TRABAJO DE FIN DE GRADO

Grado en Odontología

MANIFESTACIONES ORALES, BUCALES Y FACIALES DE LA COVID 19 EN EL NIÑO

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RESUMEN

INTRODUCCIÓN En el mes de diciembre de 2019 un nuevo *virus* comúnmente conocido como Coronavirus, Covid-19 o mejor SARS-CoV-2, se descubrió por primera vez en Wuhan. El nuevo *virus* se expandió de manera rápida a nivel mundial, así que la Organización Mundial de la Salud (OMS) declaró la emergencia a nivel sanitario y después elevó la alarma al nivel de pandemia.

OBJETIVOS El objetivo general es conocer las manifestaciones orales y faciales presentes en niños afectados por la Covid-19.

MATERIALES Y METODOS Se realizó una búsqueda bibliográfica mediante diferentes bases de datos como PubMed, Medline complete a través de la biblioteca "CRAI Dulce Chacón" de la Universidad Europea de Madrid obteniendo artículos de revistas de impacto.

DISCUSIÓN La enfermedad se manifestó con varios síntomas comunes como fiebre y tos hasta que progresó a una crisis respiratoria severa o incluso a la muerte. Los pacientes se subdividen en sintomáticos y asintomáticos, y los niños son más asintomáticos en comparación con los adultos. Manifestaciones relevantes de la enfermedad también son la depapilación de la lengua con la consecuente pérdida del gusto y los exantemas faciales que son características de detección temprana de la Covid-19.

CONCLUSIÓN No existe un tratamiento específico, es principalmente sintomático según la gravedad de la enfermedad. La prevención para evitar el contagio es fundamental y por ello las medidas de seguridad en el consultorio odontológico son de gran importancia para la protección del paciente y del odontólogo o asistente.

PALABRAS CLAVES manifestaciones clínicas por Covid-19, manifestaciones orales pediátricas por Covid-19, manifestaciones faciales por Covid-19.

ABSTRACT

INTRODUCTION In the month of December 2019, a new *virus* commonly known as Coronavirus, Covid-19 or better SARS-CoV-2, was discovered for the first time in Wuhan. The new *virus* spread rapidly worldwide, so the World Health Organization (WHO) declared a health level emergency and then raised the alarm to the level of a pandemic.

OBJECTIVES The main objective is to know the oral and facial manifestations present in children affected by Covid19.

MATERIALS AND METHODS A bibliographic search was carried out using different databases such as PubMed, Medline complete through the "CRAI Dulce Chacon" library of the European University of Madrid, obtaining articles from high-impact journals.

DISCUSSION The disease manifested itself with several common symptoms such as fever and cough until it progressed to severe respiratory crisis or even death. Patients can be divided into symptomatic and asymptomatic, and children are more asymptomatic compared to adults. Relevant manifestations of the disease are also tongue depapillation with consequent loss of taste and facial exanthemas, that are early detection features of Covid-19.

CONCLUSION There is no specific treatment, it is mainly symptomatic depending on the severity of the disease. Prevention to avoid contagion is fundamental and therefore the safety measures in the dental office are of great importance for the protection of the patient and the dentist or assistant.

KEYWORDS *clinical manifestation for covid, oral pediatric manifestation for covid, facial manifestation for covid.*

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1. INTRODUCCIÓN

En el mes de diciembre de 2019, por primera vez en Wuhan en la comunidad del Hubei en China, se detectó el primer caso de una nueva neumonía, al principio de origen desconocida, a la que posteriormente se denominó Síndrome respiratorio agudo severo, más conocido como SARS-CoV-2 o Covid-19. El agente etiológico se identificó como un β-coronavirus, el *virus* SARS-Covid-19. Este *virus* pertenece a la familia de los Coronaviridae y a la subfamilia de Orthocoronavirinae y está dividido en varios subtipos como el Alphacoronavirus, Betacoronavirus, Gammacoronavirus y Deltacoronavirus [(1)(2)]. Los más conocidos de la familia de Betacoronavirus son 3 : SARS-CoV-1, SARS-CoV-2 y MERS-Cov [(1)(3)(4)].

La transmisión del Coronavirus a través de gotitas respiratorias de persona a persona ha dado origen a un brote mundial definido pandemia el 11 de marzo de 2020 por la OMS. El SARS se desarrolló en los primeros años 2000, en China y puede desarrollar hasta una insuficiencia respiratoria progresiva muy grave. Se transmitió por primera vez de un búho a una persona, y luego de persona a persona a través de contacto personal y gotitas respiratorias de tos. El MERS se extendió al Medio Oriente, principalmente en la península Arábiga, en el Junio de 2012 y se transmitió de un dromedario a una persona, para extenderse después de persona a persona con gran rapidez [(4)].

Respecto a la patología, SARS y MERS llegan a provocar infecciones respiratorias potencialmente mortales [(1)]. Las personas que están afectadas se dividen en sintomáticas y asintomáticas. La mayor parte de los casos sintomáticos se han producido en la población adulta y los síntomas más comunes desarrollados son fiebre, tos, fatiga y malestar general

mientras los niños presentan síntomas más leves. Presenta alta infectividad, lo que hace que este *virus* resulte más peligroso respeto a una normal gripe estacional [5][6][7].

Para la diagnosis precoz del *virus* hay varios tipos de test entre los cuales el test molecular o PCR presenta más evidencia clínica, aunque hay también test serológicos que con la detección de las inmunoglubolinas IgM y IgG han permitido la diagnosis serológica [8][9]. También es importante la tomografía para la diagnosis y el seguimiento de la enfermedad, verificando las complicaciones, fundamentalmente a nivel pulmonar.

El tratamiento todavía no es único para todos y se ajusta de persona a persona según los síntomas que el paciente presenta aunque ahora las principales terapias son los fármacos antivirales y el oxígeno [10].

En este trabajo se realiza un análisis sobre la enfermedad de la Covid-19 con su sintomatología, diagnosis y posibles soluciones terapéuticas, prestando especial atención a las manifestaciones en los niños, y sobre todo en sus repercusiones a nivel bucal y facial.

2. OBJETIVOS

El objetivo general es conocer las manifestaciones orales y faciales presentes en niños afectados por la Covid-19.

Los objetivos específicos del presente trabajo son:

- Ilustrar que es la Covid-19, hablar de su genoma, patogenia y diagnostico;
- Describir los principales síntomas y las manifestaciones clínicas y generales de la Covid-19;
- Determinar con particular atención las manifestaciones orales, bucales y faciales de la Covid-19 en los niños;

- Explicar los posibles tratamientos para el Covid-19 a nivel sistémico y específicamente a nivel facial y oral en el paciente infantil;
- Identificar las posibles medidas preventivas en la consulta dental para el odontólogo y para el paciente.

3. METODOLOGIA

Para realizar el estudio se realizó una búsqueda bibliográfica mediante diferentes bases de datos como Pubmed, Medline complete, PMC y Access Medicine a través del portal digital de la biblioteca "CRAI Dulce Chacon" de la Universidad Europea de Madrid. De estas bases de datos se han obtenido artículos de varias revistas, como "The Lancet", "Journal of Medical Virology", "The New England Journal of Medicine", "Internation Journal of pediatric dentistry", "Journal of Clinical Virology". Por otro lado, se utilizaron también páginas web de la OMS o de la CDC. Las imágenes 1 y 4 de elaboración propia se realizaron a través del programa Biorender.com.

Para la búsqueda se han utilizado palabras clave como Covid-19, SARS-Covid-19, *oral manifestation for covid, clinical manifestation for covid, oral pediatric manifestation for covid, virus, facial manifestation for covid*. La información obtenida es reciente al ser una temática de gran relevancia en la actualidad. Los criterios de inclusión han sido:

1. Artículos referentes a la Covid-19, en adultos y niños, y con especial relevancia, aquellos que hagan referencia a los síntomas orales, bucales y faciales en población infantil.

2. Artículos con texto completo, publicados principalmente en los años 2019, 2020 y 2021 en revistas médicas y odontológicas de impacto y algunos más antiguos publicados en 2005, 2006 y 2015 relacionados al MERS y la estructura de la SARS en general.

3. Artículos con texto completo en idioma inglés, español, italiano y francés.

Los articulos que no han cumplido los requisitos se han excluido automaticamente. Para la realización del trabajo al final se han utilizado 60 artículos.

4. DISCUSIÓN Y RESULTADOS

A continuación, desarrollaremos los resultados obtenidos.

4.1. GENERALIDAD DEL CORONAVIRUS

4.1.1 ESTRUCTURA DEL CORONAVIRUS

Los *virus*, palabra latina que a nivel etiológico significa "veneno", son pequeñas partículas con una organización estructural muy simple, constituidas por DNA o RNA. Los Coronavirus presentan una estructura redonda y son de dimensiones muy pequeñas. Están formados por Rna y proteína N, envoltura, proteína E, proteína M, dímero hemoglutinina esterasa y glicoproteína S.

La glicoproteína S es la que más se destaca a nivel de importancia respeto al Coronavirus. Se localiza en las proyecciones situadas en la superficie del virus. Se produce una unión entre 3 de ellas y van a formar un trímero; todos los trímeros se juntan y rodean el virión [(11)(12)]. Esta glicoproteína concreta es la que determina la especificidad del *virus* por las células epiteliales respiratorias. Es la proteína encargada de la entrada del virión en la célula interactuando con algunos receptores del huésped. Para que el *virus* se una a los receptores del huésped, tiene lugar una división de la proteína S en dos subunidades más pequeñas denominadas S1 y S2. La subunidad S1 es la que se une al receptor del huésped, en este caso al receptor de enzima convertidora de angiotensina II mientras la subunidad S2 es la que se encarga de que el *virus* entre en la célula para luego infectarla [(11)].

La proteína M es la más abundante en la estructura de la SARS-CoV-2 y es la que pasa a través de la envoltura interactuando dentro de la célula con el conjunto RNA-proteína dando encaje al coronavirus [11][13].

La proteína E, al contrario de la proteína M, es la más pequeña de la estructura y la más críptica. Presenta un papel esencial en la patogenia, en el encaje y liberación del *virus* [11][14]. Además, ayuda la glicoproteína S a adherirse a la membrana de la célula diana.

La proteína N presenta diferentes funciones, se une a la hebra positiva de RNA en el genoma del *virus* que aumenta su estabilidad [15], luego facilita la eficacia en la transcripción del *virus* y además interacciona con la proteína M en la formación del virión [11][16].

El dímero hemaglutinina esterasa es la proteína que rodea todo y actúa en la fase de liberación del *virus* [15].

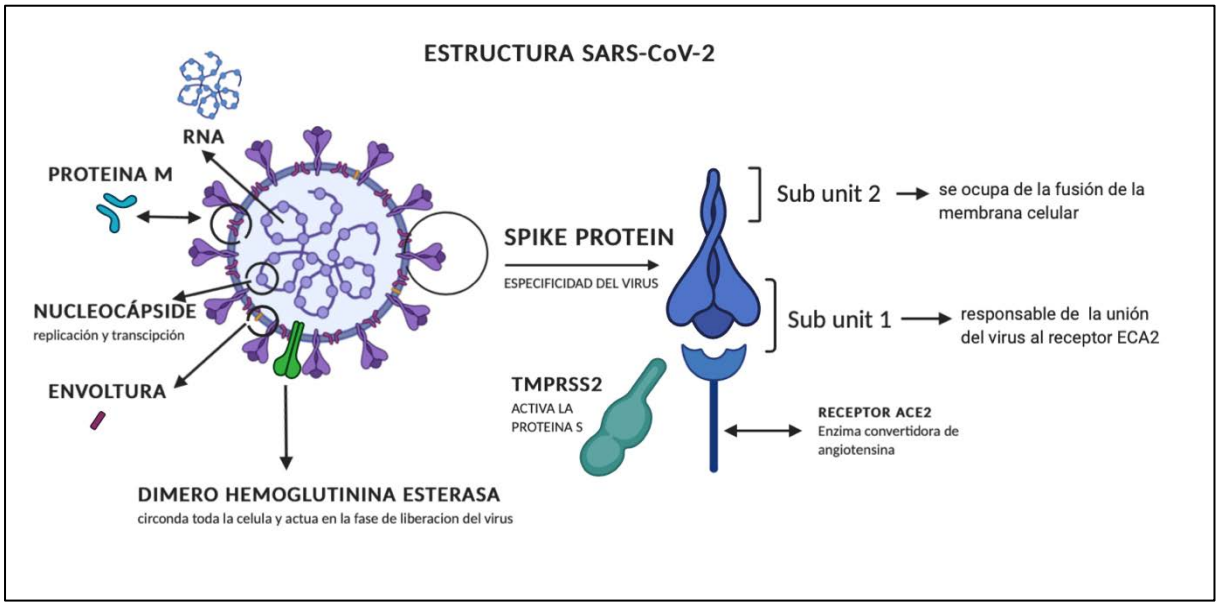

Figura 1. Estructura de la Covid-19. Dibujo de elaboración propia a través de biorender.com

4.1.2 PATOGENIA DEL VIRUS

El SARS-CoV-2 a través de la proteína S se une a la enzima convertidora de angiotensina o ACE2 permitiendo que el *virus* ingrese al interior de la célula, infectándola. Para que la Covid-19 complete la entrada en la célula después de este proceso inicial, la proteína de pico tiene que ser cebada por la proteasa. La proteasa llamada TMPRSS2, para completar el proceso de infección, se tiene que activar para poder obtener la unión del receptor del *virus* a la enzima convertidora de angiotensina. Después de la entrada del *virus* en la célula huésped, el genoma se transcribe y traduce. La replicación y transcripción del genoma del Coronavirus tiene lugar en las membranas citoplasmáticas y implican proceso coordinados de síntesis de ARN de manera continúa y discontinua [(17)(18)].

7.1.3 INCIDENCIA DEL VIRUS

El Sars-CoV-2 o simplemente llamado Covid-19, es el que hoy en día ha afectado a toda la población mundial, creando un escenario nunca visto antes. Ese *virus* es un *virus* RNA con envoltura, que puede causar enfermedad respiratoria de diversa gravedad a partir del normal resfriado hasta llegar a la neumonía mortal. Se desarrolló por primera vez en Hubei, en la ciudad de Wuhan, en China, a finales de 2019, hasta llegar a todo el mundo en solo pocos meses, debido a presentar una transmisión rápida e importante de persona a persona [(19)]. Los países afectados por el *virus* fueron muchos; en Europa, destacan Italia, con Bérgamo que fue uno de los focos principales de la epidemia italiana, España con Madrid que fue una de las ciudades más afectadas en toda Europa, así como Inglaterra, China e India en Asia, Estados Unidos y Brasil en el continente americano [(11)].

4.1.4 DIAGNOSTICO DE LA COVID

Para diagnosticar la Covid-19 tenemos dos tipos de pruebas principales que son el test molecular o PCR y el test serológico. **El test molecular** es el más preciso de los dos, ya que está basado en el material genético viral y dice si el *virus* está activo en una persona [20]. La prueba de PCR consiste en una colección de muestras de las vías respiratorias nasofaríngea y orofaríngea que detecta si existe o no infección en el momento en el cual se realiza el test [10].

El **test serológico** está basado en los anticuerpos contra las proteínas virales y con este se detectan las inmunoglobulinas IgM, IgG y IgA. IgM se localiza en la sangre y en el líquido linfático y es el primer anticuerpo que se desarrolla para combatir una nueva infección. IgG es la inmunoglobulina más abundante en el cuerpo humano y sirve de protección contra las bacterias y las infecciones víricas pero con respeto a IgM tarda algunos días en formarse. El test serológico en concreto sirve para saber si una persona ha tenido la infección o si está protegida contra ella[8][20].

Cuando IgM es positivo se confirma que el paciente ha tenido la enfermedad en pasado, pero no afirma si en este momento la infección está todavía activa y en consecuencia si el individuo presenta la enfermedad [8]. IgM es la primera respuesta de defensa inmunitaria y se desarrolla después, a partir de 3 días de la infección, aumentando durante la semana sucesiva progresivamente llegando a su pico en 2 semanas, aunque luego se reduce su nivel.

IgG juega un papel clave en la inmunidad a lo largo del tiempo y generalmente se genera después de una semana llegando a su pico en 3 semanas mientras se mantiene principalmente por un periodo de tiempo de más de 48 días. Cuando IgG es positivo significa que la fase de la

enfermedad está casi o ya del todo solucionada. Mientras cuando tenemos IgM negativo, si está asociado a IgG también negativos se habla de una fase inicial de la infección, mientras cuando IgM es negativo e IgG es positivo refiere que la enfermedad está en la fase final o ya se ha solucionado [8].

