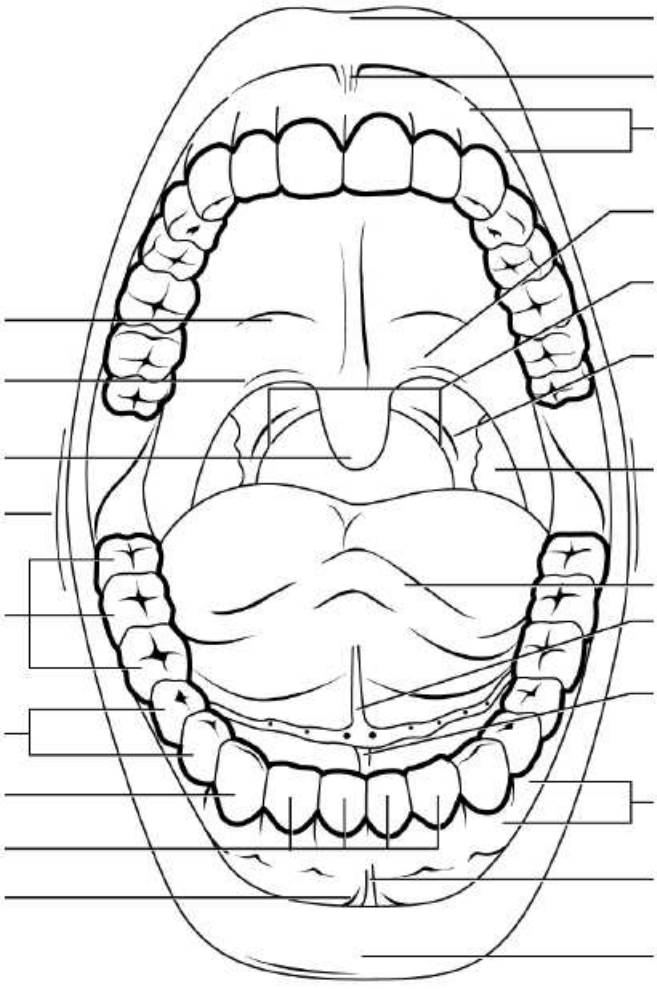
48												

Lesões Orais:



Anterior view