En la siguiente tabla se detallan las diferentes fases de la enfermedad por Coronavirus según su evolución relacionadas con el resultado de la PCR y de las inmunoglobulinas IgG y IgM.

PCR POSITIVO	**IgG**	**IgM**	**Resultado clínico**
Positivo	Negativo	Negativo	Fase inicial de la enfermedad
Positivo	Negativo	Positivo	Fase intermedia de la enfermedad
Positivo	Positivo	Negativo	Fase final de la enfermedad

Figura 2. Interpretacion de los resultados del PCR positivo relacionado con los valores de IgG y IgM. (Tabla de elaboración propia a partir de datos recogidos en la referencia [8])

PCR NEGATIVO	**IgG**	**IgM**	**Resultado clínico**
Negativo	Positivo	Positivo	Fase de recuperación de la enfermedad
Negativo	Negativo	Positivo	Fase intermedia de la enfermedad
Negativo	Positivo	Negativo	Fase ya solucionada de la enfermedad

Figura 3. Interpretación de los resultados del PCR negativo relacionado con los valores de IgG y IgM. (Tabla de elaboración propia a partir de datos recogidos en la referencia [8])

4.1.5 TRATAMIENTO DE LA COVID

Hasta ahora no hay un tratamiento antiviral específico universal aprobado que sea igual para todos los pacientes que presenten el *virus*. Dependiendo de la gravedad de la enfermedad se actuará de manera diferente. En los casos leves el tratamiento será sintomático, mientras para los casos más graves que precisen ingreso en los centros hospitalarios, además de un tratamiento específico para aliviar los síntomas, se necesitará también oxigenoterapia o en los casos más severos soporte respiratorio. Remdesivir es uno de los fármacos más usados en casos severos de paciente con la Covid-19 [(10)].

4.2. SINTOMAS Y MANIFESTACIONES CLINICAS GENERALES

El curso de la enfermedad varia de persona a persona y puede cambiar de una infección asintomática hasta una neumonía grave que puede llegar a ser mortal. Las formas asintomáticas son más frecuentes en los niños o adolescentes mientras en los adultos con una edad mayor a los 65 años hay más probabilidad de encontrar una forma grave. Hay varias manifestaciones sistémicas a nivel pulmonar, gastrointestinal, circulatorio, neurológico o cutáneo.

El periodo de incubación de la Sars-CoV-2 varía de 2 hasta 14 días y el síntoma más común en todas las personas afectadas es la fiebre. Sigue la tos con un porcentaje ligeramente menor. Menos frecuentes son la falta de aliento, el cansancio, escalofríos, problemas respiratorios, dolores musculares, garganta inflamada, pérdida de gusto y/o olfato [(20)]. También existen síntomas menos comunes de encontrar como odinofagia, vómitos, diarrea y hemoptisis.

En el curso de la enfermedad pueden aparecer complicaciones graves como disnea, cardiopatías, arritmias, miocardiopatía, trastornos de la coagulación, septicemia, fallo de varios órganos y síndrome de Guillain-Barré [19]. Aparte de los síntomas que puede presentar un paciente con esa patología, en su historia clínica puede presentar linfocitopenia, leucopenia, disfunción renal y hepática, alteraciones cardiacas e inflamatorios elevadas y además niveles de albúmina disminuidos [21].

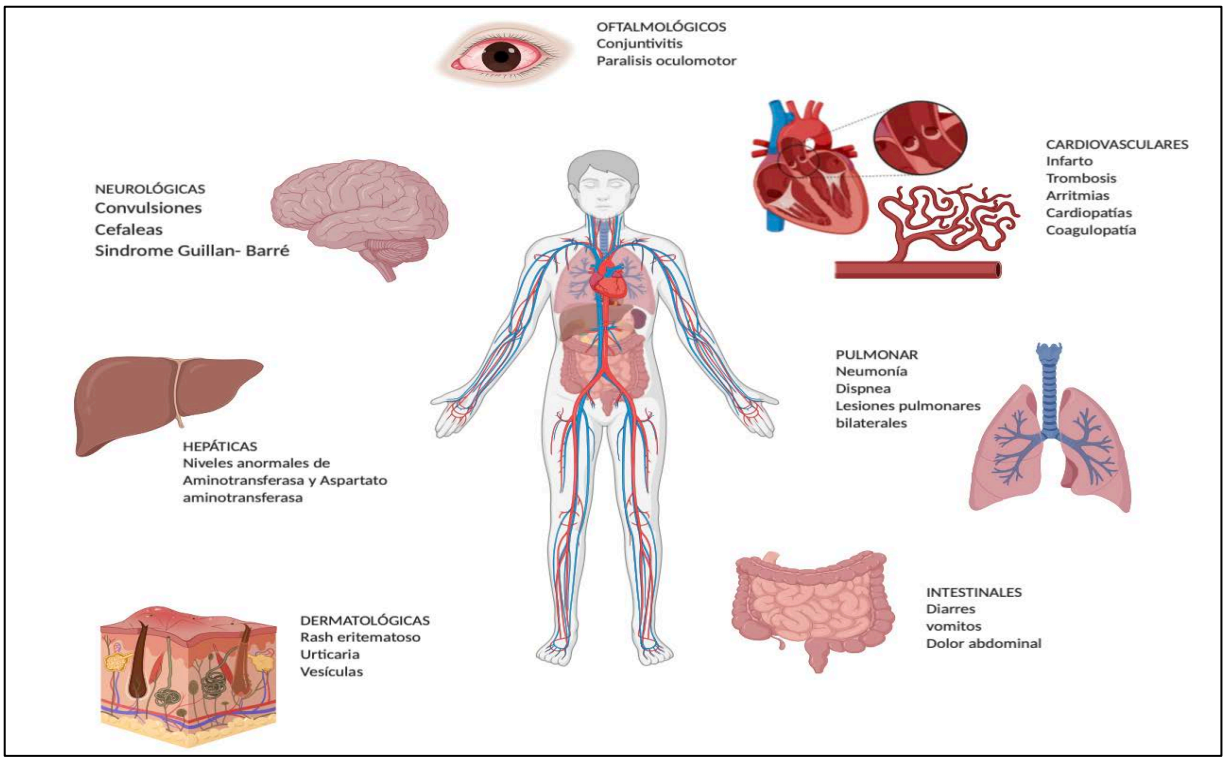

Figura 4. Síntomas y manifestaciones más frecuentes de la Covid-19. (Imagen de elaboración propia con los datos recogidos en las referencias [19][20][21][22]). Se ha utilizado el programa Biorender.com.

En la figura 4, podemos observar diversas afectaciones a nivel sistémico relacionadas con el Coronavirus. A nivel cardiovascular existe el riesgo de trombosis o infarto, a nivel pulmonar, además de padecer neumonía que es la principal manifestación de la Covid-19 y es la más

grave, hay también mucha probabilidad de padecer disnea severa. El aparato digestivo, sobre todo el intestino y el hígado, está bastante afectado por el *virus*, dado que diarreas y vómitos son algunos de los síntomas más frecuentes, por lo que es normal encontrar en la analítica de un paciente con SARS-CoV-2 valores anormales de aminotransferasa y aspartato aminotransferasa [19][20][21].

Las lesiones dermatológicas se encuentran también con bastante frecuencia mientras lesiones neurológicas debidas a convulsiones tienen menor prevalencia como manifestaciones y suelen aparecer en pacientes con un cuadro clínico grave de Coronavirus.

La principal manifestación de la enfermedad es la neumonía, al ser el pulmón el órgano diana cuando se habla del Coronavirus. En un estudio realizado en Wuhan por los autores Shi et al. sobre 81 pacientes con Covid-19, todos presentaban anormalidades en el TAC pulmonar. Se observó que 64 pacientes desarrollaron lesiones pulmonares difusas bilaterales y subpleurales, siendo la imagen predominante la "opacidad de vidrio" en el fondo con márgenes irregulares y engrosamiento de la parte interlobular y de la pleura adyacente [22].

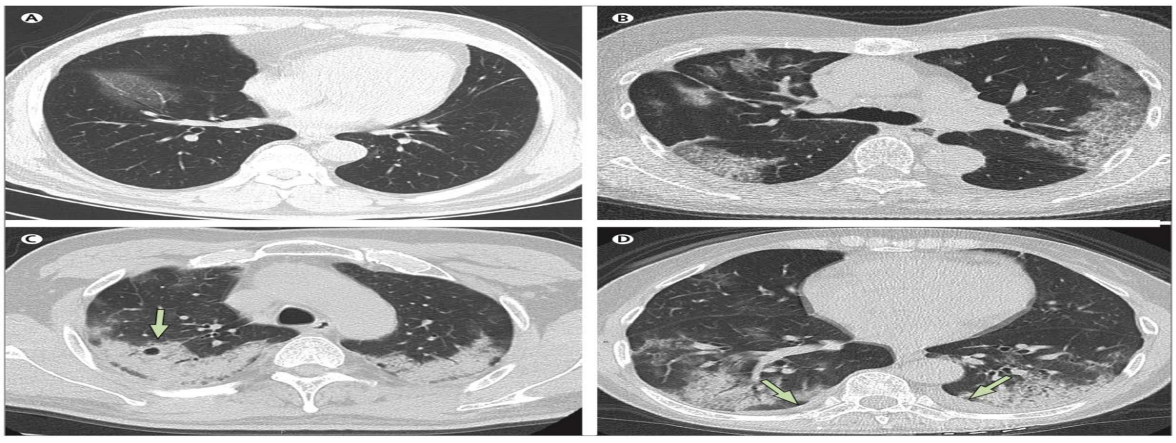

Figura 5. Imagen TAC : sección transversal pulmonar in pacientes con Coronavirus. Imagen del articulo https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930086-4 (22).

En otro estudio realizado por los dermatólogos Tang et al. sobre 228 pacientes, varios de ellos en una edad comprendida entre 8 y 84 años desarrollaron lesiones cutáneas exantematosas variables que fueron relacionadas con la Covid-19. Algunas de las lesiones cutáneas frecuentes en pacientes con Coronavirus fueron lesiones eritomatosas y vesiculares parecidas a la varicela. En algunos casos se observa también una reactivación el *virus* del Herpes simple oral (HSV-1) [(23)].

También en la cavidad oral se pueden encontrar lesiones o signos que permiten sospechar que el paciente ha desarrollado la Covid-19. Según un estudio del *Int. Journal of Odontostomatoly*, se subraya la relación entre el Coronavirus y la cavidad bucal, debido a la gran afinidad del *virus* por la enzima convertidora de angiotensina que se encuentra en la mucosa oral, lengua y glándulas salivales. La SARS-CoV-2 presenta la capacidad de generar un cierto desequilibrio en la microbiota oral, provocando lesiones herpéticas, ulceras, gingivitis descamativa, hiposalivación y pérdida de gusto. Personas con xerostomía e hiposalivación presentan mayor riesgo de padecer el Coronavirus porque al tener una escasa cantidad de saliva con la consecuente disminución de las mucinas, lisozima, peroxidasa y lactoferrina, hay una alteración de la barrera de la mucosa y en consecuencia hay más facilidad para la adhesión viral [(24)].

Figura 6. Paciente con Coronavirus que presenta ulcera en la lengua de https://onlinelibrary.wiley.com/doi/10.1111/odi.13635 (25)

La pérdida de gusto y la pérdida total de olfato hoy en día son unos de los síntomas claves de las manifestaciones por Covid-19 y siguen en importancia a la fiebre y la tos [(26)]. La anosmia se ha demostrado que es uno de los primeros síntomas en aparecer.

Lechien et al. demuestran que la anosmia y la pérdida de gusto afectan sobre todo a pacientes con una severidad de leve a moderada y algunas veces con mayor prevalencia en personas de sexo femenino [(27)].

Además, el síndrome respiratorio agudo puede asociarse también a coagulopatias. La Covid-19 presenta un cierto tropismo con la enzima convertidora de angiotensina II y por eso puede dar lugar a una alteración probable del estado antitrombótico. La coagulación alterada asociada con Covid-19 hace que los niveles de dímero D sean elevados [(28)].

En un artículo publicado en la revista Lancet por Lee et al. se demuestra que el ARN de la SARS-CoV-2 se podría detectar también en las heces, y por eso se sospecha que la transmisión de la Covid-19 podría ser igualmente por vía fecal-oral[(29)(30)(31)]. La posibilidad de infección a través de la vía fecal-oral destaca la importancia de una higiene de manos adecuada, sobre todo en los países con condiciones pobres de higiene.

Además, según un estudio realizado por Cheng Lee et al. en Taiwan en 2020 en el hospital de medicina en Taipei se probó que un porcentaje de las personas con Covid-19 podrían desarrollar lesiones hepáticas con anormalidades en los niveles de aminotransferasa (ALT) y aspartato aminotransferasa (AST)[29]. La lesión hepática en pacientes con Sars-CoV-2 podría deberse a una infección en las células hepáticas o a lesiones hepáticas inducidas por fármacos aunque según algunos estudios se ha demostrado que la carga viral de la Covid-19 en el tejido hepático es relativamente bajo [32].

Además hay otras vías de contagio como el contacto humano o a través de superficies contaminadas[33][34]. Asimismo, en otro estudio se evidencia la relación entre Covid-19 y algunos casos de retinopatía y paralisis oculomotores. Sin embargo, la única complicación confirmada a nivel oftalmológica fue la conjuntivitis que se puede presentar en pacientes infectados con marcada hiperemia cilio-conjuntival, queratitis superficial, edema palpebral y secreción mucosa, aunque esto es poco frecuente [33].

4.3. MANIFESTACIONES ORALES, BUCALES Y FACIALES DE LA COVID EN LOS NIÑOS

En los niños el curso de la infección por SARS-CoV-2 es parecido al de los adultos, pero las manifestaciones generalmente suelen ser más leves. Los niños suelen ser más asintomáticos, con menor probabilidad de llegar a tener complicaciones más graves, aunque sí que hay posibilidad de padecerlas.

A principio de la existencia de la enfermedad, las primeras complicaciones que se conocían eran casi solo respiratorias, mientras que con el paso del tiempo y al irse realizando más estudios, se han descubierto varias manifestaciones también sistémicas a otros niveles, así

por ejemplo se ha visto que es poco frecuente encontrar niños con Covid-19 que presenten neumonía.

Las manifestaciones de la Covid-19 en la población infantil no son tan específicas como en la población adulta aunque son bastante frecuentes fiebre, tos, dolor muscular, anosmia, ageusia y erupciones a nivel cutáneo [35].

La poca sintomatología en los niños por Coronavirus es debida a que la SARS-CoV-2 entra en el organismo humano y lo infecta a través del receptor de la enzima convertidora de angiotensina II que pero en los pequeños suele estar meno desarrollada respeto a los adultos, entonces por eso hay menor riesgo de padecer complicaciones más importantes por la reducida capacidad del *virus* de unirse a las células humanas [36].

La enzima convertidora de angiotensina II o ECA2 se localiza principlamente en el pulmón, corazón, riñon y en la cavidad oral sobretodo en el epitelio de las papilas gustativas y en las glándulas salivales. Con la entrada del *virus* en la célula a través de ECA2 hay alta probabilidad de un daño a las glándulas salivales y a las células de las papilas gustativas de la lengua provocando disgeusia. En un estudio llevado a cabo por la Universidad Nacional de Colombia por los científicos Parra y Bermúdez se muestra una cierta relación entre las manifestaciones orofaciales y la Covid-19. Pacientes con Coronavirus desarrollan lesiones frecuentes en la mucosa masticatoria con el 31% y en lengua con el 15% [37].

Ciccares et al. con otro estudio confirman que en la Covid-19 la ECA2 se expresa en la mucosa oral provocando úlceras y erosiones. Además, en un articulo publicado por el *New York Times* por Rabin sobre más de 2000 pacientes evaluados se subraya la conexión de los síntomas de anosmia y disgeusia con la Covid-19. Todo esto confirma la evidencia de posibles trastornos quimiosensibles en pacientes afectados por Coronavirus. La perdida de la función gustativa

concomita con la disminución del flujo salival como consecuencia de la pérdida del sabor. La disminución del gusto puede ser un signo precoz de detección primaria del Coronavirus [37]. Pedrosa y sus colegas estudian la posible afinidad de la SARS-CoV-2 con las proteínas ricas de ácido siálico altamente contenidas en las glándulas salivales junto a la enzima convertidora de angiotensina II. El ataque del *virus* a las glándulas salivales produce sequedad de la cavidad oral. La hiposalivación expone el paciente a un riesgo más alto de padecer la SARS-CoV-2 aunque esto es más frecuente que suceda en las personas mayores de edad dado que la cantidad de saliva diaria se reduce avanzando con los años [38].

En los pacientes positivos a la SARS-CoV-2 es bastante frecuente encontrar **síntomas a nivel oral**. El rasgo más común es la pérdida del gusto aunque hay otras manifestaciones en la mucosa como úlceras, enantemas, depapilación lingual, vesículas, erosiones y petequias que se localizan con más frecuencia en lengua, labios, paladar y encías como demuestra un estudio de Jimenez y cols donde el 29% de las personas con PCR con resultado positivo presentan esas lesiones. Según un ensayo de pacientes con Coronavirus realizado por Biadsee se demuestra que el 7% de estos presentan placas en el dorso de la lengua y un 8% desarrollan abultamiento de la cavidad oral. Además placas blancas y rojas en el dorso de la lengua han demostrado ser una manifestación de la enfermedad por Coronavirus. Otras lesiones frecuentes de la cavidad bucal son lesiones herpetiforme y erosiones [39].

En una publicación del *International Journal of Dermatology* por los científicos Adhazadeh y sus colaboradores se ponen en evidencia las manifestaciones orales en los niños con Coronavirus. Hay varios casos de niños con ulceras en la cavidad oral y que al mismo tiempo han dado positivo al test de la PCR y se ponen en evidencia una niña de 9 años que muestra

vesículas y erosiones en la mucosa bucal, en los labios y en la lengua y un niño siempre positivo a la Covid-19 que presenta erupciones orales vesiculares y herpetiforme [40].

Figura 7. Vesículas en la lengua y en labios de una niña con Covid-19 de https://onlinelibrary.wiley.com/doi/full/10.1111/ijd.15047 (40)

Un grupo de profesionales del hospital universitario de La Paz en Madrid realizó una reciente investigación publicada en el *British Journal of Dermatology* de 666 pacientes ingresados por Coronavirus en el hospital de urgencia creado en el IFEMA en el mes de Abril 2020 durante la pandemia donde se confirma la existencia de otro síntoma de la SARS-CoV-2 conocido como lengua covid que consiste en un conjunto de factores como aumento del tamaño de la lengua, depapilación lingual en parche que crean zonas lisas en la lengua, edema lingual, estomatitis aftosa, lengua saburral y papilitis lingual transitoria en forma de U. Todas estas alteraciones se asocian también a la perdida del gusto [41][42].

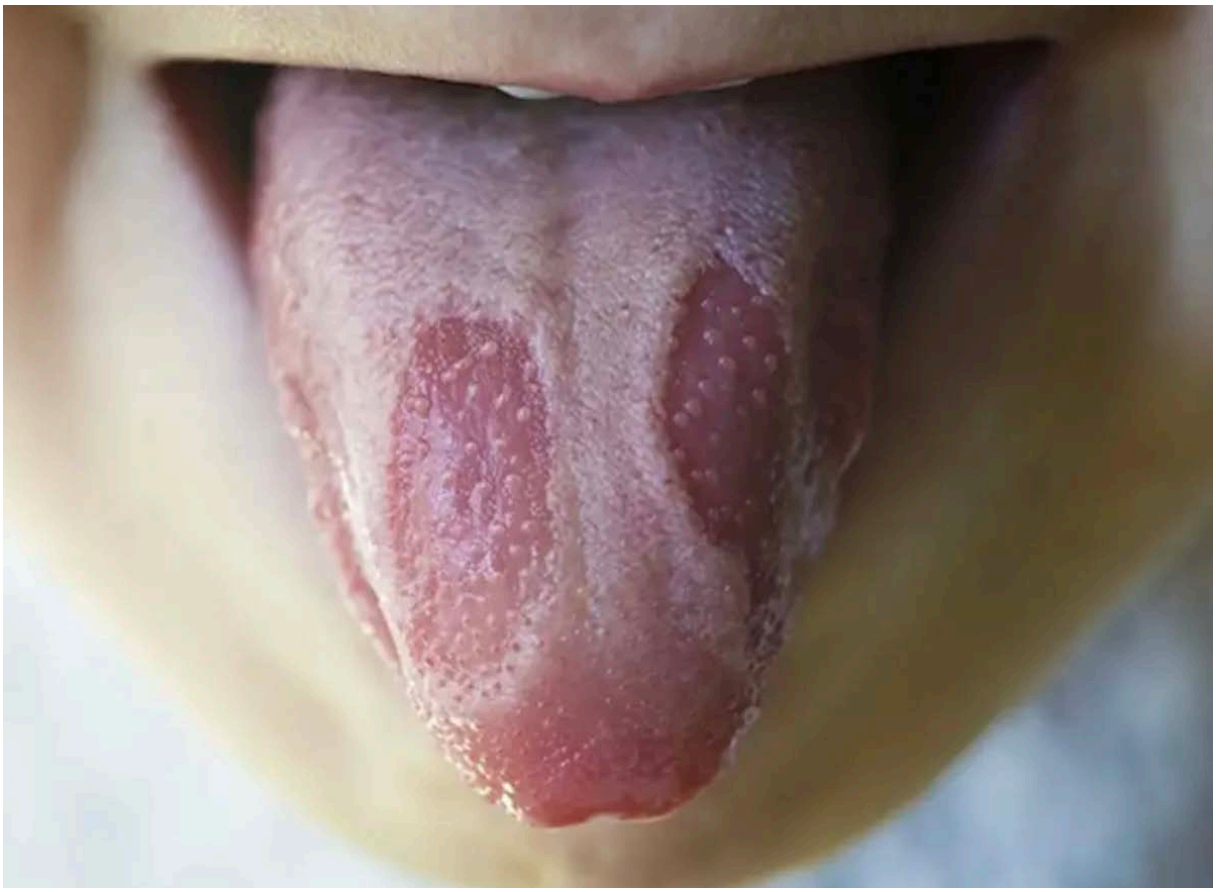

Figura 8. Lengua Covid en un niño de https://websalud.es/nuevo-sintoma-es-lengua-covi/ [43]

Frecuente en pacientes con Coronavirus es la sensación de ardor en la cavidad oral.

Características diferentes de lesiones orales en pacientes con SARS-CoV-2 fueron erupciones cutáneas, conjuntivitis, edemas en extremidades y síntomas gastrointestinales. En el mes de abril de 2020 en el *Children Hospital* de Philadelphia se valoraron 6 casos de niños positivos a la infección por Covid-19 con fiebre, tos, edema en las extremidades distales del cuerpo, erupciones cutáneas, conjuntivitis y cambios en las mucosas. El ensayo de estos 6 niños positivos a la SARS-CoV-2 demostró la peculiaridad que todos tenían fiebre subrayando que la hipertermia resuelta ser el síntoma más común en la infección por SARS-CoV-2 en los niños y en los adultos, mientras los otros síntomas como diarrea, conjuntivitis y disnea no eran

presentes en todos. Un rasgo de no subestimar a nivel de importancia en el diagnostico de la Covid-19 fue el cambio de las membranas de las mucosas en particular dos niños presentaron labios fisurados [44].

Se ha demostrado que la enzima convertidora de angiotensina II o sea el receptor clave en la infección por Coronavirus se expresa también en alta proporción en las corneas y en la conjuntiva de los ojos por lo que no hay que subestimar los **trastornos oculares** en la diagnosis por Coronavirus dado que son un síntoma clave en la detección precoz de la infección. En el *Yichang Central People's Hospital* en China se estudia el caso de un niño de 2 años positivo a la Covid-19 que presenta conjuntivitis y dermatitis en los párpados. No se sabe si la conjuntivitis está causada por la infección viral o si es secundaria a una infección bacteriana pero si que los síntomas han desaparecido con la eliminación del *virus* [45].

Según la revista de oftalmología Jama en un estudio realizado en el hospital pediátricos de Wuhan sobre 49 pacientes pediátricos manifestaciones oculares en los niños afectados por Coronavirus tenían una alta importancia. En una muestra de 49 pacientes, 27 de ellos desarrollan conjuntivitis que se presenta en diferentes formas de los cuales 11 niños desarrollan exudado amarillo purulento a nivel ocular, 9 una mucosa ocular blanca mientras 7 niños se destacan por los ojos acuosos. Otros síntomas menos frecuentes fueron lagrimeo y hinchazón de parpado. El lagrimeo se encuentra principalmente en infantes mientras los parpados inflamados se encuentran con más frecuencia en niños un poco más adultos [46].

Figura 9. Ojo con conjuntivitis en un niño que presenta la infección por la Covid-19 de https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7181963/ (45).

Una característica frecuente en jóvenes adultos con SARS-CoV-2 poco conocida son las **manifestaciones a nivel cutáneo**. Lesiones diana en los niños con Coronavirus son el eritema multiforme o enantemas vesiculares y maculopapular, lesiones urticarianas y erupciones tipo varicela. La sociedad francesa de dermatología ha creado un programa nacional donde los médicos y los dermatólogos pueden señalar a pacientes con lesiones cutáneas y con Coronavirus. Un grupo de 113 personas positivas a la Covid-19 presenta con mayor frecuencia lesiones parecidas a lesiones por congelación. Mientras en otro estudio de 16 personas, 6 con Coronavirus presentan además asociadas lesiones cutáneas eritematosas maculopapular sobre la cara [(47)].

De igual manera en otro estudio realizado por Hoenig y cols. se evidenció la relación que hay entre la SARS-CoV-2 y las manifestaciones cutáneas a nivel facial a través de un caso de un paciente joven con brote facial eritematoedematosos en la región malar la cuya evolución fue asociada a Coronavirus [(48)].

Andina e Belloni en el *Journal of clinical and experimental Dermatology* refieren que en numerosos estudios, los niños con la infección por Coronavirus presentan principalmente lesiones rojo-violáceas conocidas como saboñosas o perniosiformes que interesan las extremidades distales del cuerpo como manos y pies y suelen aparecer con dolor y hinchazón y son múltiples y de pequeño diámetro [(49)].

Otras lesiones frecuentes en los niños corresponden al eritema multiforme o exantema vesicular. El eritema multiforme es bastante común cuando hay una infección a nivel sistémico y está caracterizada por erupciones simétricas llamadas iris. Se ha demostrado su alta correlación con el Coronavirus. Mientras, el exantema vesicular al principio era un erupción papulovesicular parecida a la varicela frecuente en las mujeres adolescentes y en los niños [(50)]. Recalcati en un análisis de 18 pacientes con manifestaciones cutáneas y con síndrome respiratoria agudo pone en evidencia la importancia de las lesiones en la cavidad oral porque todavía no hay bastante claridad si las lesiones cutáneas son relacionadas con la SARS-CoV-2 debido a que muchísimas veces reacciones secundarias a algunos medicamentos son exantemas. Para saber si las manifestaciones cutáneas son relacionadas con el síndrome respiratorio agudo o no se hace el diagnostico diferencial con las lesiones orales. Si los pacientes además de presentar manifestaciones cutáneas desarrollan heridas a nivel bucal pues se sabe que los hallazgos cutáneos son relacionados con la Covid-19 [(51)].

Figura 10. Lesiones de pies en niños con Coronavirus tomado de https://onlinelibrary.wiley.com/doi/full/10.1111/ced.14481 (49)

Figura 11. Niño con exantema maculopapular eritematoso y con Covid de https://onlinelibrary.wiley.com/doi/10.1111/ced.14482 (50) .

La letalidad en niños y adolescente es menor del 10%. Es difícil que los niños progresan a una fase avanzada y critica de la enfermedad, por eso la mayor parte de los pacientes en edad pediátrica podrán ser atendidos en casa, no necesitan hospitalización y solo recibirán tratamiento para los síntomas específicos [52].

En Londres, Chiotos et Bassiri en el mayo del año pasado estudiaron un grupo de 8 niños positivos al Coronavirus y manifestaron que sus características clínicas eran parecidas a niños con la síndrome de Kawasaki como erupciones cutáneas y conjuntivitis [44] .

En un ensayo realizado por la revista de pediatría mexicana por Reyes A. se evidenció que siempre en el mes de abril de 2020 en Reino Unido se encontraron niños con una enfermedad que se descubrió ser parecida a la de Kawasaki y fue asociada a la SARS-CoV-2 conocida como síndrome inflamatorio multisistémico o MIS o síndrome choque tóxico. En segundo momento en México se encontraron casos de niños con síndrome multisistémico asociados también con Covid-19 y todos manifestaron fiebre, exantemas, conjuntivitis no supurativa, mucositis oral y quielitis en los labios [53] . La sociedad dental Americana con los scientificos Halepas y Lee realizó otro estudio sobre 47 pacientes pediátricos con edad media de 9 años positivos a la Covid-19 y con MIS todos con fiebre entre los cuales 23 presentaban labios rojos hinchados y 5 lengua de fresa. La lengua de fresa en príncipio es un rasgo común de la enfermedad de Kawasaki pues no está claro si está asociada o no al síndrome. Casi todos estos hallazgos se asociaron a la presencia de exantemas faciales y conjuntivitis [54]. Aun así, todavía no está clara la relación entre el síndrome inflamatorio multisistémico y la enfermedad da Kawasaki y del MIS relacionado con Coronavirus y se están realizando otros estudios para comprobar si hay correlacion entre Kawasaki y el síndrome de choque tóxico y si el sindrome multisistémico se

desarrolla como manifestación secundaria de la SARS-CoV-2 o si la patología se puede desarrollar también sin estar asociada a la Covid-19.

4.4. POSIBLES TRATAMIENTO PARA EL COVID19 A NIVEL SISTÉMICO Y ESPECIFICAMENTE A NIVEL FACIAL Y ORAL EN EL PACIENTE INFANTIL

Aunque ya ha pasado tiempo del principio de la pandemia y cada día se sigue estudiando sobre el *virus*, todavía no hay un tratamiento que sea especifico y universal para todos los pacientes con Coronavirus. Al ser una enfermedad vírica nueva y poco conocida, no hay bastantes estudios que demuestren que un tratamiento es eficaz al 100%.

A pesar de esto, hay varios grupos de fármacos utilizados para contrarrestar la infección por la SARS-CoV-2. Entre los que encontramos antivirales, anticoagulantes, terapias de soporte respiratorio, inmunomoduladores e inmunoestimulantes.

Los antivirales son un tratamiento casi de elección contra la SARS-CoV-2. Se han evaluado varios fármacos antivirales como Remdesivir que se destaca de otros antivirales por su beneficio contra el Coronavirus y también lopinavir-ritonavir, aunque no mostraron su eficacia contra la infección [(55)].

Otra terapia está basada en el plasma, o sea una terapia de anticuerpos que sirven de ayuda al sistema inmunitario aportando anticuerpos contra el *virus*. Se utiliza sobre todo en la fase inicial de la enfermedad transfiriendo anticuerpos de un paciente recuperado a un paciente con la infección en curso.

En el tratamiento de la Covid-19 también se están utilizando los corticoides, principalmente en pacientes con la enfermedad en un nivel más avanzado. En algunos casos se suministra

heparina para permitir la reducción de riesgo de trombosis que es frecuente en pacientes con Coronavirus.

En los pacientes con manifestaciones más graves se utilizaría oxigenoterapia cuando hay una saturación de oxigeno menor del 93% y el paciente presenta dificultad respiratoria. La oxigenoterapia se aplica con el soporte de una cánula nasal y una ventilación no invasiva. Cuando no se llega a un nivel suficientemente alto de saturación pulmonar se requiere una ventilación invasiva y mecánica con intubación traqueal [10].

La hidroxicloroquina fue el primer medicamento que demostró su beneficio contra el Coronavirus. En China en un ensayo piloto se pusieron a comparación la hidroxicloroquina con los antivirales lopinavir-ritonavir y la cloroquina fue bastante superior en los resultados.

Siempre en China se realizó otro ensayo clínico con 62 pacientes con Coronavirus divididos en dos grupos: un grupo en tratamiento de hidroxicloroquina llamado grupo 1 y otro grupo control en tratamiento con oxigenoterapia, antivirales y inmunoglobulinas con o sin corticoides llamado grupo 2. Los resultados demostraron que el grupo 1 mejoró antes del grupo 2 teniendo reducido el tiempo de duración de la enfermedad y con una mejoría en la evolución de la tos y también en las imágenes radiográficas de los pulmones [56].

En las manifestaciones a nivel oral como tratamiento se utiliza colutorio o clorhexidina, nistatina y fluconazol oral. Aciclovir a nivel sistémico y corticoides según la gravedad y la tipología de la lesión [39].

En niños con Síndrome inflamatorio multisistémico se utiliza terapia con corticosteroides e inmunoglobulinas [54] .

4.5. POSIBLES MEDIDAS PREVENTIVAS EN LA CONSULTA ODONTOPEDIATRICA PARA EL PACIENTE Y PARA EL ODONTOLOGO

Con la proclamación de la pandemia el 11 de marzo de 2020 por la OMS han cambiado todos los recursos y las medidas de seguridad en el ámbito odontológico, dada la alta transmisibilidad del Coronavirus a través de la via orofaríngea [57].

Las medidas básicas y fundamentales para una prevención más segura posible son varias. Se recomienda la importancia de un triaje telefónico al paciente antes de acudir a la consulta con preguntas específicas para identificar si hay los posibles signos de enfermedad por Coronavirus y descartar un posible sospecho. Además es importante preguntar al paciente si ha tenido recientemente algún contacto con una persona con Covid-19 o si ha acudido en los últimos días en algún centro hospitalario donde ha tenido la posibilidad de contagiarse. Hay que evitar grupos de personas en la sala de espera de la consulta, si no pertenecen al mismo núcleo familiar, y es fundamental mantener la distancia de seguridad entre personas; asimismo se insistirá en que el paciente deberá respetar el horario de la cita, evitando llegar antes o después y preferiblemente tendrá que acudir solo haciendo excepciones con personas minusválida o menores de edad que pueden ir acompañados [58].

A la llegada al centro clínico se mide la temperatura a los pacientes y si presentan más de 37.5 °C se deberá posponer la cita.

A la entrada de la clínica hay que tener dispensadores de gel hidroalcohólico para higiene de las manos. Se recomienda seguir el protocolo de desinfección de las manos según la Organización Mundial de la Salud [59].

Figura 12. Protocolo desinfección de manos según OMS tomado de https://www.consejodentistas.es/comunicacion/actualidad-consejo/notas-de-prensa-consejo/item/1763-plan-estrategico-de-accion-para-el-periodo-posterior-a-la-crisis-creada-por-el-covid-19.html (59)

Se ha demostrado la eficacia del enjuague preventivo con peróxido de hidrogeno para reducir la posible carga viral del paciente. Se hace antes de empezar cualquier tratamiento después de haberse quitado la mascarilla. El sillón, los puntos de apoyo de hombro, lámpara y mangueras de los instrumentos rotatorios y de aspiración tienen que estar cubiertos con una película transparente para evitar la transmisión cruzada.

Es importante minimizar todo lo posible el uso de aerosoles ya que las gotitas y la saliva son las principales fuentes de transmisión de la infección por SARS-CoV-2 [60]. Para ello, la ventilación de las zonas de trabajo juega un papel fundamental para evitar la transmisión del virus. Será necesario desinfectar todos los espacios entre paciente y paciente.

También son de gran importancia los equipos de protección individual conocidos como EPI.

Los EPI recomendados para los profesionales sanitarios son:

- mascarilla FFP2 y mascarilla quirúrgica por encima

- protección ocular y pantalla de protección

- doble par de guantes

- bata desechable y bata impermeable desechable cuando se utilizan aerosoles

- gorro impermeable desechable

Los EPI para los pacientes son:

- bata desechable

- gorro desechable

- mascarilla que se quita solo en el momento del tratamiento

- gafas [58].

Las gafas hay que desinfectarla para cada paciente con alcohol y hay que tirar todos los EPI en un cubo de basura específico que tenga pedal para no tocar el cubo con las manos sucias y evitar el contagio.

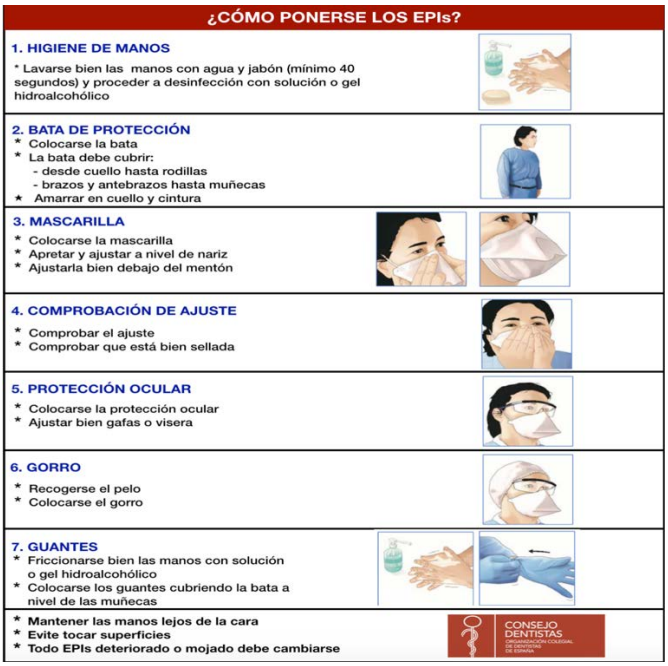

Figura 13. Explicación de como se ponen los EPI tomado de https://www.consejodentistas.es/comunicacion/actualidad-consejo/notas-de-prensa-consejo/item/1763-plan-estrategico-de-accion-para-el-periodo-posterior-a-la-crisis-creada-por-el-covid-19.html [59]

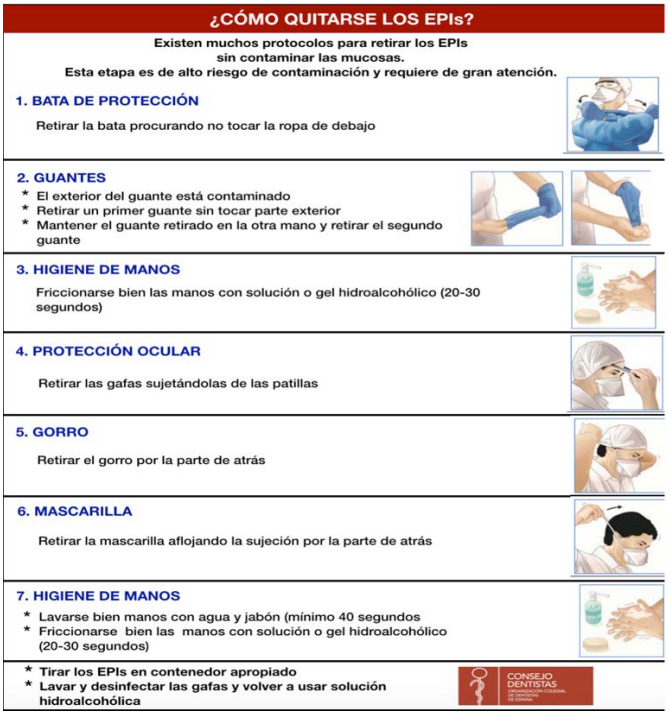

Figura 14. Explicación de como se quitan los EPi para no contagiarse tomado de https://www.consejodentistas.es/comunicacion/actualidad-consejo/notas-de-prensa-consejo/item/1763-plan-estrategico-de-accion-para-el-periodo-posterior-a-la-crisis-creada-por-el-covid-19.html [59]

5. CONCLUSIÓN

- El Coronavirus presenta una estructura redonda y está formado por RNA y algunas proteínas. La proteína S o Spike es la que presenta un papel clave en la especificidad de la SARS-CoV-2 y es la que se une a la enzima convertidora de angiotensina II permitiendo que la Covid-19 ingrese al interior de la célula infectándola. Se desarrolló por primera vez en Wuhan en China en diciembre de 2019 hasta llegar a todo el mundo. En el diagnostico de la Covid-19 tenemos dos tipos de pruebas que son el test molecular conocido como prueba PCR y el test serológico. El test molecular detecta si el paciente presenta la infección en el momento en que se realiza la prueba mientras el test serológico se basa en los anticuerpos. Esto no confirma si el paciente presenta la enfermedad en el momento de la prueba, pero sí detecta IgG e IgM que son las inmunoglobulinas que el paciente ha desarrollado después de haber cursado con la enfermedad.
- La Covid-19 se presenta en varias formas cambiando de persona a persona pudiendo ser asintomática hasta llegar a una neumonía grave. Los principales síntomas de la enfermedad son: fiebre, tos, cansancio general, perdida de gusto y olfato. Las manifestaciones que se pueden presentar en personas con Coronavirus son: neurológicas, hepáticas, dermatológicas, pulmonares, cardiovasculares, oftalmológicas, intestinales etc. Las lesiones pulmonares, dermatológicas e intestinales se encuentran con bastante frecuencia, mientras lesiones neurológicas y cardiovasculares son menos frecuentes. En la cavidad oral también podemos encontrar varias lesiones relacionadas con la Covid-19 por la gran afinidad del virus a

la enzima convertidora de angiotensina II que está presente en alta cantidad en la mucosa oral y sobretodo en la lengua.

- Los niños son más asintomáticos con respeto a los adultos, aunque también pueden presentar lesiones. Las más frecuentes son: ageusia, conjuntivitis y erupciones a nivel cutáneo. En varios estudios hemos visto una correlación entre lesiones de la cavidad oral y niños con Coronavirus. Es frecuente encontrar niños con úlceras y vesículas en la mucosa bucal, en lengua y en los labios. La manifestación que actualmente se destaca como síntoma de la SARS-CoV-2 es la lengua Covid, un conjunto entre depapilación lingual, papilitis de la lengua transitoria y aumento del tamaño de la lengua. Además de las manifestaciones en la cavidad oral, se encontraron también manifestaciones cutáneas como conjuntivitis y erupciones a nivel facial. A nivel facial presentan un papel clave en la diagnosis de la Covid-19 lesiones parecidas a lesiones por congelación y lesiones eritematosas maculopapular sobre la cara.
- El tratamiento de elección por la infección por Coronavirus sigue siendo el tratamiento antiviral. En pacientes con la enfermedad en estado más avanzado se suelen dar corticoides. Se realiza oxigenoterapia cuando no hay bastante saturación de oxigeno y es menor del 93%. También se ha demostrado la eficacia del tratamiento con hidroxicloroquina. Mientras que a nivel oral se emplea colutorio con clorhexidina, nistatina y fluconazol.
- Medidas básicas y fundamentales para una prevención más segura son varias. Se recomienda seguir el protocolo de desinfección de las manos según la organización mundial de la Salud (OMS). Además, se ha demostrado la eficacia del enjuague preventivo con peróxido de hidrogeno para reducir la posible carga viral del paciente

antes de empezar el tratamiento y es importante minimizar todo el uso de aerosoles. Están recomendados los equipos de protección individual o EPI para el profesional odontológico y para el paciente. Los EPI para el odontólogo son: mascarilla FFP2 y mascarilla quirúrgica, protección ocular y pantalla de protección, doble par de guantes, gorro, bata desechable e impermeable. Para el paciente son recomendados bata y gorros desechables, gafas y mascarilla que se quita solo durante el procedimiento odontológico.

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7. ANEXOS

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MMR MILITARY MEDICAL RESEARCH

REVIEW Open Access

The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status

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Abstract

An acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV), the coronavirus disease 2019 (COVID-19) has spread throughout China and received worldwide attention. On 30 January 2020, World Health Organization (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern. The emergence of SARS-CoV-2, since the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, marked the third introduction of a highly pathogenic and large-scale epidemic coronavirus into the human population in the twenty-first century. As of 1 March 2020, a total of 87,137 confirmed cases globally, 79,968 confirmed in China and 7169 outside of China, with 2977 deaths (3.4%) had been reported by WHO. Meanwhile, several independent research groups have identified that SARS-CoV-2 belongs to β-coronavirus, with highly identical genome to bat coronavirus, pointing to bat as the natural host. The novel coronavirus uses the same receptor, angiotensin-converting enzyme 2 (ACE2) as that for SARS-CoV, and mainly spreads through the respiratory tract. Importantly, increasingly evidence showed sustained human-to-human transmission, along with many exported cases across the globe. The clinical symptoms of COVID-19 patients include fever, cough, fatigue and a small population of patients appeared gastrointestinal infection symptoms. The elderly and people with underlying diseases are susceptible to infection and prone to serious outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm. Currently, there are few specific antiviral strategies, but several potent candidates of antivirals and repurposed drugs are under urgent investigation. In this review, we summarized the latest research progress of the epidemiology, pathogenesis, and clinical characteristics of COVID-19, and discussed the current treatment and scientific advancements to combat the epidemic novel coronavirus.

Keywords: Clinical characteristics, Coronavirus disease 2019 (COVID-19), Origin, SARS-CoV-2, Therapy, Transmission

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Respirology

INVITED REVIEW SERIES:
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MERS, SARS and other coronaviruses as causes of pneumonia

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ABSTRACT

Human coronaviruses (HCoVs) have been considered to be relatively harmless respiratory pathogens in the past. However, after the outbreak of the severe acute respiratory syndrome (SARS) and emergence of the Middle East respiratory syndrome (MERS), HCoVs have received worldwide attention as important pathogens in respiratory tract infection. This review focuses on the epidemiology, pathogenesis and clinical characteristics among SARS-coronaviruses (CoV), MERS-CoV and other HCoV infections.

Key words: human coronaviruses, Middle East respiratory syndrome, pneumonia, severe acute respiratory syndrome.

Abbreviations: AKI, acute kidney injury; CAP, community-acquired pneumonia; CK, creatinine kinase; CoV, coronavirus; DPP-4, dipeptidyl peptidase 4; HCoV, human coronavirus; ICU, intensive care unit; IFN, interferon; ISG, IFN-stimulated gene; MERS, Middle East respiratory syndrome; MPA, mycophenolic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS, severe acute respiratory syndrome; WHO, World Health Organization.

INTRODUCTION

Coronaviruses (CoVs), a large family of single-stranded RNA viruses, can infect a wide variety of animals, including humans, causing respiratory, enteric, hepatic and neurological diseases.[1] As the largest known RNA viruses, CoVs are further divided into four genera: alpha-, beta-, gamma- and delta-coronavirus. In humans, CoVs cause mainly respiratory tract infections. Currently, six human coronaviruses (HCoVs) have been identified. These include the alpha-CoVs HCoV-NL63 and HCoV-229E and the beta-CoVs HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV),[2] and Middle East respiratory syndrome-CoV (MERS-CoV).[3]

Although HCoVs have been identified for decades, their clinical importance and epidemic possibility was not recognized until the outbreak of SARS and MERS.[2,3] In 2002, the SARS epidemic originated from an animal market in South China and then affected more than 8000 people, with 916 deaths in 29 countries.[4] Subsequently, the World Health Organization (WHO) was notified of 2066 laboratory-confirmed cases of MERS-CoV infection, with at least 720 deaths between 2012 and 17 August 2017.[5] While found in 27 countries, more that 80% of illnesses were reported from Saudi Arabia.

This article will review the epidemiology, pathogenesis, clinical characteristics and management of patients with HCoVs infection.

EPIDEMIOLOGY

Origin of HCOVs

Although CoVs are estimated to have circulated on earth for centuries,[6,7] the origin of CoVs remains obscure. At the beginning of the outbreak of SARS and MERS, palm civets[8] and dromedary camels,[9] respectively, were suggested to be the natural reservoir of these two HCoVs. But further virologic and genetic studies indicate that bats are reservoir hosts of both SARS-CoV[10] and MERS-CoV,[11] which then use palm civets and dromedary camels as intermediary host before dissemination to humans. Recent studies further propose that bat CoVs are the gene source of most alpha-CoVs and beta-CoVs, whereas avian CoVs are considered the gene source of most gamma- and delta-CoVs.[6,12] Meanwhile, rodents are proposed to be the reservoir for ancestors of lineage A beta-CoVs which include HCoV-HKU1 and HCoV-OC43.[13]

Transmission from animal to human

The mechanism and route of transmission of SARS-CoV and MERS-CoV remains elusive. Direct contact with intermediary host animals or consumption of milk, urine, or uncooked meat were hypothesized to be

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RESEARCH ARTICLE Open Access

Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study

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Abstract

Background: The Middle East respiratory syndrome (MERS) coronavirus has caused recurrent outbreaks in the Arabian Peninsula since 2012. Although MERS has low overall human-to-human transmission potential, there is occasional amplification in the healthcare setting, a pattern reminiscent of the dynamics of the severe acute respiratory syndrome (SARS) outbreaks in 2003. Here we provide a head-to-head comparison of exposure patterns and transmission dynamics of large hospital clusters of MERS and SARS, including the most recent South Korean outbreak of MERS in 2015.

Methods: To assess the unexpected nature of the recent South Korean nosocomial outbreak of MERS and estimate the probability of future large hospital clusters, we compared exposure and transmission patterns for previously reported hospital clusters of MERS and SARS, based on individual-level data and transmission tree information. We carried out simulations of nosocomial outbreaks of MERS and SARS using branching process models rooted in transmission tree data, and inferred the probability and characteristics of large outbreaks.

Results: A significant fraction of MERS cases were linked to the healthcare setting, ranging from 43.5 % for the nosocomial outbreak in Jeddah, Saudi Arabia, in 2014 to 100 % for both the outbreak in Al-Hasa, Saudi Arabia, in 2013 and the outbreak in South Korea in 2015. Both MERS and SARS nosocomial outbreaks are characterized by early nosocomial super-spreading events, with the reproduction number dropping below 1 within three to five disease generations. There was a systematic difference in the exposure patterns of MERS and SARS: a majority of MERS cases occurred among patients who sought care in the same facilities as the index case, whereas there was a greater concentration of SARS cases among healthcare workers throughout the outbreak. Exposure patterns differed slightly by disease generation, however, especially for SARS. Moreover, the distributions of secondary cases per single primary case varied highly across individual hospital outbreaks (Kruskal–Wallis test; $P < 0.0001$), with significantly higher transmission heterogeneity in the distribution of secondary cases for MERS than SARS. Simulations indicate a 2-fold higher probability of occurrence of large outbreaks (>100 cases) for SARS than MERS (2 % versus 1 %); however, owing to higher transmission heterogeneity, the largest outbreaks of MERS are characterized by sharper incidence peaks. The probability of occurrence of MERS outbreaks larger than the South Korean cluster (n = 186) is of the order of 1 %.

Conclusions: Our study suggests that the South Korean outbreak followed a similar progression to previously described hospital clusters involving coronaviruses, with early super-spreading events generating a disproportionately large number of secondary infections, and the transmission potential diminishing greatly in subsequent generations. Differences in relative exposure patterns and transmission heterogeneity of MERS and SARS could point to changes in hospital practices since 2003 or differences in transmission mechanisms of these coronaviruses.

Keywords: Coronavirus, Exposure pattern, Hospital transmission, MERS, Middle East, Nosocomial, Reproduction number, SARS, South Korea

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PLOS PATHOGENS

REVIEW

The hallmarks of COVID-19 disease

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that has caused a worldwide pandemic of the human respiratory illness COVID-19, resulting in a severe threat to public health and safety. Analysis of the genetic tree suggests that SARS-CoV-2 belongs to the same *Betacoronavirus* group as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Although the route for viral transmission remains a mystery, SARS-CoV-2 may have originated in an animal reservoir, likely that of bat. The clinical features of COVID-19, such as fever, cough, shortness of breath, and fatigue, are similar to those of many acute respiratory infections. There is currently no specific treatment for COVID-19, but antiviral therapy combined with supportive care is the main strategy. Here, we summarize recent progress in understanding the epidemiological, virological, and clinical characteristics of COVID-19 and discuss potential targets with existing drugs for the treatment of this emerging zoonotic disease.

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Introduction

Humans have suffered from lethal infectious diseases, including viral outbreaks, for a long time. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a newly identified virus that differs from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) but can cause similar symptomology associated with pneumonia (Table 1) [1, 2]. This viral disease was named "COVID-19" by the World Health Organization (WHO) and was first recognized in Wuhan, Hubei Province, in China in December 2019 and may originate from eating wildlife, an established tradition in the oldest of human cultures. Subsequent to its introduction in Thailand, the virus has spread to more than 200 countries and territories. WHO declared this disease to be a public health emergency of international concern (Box 1), characterized as a pandemic.

The Art of War ("Sunzi Bingfa"), the famous ancient Chinese military treatise written by Sun Tzu, describes a series of strategies to win a war. It said, "Know yourself and know your enemy, and you will never be defeated." This is also important in the current war on the invisible enemy SARS-CoV-2. Here, we summarize the hallmarks of COVID-19 in its epidemiology, virology, and clinical features and management and discuss potential targets to treat this emerging human respiratory disease.

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Research Paper

COVID-19 in 7780 pediatric patients: A systematic review

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ABSTRACT

Background: Studies summarizing the clinical picture of COVID-19 in children are lacking. This review characterizes clinical symptoms, laboratory, and imaging findings, as well as therapies provided to confirmed pediatric cases of COVID-19.

Methods: Adhering to PRISMA guidelines, we searched four medical databases (PubMed, LitCovid, Scopus, WHO COVID-19 database) between December 1, 2019 to May 14, 2020 using the keywords "novel coronavirus", "COVID-19" or "SARS-CoV-2". We included published or in press peer-reviewed cross-sectional, case series, and case reports providing clinical signs, imaging findings, and/or laboratory results of pediatric patients who were positive for COVID-19. Risk of bias was appraised through the quality assessment tool published by the National Institutes of Health. PROSPERO registration # CRD42020182261.

Findings: We identified 131 studies across 26 countries comprising 7780 pediatric patients. Although fever (59·1%) and cough (55·9%) were the most frequent symptoms 19·3% of children were asymptomatic. Patchy lesions (21·0%) and ground-glass opacities (32·9%) depicted lung radiograph and computed tomography findings, respectively. Immunocompromised children or those with respiratory/cardiac disease comprised the largest subset of COVID-19 children with underlying medical conditions (152 of 233 individuals). Coinfections were observed in 5.6% of children and abnormal laboratory markers included serum D-dimer, procalcitonin, creatine kinase, and interleukin-6. Seven deaths were reported (0·09%) and 11 children (0·14%) met inclusion for multisystem inflammatory syndrome in children.

Interpretation: This review provides evidence that children diagnosed with COVID-19 have an overall excellent prognosis. Future longitudinal studies are needed to confirm our findings and better understand which patients are at increased risk for developing severe inflammation and multiorgan failure.

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Introduction

In December 2019, an unprecedented number of pneumonia cases presented in adult individuals from Wuhan, China [1]. Despite rapid action by the Chinese government and health officials, the number of similar presenting cases continued to rise at an alarming rate [2]. By January 2020 an emerging zoonotic agent, known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was identified in respiratory samples in patients diagnosed with pneumonia who subsequently developed respiratory failure [1]. The spread of SARS-CoV-2 from human to human, through respiratory droplets, has now resulted in a worldwide outbreak, now classified as a pandemic by the World Health Organization [3].

As of June 3rd, 2020, there has been more than 6·4 million confirmed cases worldwide and >380,000 fatalities [4] Most symptomatic cases have occurred in the adult population, characterized by fever, cough, malaise, and frequent hospitalization [1]. Accordingly, most of the published data is derived from adults with coronavirus disease 2019 (COVID-19) who were hospitalized in China [5]. As the pandemic continues, we are now observing numerous reports describing the clinical presentation and hospital course of children with confirmed COVID-19 [5].

What is currently known is that children have milder symptoms and are less likely to be hospitalized when compared to adults [6]. However, on May 14th, 2020 the United States Centers for Disease Control and Prevention (CDC) released a health advisory reporting a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 [7]. This statement stemmed from a subset of pediatric patients manifesting with severe inflammation, multi-organ failure, and testing positive for SARS-CoV-2 [8,9].

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WHO Declares COVID-19 a Pandemic

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The World Health Organization (WHO) on March 11, 2020, has declared the novel coronavirus (COVID-19) outbreak a global pandemic (1).

At a news briefing , WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, noted that over the past 2 weeks, the number of cases outside China increased 13-fold and the number of countries with cases increased threefold. Further increases are expected. He said that the WHO is "deeply concerned both by the alarming levels of spread and severity and by the alarming levels of inaction," and he called on countries to take action now to contain the virus. "We should double down," he said. "We should be more aggressive."

Among the WHO's current recommendations, people with mild respiratory symptoms should be encouraged to isolate themselves, and social distancing is emphasized and these recommendations apply even to countries with no reported cases (2).

Separately, in JAMA, researchers report that SARS-CoV-2, the virus that causes COVID-19, was most often detected in respiratory samples from patients in China. However, live virus was also found in feces. They conclude: "Transmission of the virus by respiratory and extrarespiratory routes may help explain the rapid spread of disease."(3).

COVID-19 is a novel disease with an incompletely described clinical course, especially for children. In a recente report W. Liu et al described that the virus causing Covid-19 was detected early in the epidemic in 6 (1.6%) out of 366 children (≤16 years of age) hospitalized because of respiratory infections at Tongji Hospital, around Wuhan. All these six children had previously been completely healthy and their clinical characteristics at admission included high fever (>39°C) cough and vomiting (only in four). Four of the six patients had pneumonia, and only one required intensive care. All patients were treated with antiviral agents, antibiotic agents, and supportive therapies, and recovered after a median 7.5 days of hospitalization. (4).

Risk factors for severe illness remain uncertain (although older age and comorbidity have emerged as likely important factors), the safety of supportive care strategies such as oxygen by high-flow nasal cannula and noninvasive ventilation are unclear, and the risk of mortality, even among critically ill patients, is uncertain. There are no proven effective specific treatment strategies, and the risk-benefit ratio for commonly used treatments such as corticosteroids is unclear (3,5).

Septic shock and specific organ dysfunction such as acute kidney injury appear to occur in a significant proportion of patients with COVID-19–related critical illness and are associated with increasing mortality, with management recommendations following available evidence-based guidelines (3).

Novel COVID-19 "can often present as a common cold-like illness," wrote Roman Wöelfel et al. (6). They report data from a study concerning nine young- to middle-aged adults in Germany who developed COVID-19 after close contact with a known case. All had generally mild clinical courses; seven had upper respiratory tract disease, and two had limited involvement of the lower respiratory tract. Pharyngeal virus shedding was high during the first week of symptoms, peaking on day 4. Additionally, sputum viral shedding persisted after symptom resolution. The German researchers say the current case definition for COVID-19, which emphasizes lower respiratory tract disease, may need to be adjusted(6). But they considered only young and "normal" subjecta where-

Scientific consensus on the COVID-19 pandemic: we need to act now

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 35 million people globally, with more than 1 million deaths recorded by WHO as of Oct 12, 2020. As a second wave of COVID-19 affects Europe, and with winter approaching, we need clear communication about the risks posed by COVID-19 and effective strategies to combat them. Here, we share our view of the current evidence-based consensus on COVID-19.

SARS-CoV-2 spreads through contact (via larger droplets and aerosols), and longer-range transmission via aerosols, especially in conditions where ventilation is poor. Its high infectivity,[1] combined with the susceptibility of unexposed populations to a new virus, creates conditions for rapid community spread. The infection fatality rate of COVID-19 is several-fold higher than that of seasonal influenza,[2] and infection can lead to persisting illness, including in young, previously healthy people (ie, long COVID).[3] It is unclear how long protective immunity lasts,[4] and, like other seasonal coronaviruses, SARS-CoV-2 is capable of re-infecting people who have already had the disease, but the frequency of re-infection is unknown.[5] Transmission of the virus can be mitigated through physical distancing, use of face coverings, hand and respiratory hygiene, and by avoiding crowds and poorly ventilated spaces. Rapid testing, contact tracing, and isolation are also critical to controlling transmission. WHO has been advocating for these measures since early in the pandemic.

In the initial phase of the pandemic, many countries instituted lockdowns (general population restrictions, including orders to stay at home and work from home) to slow the rapid spread of the virus. This was essential to reduce mortality,[6,7] prevent health-care services from being overwhelmed, and buy time to set up pandemic response systems to suppress transmission following lockdown. Although lockdowns have been disruptive, substantially affecting mental and physical health, and harming the economy, these effects have often been worse in countries that were not able to use the time during and after lockdown to establish effective pandemic control systems. In the absence of adequate provisions to manage the pandemic and its societal impacts, these countries have faced continuing restrictions.

This has understandably led to widespread demoralisation and diminishing trust. The arrival of a second wave and the realisation of the challenges ahead has led to renewed interest in a so-called herd immunity approach, which suggests allowing a large uncontrolled outbreak in the low-risk population while protecting the vulnerable. Proponents suggest this would lead to the development of infection-acquired population immunity in the low-risk population, which will eventually protect the vulnerable.

This is a dangerous fallacy unsupported by scientific evidence.

Any pandemic management strategy relying upon immunity from natural infections for COVID-19 is flawed. Uncontrolled transmission in younger people risks significant morbidity[3] and mortality across the whole population. In addition to the human cost, this would impact the workforce as a whole and overwhelm the ability of health-care systems to provide acute and routine care. Furthermore, there is no evidence for lasting protective immunity to SARS-CoV-2 following natural infection,[4] and the endemic transmission that would be the consequence of waning immunity would present a risk to vulnerable populations for the indefinite future. Such a strategy would not end the COVID-19 pandemic but result in recurrent epidemics, as was the case with numerous infectious diseases before the advent of vaccination. It would also place an unacceptable burden on the economy and health-care workers, many of whom have died from COVID-19 or experienced trauma as a result of having to practise disaster medicine. Additionally, we still do not understand who might suffer from long COVID.[3] Defining who is vulnerable is complex, but even if we consider those at risk of severe illness, the proportion of vulnerable people constitute as much as 30% of the population in some regions.[8] Prolonged isolation of large swathes of the population is practically impossible and highly unethical. Empirical evidence from many countries shows that it is not feasible to restrict uncontrolled outbreaks to particular sections of society. Such an approach also risks further exacerbating the socio-economic inequities and structural discriminations already laid bare by the pandemic. Special efforts to protect the most vulnerable are essential but must go hand-in-hand with multi-pronged population-level strategies.

Once again, we face rapidly accelerating increase in COVID-19 cases across much of Europe, the USA, and many other countries across the world. It is critical to act decisively and urgently. Effective measures that suppress and control transmission need to be implemented widely, and they must be supported by financial and social programmes that encourage community responses and address the inequities that have been amplified by the pandemic. Continuing restrictions will probably be required in the short term, to reduce transmission and fix ineffective pandemic response systems, in order to prevent future lockdowns. The purpose of these restrictions is to effectively suppress SARS-CoV-2 infections to low levels

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For the **WHO COVID-19 dashboard** see https://covid19.who.int/

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ORIGINAL ARTICLE

Detection of IgM and IgG antibodies in patients with coronavirus disease 2019

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Abstract

Objectives. This study aimed to determine the IgM and IgG responses against severe acute respiratory syndrome coronavirus (SARS-CoV)-2 in coronavirus disease 2019 (COVID-19) patients with varying illness severities. **Methods.** IgM and IgG antibody levels were assessed via chemiluminescence immunoassay in 338 COVID-19 patients. **Results.** IgM levels increased during the first week after SARS-CoV-2 infection, peaked 2 weeks and then reduced to near-background levels in most patients. IgG was detectable after 1 week and was maintained at a high level for a long period. The positive rates of IgM and/or IgG antibody detections were not significantly different among the mild, severe and critical disease groups. Severe and critical cases had higher IgM levels than mild cases, whereas the IgG level in critical cases was lower than those in both mild and severe cases. This might be because of the high disease activity and/or a compromised immune response in critical cases. The IgM antibody levels were slightly higher in deceased patients than recovered patients, but IgG levels in these groups did not significantly differ. A longitudinal detection of antibodies revealed that IgM levels decreased rapidly in recovered patients, whereas in deceased cases, either IgM levels remained high or both IgM and IgG were undetectable during the disease course. **Conclusion.** Quantitative detection of IgM and IgG antibodies against SARS-CoV-2 quantitatively has potential significance for evaluating the severity and prognosis of COVID-19.

Keywords: COVID-19, illness severity, immunoglobulin G, immunoglobulin M, SARS-CoV-2

INTRODUCTION

The novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV)-2, has been identified as the causative pathogen of coronavirus disease 2019 (COVID-19).[1-4] This disease has been called a public health emergency of international concern by the World Health Organization (WHO). Since December 2019, a serious outbreak of the disease has spread via human-to-human transmission from China to more than 200 countries and territories worldwide.[5,6] The numbers of infected cases and deaths associated with COVID-19 are still

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RESEARCH ARTICLE

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Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis

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Abstract

The outbreak of the novel coronavirus disease (COVID-19) quickly spread all over China and to more than 20 other countries. Although the virus (severe acute respiratory syndrome coronavirus [SARS-Cov-2]) nucleic acid real-time polymerase chain reaction (PCR) test has become the standard method for diagnosis of SARS-CoV-2 infection, these real-time PCR test kits have many limitations. In addition, high false-negative rates were reported. There is an urgent need for an accurate and rapid test method to quickly identify a large number of infected patients and asymptomatic carriers to prevent virus transmission and assure timely treatment of patients. We have developed a rapid and simple point-of-care lateral flow immunoassay that can detect immunoglobulin M (IgM) and IgG antibodies simultaneously against SARS-CoV-2 virus in human blood within 15 minutes which can detect patients at different infection stages. With this test kit, we carried out clinical studies to validate its clinical efficacy uses. The clinical detection sensitivity and specificity of this test were measured using blood samples collected from 397 PCR confirmed COVID-19 patients and 128 negative patients at eight different clinical sites. The overall testing sensitivity was 88.66% and specificity was 90.63%. In addition, we evaluated clinical diagnosis results obtained from different types of venous and fingerstick blood samples. The results indicated great detection consistency among samples from fingerstick blood, serum and plasma of venous blood. The IgM-IgG combined assay has better utility and sensitivity compared with a single IgM or IgG test. It can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories.

KEYWORDS

COVID-19, fingerstick blood, lateral flow immunoassay, point-of-care testing, rapid IgM-IgG combined test, SARS-CoV-2 virus infection

JIM Review

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COVID-19 diagnosis and management: a comprehensive review

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Abstract. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE (Campus Bio Medico University and Teaching Hospital, Rome; Humanitas Mater Domini Hospital, Castellanza; and Campus Bio Medico University and Teaching Hospital, Rome, Italy). COVID-19 diagnosis and management: a comprehensive review (Review). *J Intern Med* 2020; https://doiorg/10.1111/joim.13091

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus, has spread worldwide leading the World Health Organization to declare a pandemic. The disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), presents flu-like symptoms which can become serious in high-risk individuals. Here, we provide an overview of the known clinical features and treatment options for COVID-19. We carried out a systematic literature search using the main online databases (PubMed, Google Scholar, MEDLINE, UpToDate, Embase and Web of Science) with the following keywords: 'COVID-19', '2019-nCoV', 'coronavirus' and 'SARS-CoV-2'. We included publications from 1 January 2019 to 3 April 2020 which focused on clinical features and treatments. We found that infection is transmitted from human to human and through contact with contaminated environmental surfaces. Hand hygiene is fundamental to prevent contamination. Wearing personal protective equipment is recommended in specific environments. The main symptoms of COVID-19 are fever, cough, fatigue, slight dyspnoea, sore throat, headache, conjunctivitis and gastrointestinal issues. Real-time PCR is used as a diagnostic tool using nasal swab, tracheal aspirate or bronchoalveolar lavage samples. Computed tomography findings are important for both diagnosis and follow-up. To date, there is no evidence of any effective treatment for COVID-19. The main therapies being used to treat the disease are antiviral drugs, chloroquine/hydroxychloroquine and respiratory therapy. In conclusion, although many therapies have been proposed, quarantine is the only intervention that appears to be effective in decreasing the contagion rate. Specifically designed randomized clinical trials are needed to determine the most appropriate evidence-based treatment modality.

Keywords: COVID-19, COVID-19 diagnosis, COVID-19 management, COVID-19 treatment, novel coronavirus, SARS-CoV-2.

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel RNA coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), was identified in early January 2020 as the cause of a pneumonia epidemic affecting the city of Wuhan, the capital of Hubei province, from where it rapidly spread across China. After infecting and causing the death of thousands of persons in China, the virus has spread, reaching Italy and other European countries [1-3] and the USA, with the number of confirmed new cases currently increasing every day.

The World Health Organization named the disease coronavirus disease 2019 (COVID-19) and subsequently declared it a pandemic due to the widespread infectivity and high contagion rate. Human coronaviruses typically cause respiratory and enteric infections [4]. The new coronavirus has become a worldwide health threat [5]: up to 28 March 2020, COVID-19 has caused the death of 26 495 individuals worldwide and infected more than 570 000 [6]. The SARS-CoV-2 infection

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REVIEW

Coronavirus Disease 2019–COVID-19

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SUMMARY In recent decades, several new diseases have emerged in different geographical areas, with pathogens including Ebola virus, Zika virus, Nipah virus, and coronaviruses (CoVs). Recently, a new type of viral infection emerged in Wuhan City, China, and initial genomic sequencing data of this virus do not match with previously sequenced CoVs, suggesting a novel CoV strain (2019-nCoV), which has now been termed severe acute respiratory syndrome CoV-2 (SARS-CoV-2). Although coronavirus disease 2019 (COVID-19) is suspected to originate from an animal host (zoonotic origin) followed by human-to-human transmission, the possibility of other routes should not be ruled out. Compared to diseases caused by previously known

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Architecture of the SARS coronavirus prefusion spike

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The emergence in 2003 of a new coronavirus (CoV) responsible for the atypical pneumonia termed severe acute respiratory syndrome (SARS) was a stark reminder that hitherto unknown viruses have the potential to cross species barriers to become new human pathogens. Here we describe the SARS-CoV 'spike' structure determined by single-particle cryo-EM, along with the docked atomic structures of the receptor-binding domain and prefusion core.

The surface protein, or 'spike,' of enveloped viruses is an essential component for infection of the host cell, responsible for both binding to cellular receptors and subsequent fusion of viral and cellular membranes. Cell attachment and entry are crucial functions affecting the host range and cell tropism of viral infections. Fusion is achieved through conformational changes in the fusion core of the spike molecule[1], allowing entry of viral nucleocapsids into the host cell to initiate replication. Coronaviruses commonly cause relatively mild respiratory infections in humans[2], and their spike protein gives these viruses their distinctive crown-like appearance[3]. Coronavirus spikes are trimeric globular proteins approximately 150 Å in diameter and are attached to the virion envelope by a narrow stalk (**Fig. 1**). In SARS-CoV, the spike has a mass of about 500 kDa[3], making it the largest type 1 viral fusion spike protein[4,5]. Only a small part (18%) of the prefusion SARS-CoV spike structure, including the fusion core[6] and receptor-binding domain[7], has hitherto been solved to atomic resolution. The fusion core of SARS-CoV consists of two heptad-repeat regions and is highly similar to those of other coronaviruses[8] and to other type 1 fusion proteins, such as hemagglutinin (HA) from influenza[5], gp41 from human immunodeficiency virus[4] and the fusion protein of paramyxovirus[9]. The entire spike gene is highly conserved across all three main coronavirus groups, suggesting that these groups are specialized for a common mode of attachment in addition to sharing a similar fusion mechanism with other type 1 fusion proteins[8]. We set out to delineate the complete SARS-CoV spike structure, using cryo-EM and molecular docking to determine the positions of the fusion core and receptor-binding domains.

For structural investigations, we inoculated Vero E6 cells with SARS-CoV, purified virus particles from the supernatant using an iodoxanol density gradient (**Supplementary Methods** and **Supplementary Fig. 1** online) and analyzed intact virion preparations by cryo-EM (**Fig. 1**) and three-dimensional image processing (**Supplementary Figs. 2** and **3** online). To ensure biological safety, specimens were γ-irradiated and viral inactivation was verified. The irradiation dose used (2 Mrad) caused no obvious changes in virion structure, and we observed no radiolysis of viral proteins in SDS-PAGE results. Moreover, antigenicity to both patient sera and monoclonal antibodies was retained, as measured by ELISA and western blotting (**Supplementary Fig. 1**), indicating that epitopes were structurally intact. Radiation effects are random, so no structural changes were expected to appear after image averaging. Although SARS-CoV virions appear to be pleomorphic in negative-staining images, they are much more regular in shape when observed by cryo-EM (**Fig. 1**).

Virions average 1,185 Å in diameter, including the spikes, with a 36-Å-thick lipid bilayer envelope that is approximately spherical and has an average diameter of 865 Å (**Fig. 1**). Most are rounded and are

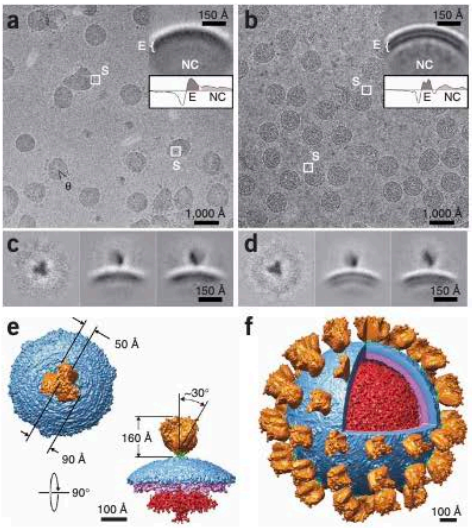

Figure 1 Cryo-EM and three-dimensional reconstruction of SARS-CoV. (**a**,**b**) Images at 8 μ (**a**) and 5.5 μ (**b**) defocus. S indicates spikes; arrowhead marks angle (θ) measured between two spikes. Inset shows envelope (E) and nucleocapsid (NC). (**c**,**d**) Select two-dimensional class averages from the defocus data in **a** and **b**, respectively. (**e**) Spike attached to the viral envelope by a narrow stalk. (**f**) Model of SARS-CoV with spikes spaced isotropically at 23.8°, surface-sectioned to reveal the interior. Orange, spike; green, stalk; blue and pink, envelope bilayer; red, nucleocapsid.

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Differential maturation and subcellular localization of severe acute respiratory syndrome coronavirus surface proteins S, M and E

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Post-translational modifications and correct subcellular localization of viral structural proteins are prerequisites for assembly and budding of enveloped viruses. Coronaviruses, like the severe acute respiratory syndrome-associated virus (SARS-CoV), bud from the endoplasmic reticulum-Golgi intermediate compartment. In this study, the subcellular distribution and maturation of SARS-CoV surface proteins S, M and E were analysed by using C-terminally tagged proteins. As early as 30 min post-entry into the endoplasmic reticulum, high-mannosylated S assembles into trimers prior to acquisition of complex *N*-glycans in the Golgi. Like S, M acquires high-mannose *N*-glycans that are subsequently modified into complex *N*-glycans in the Golgi. The *N*-glycosylation profile and the absence of *O*-glycosylation on M protein relate SARS-CoV to the previously described group 1 and 3 coronaviruses. Immunofluorescence analysis shows that S is detected in several compartments along the secretory pathway from the endoplasmic reticulum to the plasma membrane while M predominantly localizes in the Golgi, where it accumulates, and in trafficking vesicles. The E protein is not glycosylated. Pulse-chase labelling and confocal microscopy in the presence of protein translation inhibitor cycloheximide revealed that the E protein has a short half-life of 30 min. E protein is found in bright perinuclear patches colocalizing with endoplasmic reticulum markers. In conclusion, SARS-CoV surface proteins S, M and E show differential subcellular localizations when expressed alone suggesting that additional cellular or viral factors might be required for coordinated trafficking to the virus assembly site in the endoplasmic reticulum-Golgi intermediate compartment.

INTRODUCTION

Virus particle assembly and budding is the last step of the virus life-cycle. It requires correct folding and post-translational modifications of structural proteins and their precise subcellular localization at the virus budding site. Assembly and budding of the recently identified severe acute respiratory syndrome coronavirus, SARS-CoV, (Kuiken *et al.*, 2003; Peiris *et al.*, 2003) is a complex process that requires coordinated maturation and trafficking of the four structural proteins, the nucleocapsid (N), the Spike (S), the membrane (M) and the envelope (E) proteins. Little is known about SARS-CoV membrane proteins trafficking and function. By analogy with other animal and human coronaviruses it is assumed that SARS-N protein forms a ribonucleoprotein complex with RNA, which buds into the membrane of an endoplasmic reticulum-Golgi intermediate compartment (ERGIC) where the surface proteins S, M and E need to be located for virus budding.

Protein glycosylation is a highly regulated process that plays a fundamental role in membrane protein folding, oligomerization, sorting and transport by the intracellular machinery (Helenius & Aebi, 2001). The S protein is a 150–180 kDa highly glycosylated trimeric class I fusion protein (Bosch *et al.*, 2003; Delmas & Laude, 1990; Tripet *et al.*, 2004) responsible for receptor binding (Delmas *et al.*, 1992; Williams *et al.*, 1991; Yeager *et al.*, 1992), virus-membrane fusion and tissue tropism of coronaviruses

†These authors contributed equally to this work.

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Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude?

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ABSTRACT

In the present study we analyze the epidemiological data of COVID-19 of Tibet and high-altitude regions of Bolivia and Ecuador, and compare to lowland data, to test the hypothesis that high-altitude inhabitants (+2,500 m above sea-level) are less susceptible to develop severe adverse effects in acute SARS-CoV-2 virus infection. Analysis of available epidemiological data suggest that physiological acclimatization/adaptation that counterbalance the hypoxic environment in high-altitude may protect from severe impact of acute SARS-CoV-2 virus infection. Potential underlying mechanisms such as: (i) a compromised half-live of the virus caused by the high-altitude environment, and (ii) a hypoxia mediated down regulation of angiotensin-converting enzyme 2 (ACE2), which is the main binding target of SARS-CoV-2 virus in the pulmonary epithelium are discussed.

1. Introduction

The SARS-CoV-2 virus, the pathogen causing COVID-19, infects its host cells by recognizing the angiotensin converting enzyme 2 (ACE2) (Lu et al., 2020). ACE2 is a trans-membrane protein located in the cells of the respiratory tract, lung, heart, arteries, veins, kidney and intestines (Hamming et al., 2004). In the pulmonary epithelium ACE2 acts as a vasodepressor, balancing the action of its counterpart the homologous enzyme ACE1 which acts as vasoconstrictor, and both enzymes form the oxygen-sensitive renin-angiotensin-system (RAS) (Hampl et al., 2015). In normoxia, the RAS system is regulated by the dynamic equilibrium between the expression of ACE1 and ACE2. However, under chronic hypoxia (O_2 2% for 12 days) ACE1 is upregulated by the hypoxia-inducible factor 1 (HIF-1) (a master regulator of the response to hypoxia) in human pulmonary artery smooth muscle cells (hPASMC), while the expression of ACE2 is markedly decreased (Zhang et al., 2009). Similar results were obtained in rats (males, SD) exposed to conditions equivalent to 4,500 m of altitude, which after 28 days showed increased levels of ACE1 and decreased expression of ACE2 in heart cells (Dang et al., 2020). These observations are highly relevant for the pathogenesis of COVID-19, since the level of expression of ACE2 in pulmonary epithelial cells has been demonstrated to be positively correlated with the rate of infection of the first SARS-CoV (Jia et al., 2005; Lu et al., 2020; Ren et al., 2020; Rothan and Byrareddy, 2020). These studies clearly may suggest that high-altitude inhabitants (i.e., chronically exposed to hypoxic conditions) express reduced levels of ACE2 in their lungs (and other tissues). Thus, succesful acclimatization to high-altitude environment could render local inhabitants less susceptible to SARS-CoV-2 virus penetration and consequently are protected from the development of the disease defining acute respiratory distress syndrome.

2. Methods

We analyzed the epidemiological data in: (i) the Tibetan region of China, in which the peak of the epidemic is over (no more domestic

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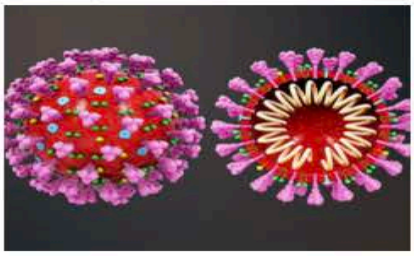
1569-9048/

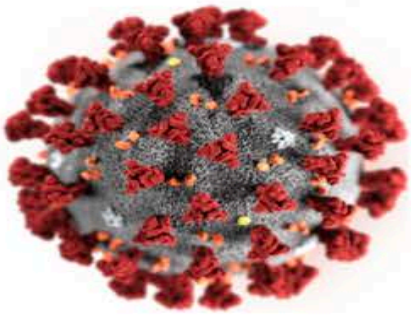
Viaggio al centro del virus: com'è fatto SARS-CoV-2

03 marzo 2020

Ricerca



I ***Coronavirus*** sono una **vasta famiglia di virus** noti per causare malattie che vanno dal comune raffreddore a malattie più gravi come la Sindrome respiratoria mediorientale (**MERS**) e la Sindrome respiratoria acuta grave (**SARS**). I Coronavirus sono stati identificati a metà degli anni '60 e sono noti per infettare l'uomo ed alcuni animali (inclusi uccelli e mammiferi).



[L'illustrazione, creata dai Centers for Disease Control and Prevention (CDC) statunitense, rivela la morfologia ultrastrutturale del SARS-CoV-2. È possibile notare sulla superficie le glicoproteine S (in rosso) che decorano la superficie esterna del virus, conferendogli l'aspetto di una corona (da cui il nome). Credit: https://phil.cdc.gov/Details.aspx?pid=23312]

Nel Dicembre 2019 a Wuhan, in Cina, è stato isolato un nuovo virus appartenente a questa famiglia, denominato **SARS-CoV-2**. La sequenza virale di questo nuovo Coronavirus ha **un'omologia di circa il 76% rispetto al virus che causò la pandemia di SARS nel 2002/2003, dunque i due virus sono molto simili**. *Ma com'è composto questo virus? Che struttura ha?*

La struttura del "nuovo Coronavirus"

Per analizzarne la struttura ci faremo aiutare dalla seguente illustrazione, che mostra un **virione** (la singola particella infettiva virale) completo e in sezione (credit: https://www.scientificanimations.com/wiki-images/).

I Coronavirus hanno **morfologia rotondeggiante** e dimensioni di 100-150 nm di diametro (circa 600 volte più piccolo del diametro di un capello umano!).

Partendo dallo strato più esterno e procedendo via via verso l'interno del virus, è possibile notare diverse componenti:

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Modular organization of SARS coronavirus nucleocapsid protein

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Key words: capsid protein, coronavirus, domain arrangement, intrinsically disordered protein, NMR, oligomerization, SARS

Abstract

The SARS-CoV nucleocapsid (N) protein is a major antigen in severe acute respiratory syndrome. It binds to the viral RNA genome and forms the ribonucleoprotein core. The SARS-CoV N protein has also been suggested to be involved in other important functions in the viral life cycle. Here we show that the N protein consists of two non-interacting structural domains, the N-terminal RNA-binding domain (RBD) (residues 45–181) and the C-terminal dimerization domain (residues 248–365) (DD), surrounded by flexible linkers. The C-terminal domain exists exclusively as a dimer in solution. The flexible linkers are intrinsically disordered and represent potential interaction sites with other protein and protein-RNA partners. Bioinformatics reveal that other coronavirus N proteins could share the same modular organization. This study provides information on the domain structure partition of SARS-CoV N protein and insights into the differing roles of structured and disordered regions in coronavirus nucleocapsid proteins.

Introduction

Coronaviruses are the causative agents of a number of mammalian diseases which often have significant economic and health-related consequences [1, 2]. Diseases such as transmissible gastroenteritis in pigs and avian infectious bronchitis in chicken often have great impact on the agricultural industry of a nation [3]. In humans, coronaviruses are often associated with mild respiratory illnesses, including common cold. However, a novel coronavirus has been identified as the etiology agent of severe acute respiratory syndrome (SARS), which has a case fatality rate of ca. 8% [4]. Sequence analysis reveals that SARS-CoV represents either a new coronavirus group or an outliner of group 2 coronaviruses [5–8].

The SARS CoV genome contains five major open reading frames that encode the replicase polyprotein, the spike protein (S), envelope (E), membrane glycoprotein (M), and the nucleocapsid protein (N). SARS-CoV is an enveloped virus with S, M and E proteins as the envelope proteins. The N protein binds to the viral RNA genome and forms the ribonucleoprotein core, which is presumed to be helical. The M protein may also be involved in the formation of the nucleocapsid through interaction with the N protein. Upon infection, the N protein enters the host cell with

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CK Chang and SC Sue contributed equally to this project.

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HEART FAILURE AND IMAGING

BEGINNER

CASE REPORT: CLINICAL CASE

Takotsubo Syndrome in the Setting of COVID-19

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ABSTRACT

A 58-year-old woman was admitted with symptoms of coronavirus disease-2019. She subsequently developed mixed shock, and an echocardiogram showed mid-distal left ventricular hypokinesis and apical ballooning, findings typical of stress, or takotsubo, cardiomyopathy. Over the next few days her left ventricular function improved, the further supporting the reversibility of acute stress cardiomyopathy. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:1321-5)

HISTORY OF PRESENTATION

A 58-year-old woman presented with productive cough, fatigue, fever, and diarrhea for the previous 5 days. Physical examination was notable for diffuse rhonchi. Initial vital signs were as follows: blood pressure, 156/95 mm Hg; heart rate, 130 beats/min; oxygen saturation, 82% on a 5-l nasal cannula; respiratory rate, 24 breaths/min; and temperature, 38.7°C. The chest radiograph showed lower lobe-predominant bilateral infiltrates. Shortly thereafter she was intubated for hypoxic respiratory failure and likely acute respiratory distress syndrome. The electrocardiogram (ECG) showed sinus tachycardia and 1-mm upsloping ST-segment elevations in leads I and aVL, mild diffuse PR interval depressions, and diffuse ST-T wave changes (Figure 1). Her initial troponin I level was negative but eventually peaked at 11.02 ng/ml. Notably there was leukopenia (absolute lymphocyte count of 1.04 K/mm^3). Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), or coronavirus disease-2019 (COVID-19), RNA detected by polymerase chain reaction returned a positive result.

LEARNING OBJECTIVES

- To recognize cardiovascular complications among COVID-19 patients.
- To demonstrate the presence of stress (takotsubo) cardiomyopathy in COVID-19.
- To manage stress cardiomyopathy in infected patients.

PAST MEDICAL HISTORY

The patient had a medical history of diabetes mellitus type 2, hypertension, and dyslipidemia. She denied

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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Review Article

Genotype and phenotype of COVID-19: Their roles in pathogenesis

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KEYWORDS
COVID-19;
Genotype;
Phenotype;
Pathogenesis

Abstract COVID-19 is a novel coronavirus with an outbreak of unusual viral pneumonia in Wuhan, China, and then pandemic. Based on its phylogenetic relationships and genomic structures the COVID-19 belongs to genera Betacoronavirus. Human Betacoronaviruses (SARS-CoV-2, SARS-CoV, and MERS-CoV) have many similarities, but also have differences in their genomic and phenotypic structure that can influence their pathogenesis. COVID-19 is containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. A typical CoV contains at least six ORFs in its genome. All the structural and accessory proteins are translated from the sgRNAs of CoVs. Four main structural proteins are encoded by ORFs 10, 11 on the one-third of the genome near the 3′-terminus. The genetic and phenotypic structure of COVID-19 in pathogenesis is important. This article highlights the most important of these features compared to other Betacoronaviruses.

Introduction

Coronaviruses are involved in human and vertebrate's diseases.[1] Coronaviruses are members of the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales. The recent emergence of a novel coronavirus with an outbreak of unusual viral pneumonia in Wuhan, China and then pandemic outbreak is 2019-nCoV or COVID-19. Based on its phylogenetic relationships and genomic

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IN QUESTO ARGOMENTO +
Sindrome respiratoria del Medio Oriente (Middle East respiratory syndrome, MERS)
Sindrome respiratoria acuta grave
ALTRI ARGOMENTI IN QUESTO CAPITOLO +
Virus respiratori
→ Panoramica sulle infezioni respiratorie virali
→ Infezioni da adenovirus
ULTERIORI CONTENUTI +

Coronavirus e sindrome respiratoria acuta (COVID-19, MERS e SARS)

CLICCA QUI PER L'EDUCAZIONE DEI PAZIENTI

*Di **Brenda L. Tesini**, MD, University of Rochester School of Medicine and Dentistry*

Ultima modifica dei contenuti feb 2021

Risorse sull'argomento

Audio (0) | Calcolatori (1) | Immagini (0) | Modelli 3D (1) | Tabelle (0) | Video (2)

I coronavirus sono virus a RNA con capsula che causano malattie respiratorie di gravità variabile dal raffreddore comune alla polmonite fatale.

Numerosi coronavirus, scoperti per la prima volta nel pollame domestico negli anni '30, causano malattie respiratorie, gastrointestinali, epatiche e neurologiche negli animali. Solo 7 coronavirus sono noti per causare malattie negli esseri umani.

Quattro dei 7 coronavirus negli esseri umani in genere si manifestano con i sintomi del raffreddore comune. I coronavirus 229E, OC43, NL63 e HKU1 causano circa il 15-30% dei casi di comune raffreddore. Raramente, possono verificarsi gravi infezioni delle basse vie respiratorie, compresa una bronchiolite e una polmonite, soprattutto nei lattanti, negli anziani e nelle persone immunocompromesse.

Tre dei 7 coronavirus causano infezioni respiratorie molto più gravi, e talvolta fatali, nell'uomo rispetto ad altri coronavirus e hanno causato gravi focolai di polmonite mortale nel XXI secolo:

- Il SARS-CoV-2 è un nuovo coronavirus identificato come la causa della malattia da coronavirus nel 2019 (COVID-19) che ha iniziato a Wuhan, in Cina, alla fine del 2019 e si è diffuso in tutto il mondo.
- Il coronavirus MERS-CoV è stato identificato nel 2012 come la causa della sindrome respiratoria del Medio Oriente (Middle East respiratory syndrome [MERS]).
- Il SARS-CoV identificato nel 2003 come la causa di un focolaio di sindrome respiratoria acuta grave che è iniziato in Cina verso la fine del 2002.

Questi coronavirus che causano gravi infezioni respiratorie sono patogeni zoonotici, che iniziano negli animali infetti e vengono trasmessi dagli animali alle persone. Il SARS-CoV-2 ha una capacità di trasmissione significativa da persona a persona.

COVID-19

Il COVID-19 è una malattia respiratoria acuta, a volte grave, causato da un nuovo coronavirus SARS-CoV-2.

COVID-19 è stato segnalato per la prima volta alla fine del 2019 a Wuhan, in Cina e da

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Biological Procedures Online

REVIEW Open Access

A comprehensive review of COVID-19 characteristics

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Abstract

In December 2019, a novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or (2019-nCoV) with unknown origin spread in Hubei province of China. The epidemic disease caused by SARS-CoV-2 called coronavirus disease-19 (COVID-19). The presence of COVID-19 was manifested by several symptoms, ranging from asymptomatic/mild symptoms to severe illness and death. The viral infection expanded internationally and WHO announced a Public Health Emergency of International Concern. To quickly diagnose and control such a highly infectious disease, suspicious individuals were isolated and diagnostic/treatment procedures were developed through patients' epidemiological and clinical data. Early in the COVID-19 outbreak, WHO invited hundreds of researchers from around the world to develop a rapid quality diagnosis, treatment and vaccines, but so far no specific antiviral treatment or vaccine has been approved by the FDA. At present, COVID-19 is managed by available antiviral drugs to improve the symptoms, and in severe cases, supportive care including oxygen and mechanical ventilation is used for infected patients. However, due to the worldwide spread of the virus, COVID-19 has become a serious concern in the medical community. According to the current data of WHO, the number of infected and dead cases has increased to 8,708,008 and 461,715, respectively (Dec 2019 –June 2020). Given the high mortality rate and economic damage to various communities to date, great efforts must be made to produce successful drugs and vaccines against 2019-nCoV infection. For this reason, first of all, the characteristics of the virus, its pathogenicity, and its infectious pathways must be well known. Thus, the main purpose of this review is to provide an overview of this epidemic disease based on the current evidence.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, 2019-nCoV, Viruses, Epidemic disease

Background

In December 2019, an *outbreak of pneumonia* with unknown origin began in China's Hubei Province, raising global health concerns due to the ease of transmission. To quickly diagnose and control the highly infectious disease, suspected people were isolated and diagnostic/therapeutic procedures were developed via patients' epidemiological and clinical data. After numerous studies, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of the disease, and the disease was dubbed "coronavirus-19" (COVID-19) by Chinese Scientists [1, 2]. The presence of COVID-19 is manifested by several symptoms, ranging from asymptomatic/mild symptoms to severe illness and death. Common symptoms include cough, fever, and shortness of breath. Other reported symptoms are weakness, malaise, respiratory distress, muscle pain, sore throat, loss of taste and/or smell [3].

Clinical diagnosis of COVID-19 is based on clinical manifestations, molecular diagnostics of the viral genome by RT-PCR, chest x-ray or CT scan, and serology

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Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study

Nanshan Chen, Min Zhou*, Xuan Dong*, Jieming Qu*, Fengyun Gong, Yang Han, Yang Qiu, Jingli Wang, Ying Liu, Yuan Wei, Jia'an Xia, Ting Yu, Xinxin Zhang, Li Zhang*

Summary

Background In December, 2019, a pneumonia associated with the 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China. We aimed to further clarify the epidemiological and clinical characteristics of 2019-nCoV pneumonia.

Methods In this retrospective, single-centre study, we included all confirmed cases of 2019-nCoV in Wuhan Jinyintan Hospital from Jan 1 to Jan 20, 2020. Cases were confirmed by real-time RT-PCR and were analysed for epidemiological, demographic, clinical, and radiological features and laboratory data. Outcomes were followed up until Jan 25, 2020.

Findings Of the 99 patients with 2019-nCoV pneumonia, 49 (49%) had a history of exposure to the Huanan seafood market. The average age of the patients was 55·5 years (SD 13·1), including 67 men and 32 women. 2019-nCoV was detected in all patients by real-time RT-PCR. 50 (51%) patients had chronic diseases. Patients had clinical manifestations of fever (82 [83%] patients), cough (81 [82%] patients), shortness of breath (31 [31%] patients), muscle ache (11 [11%] patients), confusion (nine [9%] patients), headache (eight [8%] patients), sore throat (five [5%] patients), rhinorrhoea (four [4%] patients), chest pain (two [2%] patients), diarrhoea (two [2%] patients), and nausea and vomiting (one [1%] patient). According to imaging examination, 74 (75%) patients showed bilateral pneumonia, 14 (14%) patients showed multiple mottling and ground-glass opacity, and one (1%) patient had pneumothorax. 17 (17%) patients developed acute respiratory distress syndrome and, among them, 11 (11%) patients worsened in a short period of time and died of multiple organ failure.

Interpretation The 2019-nCoV infection was of clustering onset, is more likely to affect older males with comorbidities, and can result in severe and even fatal respiratory diseases such as acute respiratory distress syndrome. In general, characteristics of patients who died were in line with the MuLBSTA score, an early warning model for predicting mortality in viral pneumonia. Further investigation is needed to explore the applicability of the MuLBSTA score in predicting the risk of mortality in 2019-nCoV infection.

Funding National Key R&D Program of China.

Introduction

Since Dec 8, 2019, several cases of pneumonia of unknown aetiology have been reported in Wuhan, Hubei province, China.[1–3] Most patients worked at or lived around the local Huanan seafood wholesale market, where live animals were also on sale. In the early stages of this pneumonia, severe acute respiratory infection symptoms occurred, with some patients rapidly developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications. On Jan 7, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient, and was subsequently named 2019-nCoV by WHO.[4]

Coronaviruses can cause multiple system infections in various animals and mainly respiratory tract infections in humans, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[5–7] Most patients have mild symptoms and good prognosis. So far, a few patients with 2019-nCoV have developed severe pneumonia, pulmonary oedema, ARDS, or multiple organ failure and have died. All costs of 2019-nCoV treatment are covered by medical insurance in China.

At present, information regarding the epidemiology and clinical features of pneumonia caused by 2019-nCoV is scarce.[1–3] In this study, we did a comprehensive exploration of the epidemiology and clinical features of 99 patients with confirmed 2019-nCoV pneumonia admitted to Jinyintan Hospital, Wuhan, which admitted the first patients with 2019-nCoV to be reported on.

Methods

Study design and participants

For this retrospective, single-centre study, we recruited patients from Jan 1 to Jan 20, 2020, at Jinyintan Hospital in Wuhan, China. Jinyintan Hospital is a hospital for adults (ie, aged ≥14 years) specialising in infectious diseases. According to the arrangements put in place by

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Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study

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Summary

Background A cluster of patients with coronavirus disease 2019 (COVID-19) pneumonia caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were successively reported in Wuhan, China. We aimed to describe the CT findings across different timepoints throughout the disease course.

Methods Patients with COVID-19 pneumonia (confirmed by next-generation sequencing or RT-PCR) who were admitted to one of two hospitals in Wuhan and who underwent serial chest CT scans were retrospectively enrolled. Patients were grouped on the basis of the interval between symptom onset and the first CT scan: group 1 (subclinical patients; scans done before symptom onset), group 2 (scans done ≤1 week after symptom onset), group 3 (>1 week to 2 weeks), and group 4 (>2 weeks to 3 weeks). Imaging features and their distribution were analysed and compared across the four groups.

Findings 81 patients admitted to hospital between Dec 20, 2019, and Jan 23, 2020, were retrospectively enrolled. The cohort included 42 (52%) men and 39 (48%) women, and the mean age was 49·5 years (SD 11·0). The mean number of involved lung segments was 10·5 (SD 6·4) overall, 2·8 (3·3) in group 1, 11·1 (5·4) in group 2, 13·0 (5·7) in group 3, and 12·1 (5·9) in group 4. The predominant pattern of abnormality observed was bilateral (64 [79%] patients), peripheral (44 [54%]), ill-defined (66 [81%]), and ground-glass opacification (53 [65%]), mainly involving the right lower lobes (225 [27%] of 849 affected segments). In group 1 (n=15), the predominant pattern was unilateral (nine [60%]) and multifocal (eight [53%]) ground-glass opacities (14 [93%]). Lesions quickly evolved to bilateral (19 [90%]), diffuse (11 [52%]) ground-glass opacity predominance (17 [81%]) in group 2 (n=21). Thereafter, the prevalence of ground-glass opacities continued to decrease (17 [57%] of 30 patients in group 3, and five [33%] of 15 in group 4), and consolidation and mixed patterns became more frequent (12 [40%] in group 3, eight [53%] in group 4).

Interpretation COVID-19 pneumonia manifests with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1–3 weeks. Combining assessment of imaging features with clinical and laboratory findings could facilitate early diagnosis of COVID-19 pneumonia.

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See Comment page 384

For the Chinese translation of the abstract see Online for appendix 1

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Introduction

Beginning in December, 2019, a cluster of cases of pneumonia with unknown cause was reported in Wuhan, in the Hubei province of China.[1] On Jan 7, 2020, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV), was identified as the causative organism by Chinese facilities via deep sequencing analysis of patients' respiratory tract samples.[2,3] SARS-CoV-2 has been shown to infect human respiratory epithelial cells through an interaction between the viral S protein and the angiotensin-converting enzyme 2 receptor on human cells; thus, SARS-CoV-2 possesses a strong capability to infect humans.[3]

Most of the initial cases of coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, were epidemiologically linked to exposure to Wuhan's Huanan seafood market, where wild animals are traded.[4,5] Although the market has been closed since Jan 1, 2020, as part of efforts to contain the outbreak, patients without exposure to the market but with a history of travel to Wuhan or close physical contact with a patient confirmed to have COVID-19, including health-care workers, have also been identified, suggesting strong human-to-human transmission. The number of cases has been increasing rapidly: by Feb 15, 2020, more than 60 000 cases of COVID-19 pneumonia had been reported in China and in other countries worldwide (including Thailand, Japan, South Korea, and the USA),[6–9] and 1524 patients had died, equivalent to a mortality rate of around 2%.

The clinical features of the initial 41 patients confirmed to be infected with SARS-CoV-2 included lower respiratory tract illness with fever, dry cough, and dyspnoea,[5] a manifestation similar to those of two other diseases caused by coronaviruses, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[10,11] However, the radiological changes in the lungs of people with COVID-19 pneumonia have not

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SHORT PAPER

DERMATOLOGIC THERAPY WILEY

Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review

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Abstract

COVID-19, first appeared in December 2019 in Wuhan, China, has been spreading quickly throughout the world. We reviewed the evidence on cutaneous manifestations of COVID-19 based on PubMed database. The searching strategy was (COVID* or coronavirus*) and (dermatol* or skin* or cutaneous*). The publication time was limited to 2019 onward. After independent review by two authors, 14 studies with 228 confirmed cases were included in the analysis. A total of 60 patients developed skin rashes, and the age ranged from 8 to 84. Exanthematous eruptions potentially related to COVID-19 infection were highly variable and heterogeneous. Skin lesions mainly appeared erythematous, urticarial, and vesicular (chicken pox-like or varicelliform). Petechiae rash, livedo reticularis, and reactivation of oral HSV-1 were also observed in single cases. Newly reported eruptions like vascular lesions and peculiar (perniosis-like) skin lesions caused concern among dermatologists. Exanthems were widely distributed and were primarily located on the trunk. Associated symptoms, latency time, treatment, and prognosis were also carefully summarized. This study reviewed the recently published COVID-19 studies with skin manifestations, which may pave the way for further research.

KEYWORDS

coronavirus, COVID-19, cutaneous manifestations, review, skin

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has been spreading quickly throughout the world since its first appearance in December 2019 in Wuhan, China. World Health Organization (WHO) declared a pandemic condition in March, with the confirmed case number gradually rising to 2 626 321 globally by April 25th, 2020. Common clinical features of this virus infection inside and outside of the respiratory system include fever, cough, headache, diarrhea, fatigue, headache, and myalgia.[1] Dermatological symptoms are reported sporadically, and the roles of skin lesions in early recognition and disease progression have not been extensively studied. In this short review, we will present evidence on cutaneous manifestations and relevant implications in the context of COVID-19, which may highlight dermatological aspects and help dermatologists understand the disease.

2 | METHODS

The literature search using the following search strategy was conducted on Pubmed database on April 25th, 2020 to identify eligible articles: (COVID* or coronavirus*) and (dermatol* or skin* or cutaneous*). The publication time was limited to 2019 onward. A total of 170 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full-texts. Reports on the range

Co-first authors: Keyun Tang and Yuanzhuo Wang authors contributed equally to this study. Keyun Tang and Yuanzhuo Wang should be considered joint first author.

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Manifestaciones Orales de la Infección por COVID-19

Oral Manifestations of COVID-19

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NEMETH, K. M. E.; MATUS, A. C. P. & CARRASCO, S. R. R. Manifestaciones orales de la infección por COVID-19. *Int. J. Odontostomat., 14(4)*:555-560, 2020.

RESUMEN: El 8 de enero de 2020, el Centro Chino para el Control y Prevención de Enfermedades anunció oficialmente la identificación de una nueva cepa de coronavirus (SARS-CoV-2) como el patógeno causante de la pandemia mundial de COVID-19. Las principales manifestaciones clínicas producidas por SARS-CoV-2 se encuentran ampliamente descritas en la literatura, sin embargo, la información acerca de las alteraciones que podrían producirse a nivel oral, es escasa. Se ha sugerido que la cavidad oral es un perfecto hábitat para la invasión por SARS-CoV-2 debido a la especial afinidad que tiene el virus por células con los receptores para la enzima convertidora de angiotensina (ECA2) como son las del tracto respiratorio, mucosa oral, lengua y glándulas salivales, pudiendo afectar, de este modo, el funcionamiento de las glándulas salivales, las sensaciones del gusto, olfato y la integridad de la mucosa oral. El nuevo coronavirus tendría la capacidad de alterar el equilibrio de la microbiota oral, lo que sumado a un sistema inmune deprimido permitiría la colonización por infecciones oportunista. Se ha establecido que un correcto higiene oral podría disminuir la incidencia y gravedad de las principales complicaciones del COVID-19. El objetivo de este estudio es realizar una revisión y análisis de la evidencia disponible en relación a las manifestaciones orales a nivel de las mucosas, trastornos de las glándulas salivales y alteraciones en el sistema olfatorio y gustativo en el contexto de la infección por SARS-CoV-2.

PALABRAS CLAVE: COVID-19, SARS-CoV-2, manifestaciones orales

INTRODUCCIÓN

El 8 de enero de 2020, el Centro Chino para el Control y Prevención de Enfermedades anunció oficialmente la identificación de una nueva cepa de coronavirus (SARS-CoV-2) como el patógeno causante de la pandemia mundial de COVID-19 (Li *et al.* 2020). En comparación con otras pandemias recientes el COVID-19 tiene, en general, una presentación clínica menos severa, sin embargo, se propaga con mayor facilidad, lo que ha generado aproximadamente 16,7 millones de contagios y más de 650.000 muertes a nivel mundial, al 29 de julio del 2020 (World Health Organization, 2020).

La información disponible acerca de las principales manifestaciones clínicas producidas por SARS-CoV-2 tales como fiebre, tos seca, diarrea y dificultad respiratoria es amplia y detallada, sin embargo, aquella sobre los síntomas reportados más recientemente, presentes en su mayoría en una etapa más temprana de la infección, tales como lesiones cutáneas, alteraciones del olfato y repercusiones a nivel oral, es escasa.

El impacto del COVID-19 en la salud oral está principalmente determinado por el sistema inmunológico del paciente, la farmacoterapia que recibe y por la patogenia del virus. Se ha sugerido que la cavidad oral es un perfecto hábitat para la invasión por SARS-CoV-2 debido a la especial afinidad que tiene el virus por células con los receptores para la enzima convertidora de angiotensina (ECA2) como son las del tracto respiratorio, mucosa oral, lengua y glándulas salivales (Xu *et al*., 2020; Peng *et al*., 2020).

Se ha demostrado que el SARS-CoV-2 es un virus neurotrópico y mucotrópico, pudiendo afectar el funcionamiento de las glándulas salivales, las sensa-

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LETTER TO THE EDITOR

ORAL DISEASES WILEY

Tongue ulcers associated with SARS-CoV-2 infection: A case series

Dear Editor,

The emerging evidence on oral manifestations of the coronavirus disease (COVID-19) has provoked large debates about their etiology, prognosis, and significance; however, these symptoms may have been underreported and discovered by accidental diagnosis due to the inability of the COVID-19 patients to seek oral health care and the low fatality of the oral mucocutaneous lesions. Larger case series following rigorous reporting guidelines are highly required to enhance evidence robustness; therefore, we aim to demonstrate the characteristics of 26 laboratory-confirmed COVID-19 patients with tongue ulcers according to the CARE guidelines (Gagnier et al., 2013; Riad, Klugar, & Krsek, 2020).

The demographic, clinical, and laboratory characteristics of the patients who visited our department with tongue ulcers in April – June 2020 were retrospectively extracted from the hospital records. The referenced patients had been originally suspected of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of having a confirmed case among their household members; therefore, they underwent polymerase chain reaction (PCR) testing which confirmed their infection. Later, they sought care at our department due to pain in the tongue. Their mean age was 36.81 ± 15.65 (16–70), and 17 (65.4%) patients were females. None of the patients had systemic comorbidities, and their respiratory symptoms were mild or absent in some cases; therefore, they did not require hospitalization. The mean cycle threshold (Ct) value was 17.23 ± 4.51 (12–31). Regarding their typical COVID-19 symptoms, four (15.4%) had a fever, one (3.8%) had a dry cough, three (11.5%) had ageusia, and two (7.7%) had a sore throat (Table 1).

The day of PCR testing has been used as the reference time point to calculate the onset of the appearance of the tongue ulcers. While the mean onset was 4.12 ± 1.39 days, 14 (53.8%) patients had the tongue ulcers after five days and seven (26.9%) after four days, and two (7.7%) patients did the PCR on the same day of ulcers manifestation. On intraoral examination, the number of ulcers varied considerably among the patients and ranged between 1 and 7 ulcers per patient, and their size ranged between 1 and 5 mm corresponding to herpes-like ulcers with scalloped borders. The majority (92.3%) of them were not bleeding, and all of them (100%) were manifested on dorsum or side of the tongue, while 4 (15.4%) patients had ulcers on the ventral surface (Figure 1).

All ulcers were painful and interfered with daily activities, and the mean score of pain severity was 4.65 ± 1.55 (3–8) which was assessed by the patient using an 11-item numerical rating scale (NRS) when with "0" denoting "no pain" and "10" denoting "pain as bad as you can imagine" (Williamson & Hoggart, 2005). On asking the patients, none of them had a history of herpetic conditions or tongue ulcers. There were no more ulcers or blisters observed inside the oral cavity apart from the ones found on the tongue.

Oral paracetamol and chlorhexidine mouthwash were prescribed as a palliative protocol for the patients. The ulcers had disappeared without a scare after either 1 or 2 weeks on the follow-up visit with a mean duration of 8.35 ± 2.81 days. All the investigated patients agreed to use their clinical and laboratory results for academic purposes while concealing their identifying personal data.

Inferential statistics revealed a statistically significant association between number of ulcers and gender, onset, duration, Ct value, and pain score (Kruskal–Wallis H = 12.86, 14.93, 14.17, 22.39, and 14.53; p = .045, .021, .028, .001, and .024, respectively). While the Ct value was inversely correlated with number of ulcers, pain score, and duration (*Pearson correlation* = −0.86, −0.40, and −0.05; p < .001, = .043, and .818, respectively), it was directly correlated with the onset (*Pearson correlation* = 0.428; p = .29).

Our results may support the hypothesis of Petrescu, Lucaciu, and Roman (2020) on the early susceptibility of oral mucosa, especially in the tongue, for SARS-CoV-2 infection due to the high expression of angiotensin-converting enzyme 2 (ACE2) in epithelial cells of the tongue (Petrescu et al., 2020). They are also in agreement with previous reports of tongue ulcers in COVID-19 patients from France and Iran which were suggested to be early COVID-19 symptoms (Ansari, Gheitani, Heidari, & Heidari, 2020; Chaux-Bodard, Deneuve, & Desoutter, 2020). In general, viral infections can cause ulceration of the oral mucosa as a direct manifestation of the infection (Clarkson et al., 2017).

Herpes zoster (HZ) cannot be ruled out in our patients as it was reported previously among the dermatologic manifestations of COVID-19 patients; however, none of our patients needed hospitalization due to mildness or lack of their respiratory symptoms. HZ was hypothesized to be an alarming symptom of SARS-CoV-2 infection even in mild and asymptomatic cases due to the decline of the absolute lymphocytes count including CD3 + and CD + 4 in response to SARS-CoV-2 infection (Elsaie, Youssef, & Nada, 2020; Tartari et al., 2020).

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VIEWPOINT

COVID-19, cilia, and smell

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Keywords
COVID-19; SARS-CoV-2; smell loss; cilia

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The novel coronavirus SARS-CoV-2 is the causative agent of the global coronavirus disease 2019 (COVID-19) outbreak. In addition to pneumonia, other COVID-19-associated symptoms have been reported, including loss of smell (anosmia). However, the connection between infection with coronavirus and anosmia remains enigmatic. It has been reported that defects in olfactory cilia lead to anosmia. In this Viewpoint, we summarize transmission electron microscopic studies of cilia in virus-infected cells. In the human nasal epithelium, coronavirus infects the ciliated cells and causes deciliation. Research has shown that viruses such as influenza and Sendai attach to the ciliary membrane. The Sendai virus enters cilia by fusing its viral membrane with the ciliary membrane. A recent study on SARS-CoV-2–human protein–protein interactions revealed that the viral nonstructural protein Nsp13 interacts with the centrosome components, providing a potential molecular link. The mucociliary escalator removes inhaled pathogenic particles and functions as the first line of protection mechanism against viral infection in the human airway. Thus, future investigation into the virus–cilium interface will help further the battle against COVID-19.

COVID-19 impairs smell

A novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus of the family Coronaviridae with a positive-sense, single-stranded RNA genome [1,2]. SARS-CoV-2 was identified as the etiological agent that causes the global outbreak of coronavirus disease 2019 (COVID-19) [1,2]. Historically, several mild common cold coronaviruses such as hCoV-OC43 were reported to infect humans [3]. However, highly pathogenic human coronaviruses have emerged during the past two decades, including SARS-CoV in 2002 and MERS-CoV in 2012, which can result in acute respiratory distress syndrome, potentially leading to a reduction in lung function or death [2,4,5]. Despite the low fatality rate, SARS-CoV-2 spreads more efficiently than SARS-CoV or MERS-CoV, which makes it challenging to contain [5,6]. By late June 2020, more than 9.4 million laboratory-confirmed infections were reported worldwide, including 0.48 million deaths [7]. The active therapeutic measures available to counteract the SARS-CoV-2 virus are limited, and the associated COVID-19 pathology is not well documented. Thus, it is urgent to understand how SARS-CoV-2 hijacks the host during infection and how the disease disrupts the cellular structure and function.

Coronavirus disease 2019 is predominantly a lung infection, causing cough, fever, and fatigue, but other symptoms have been reported throughout the body [1,8]. A previously unrecognized symptom of SARS-CoV-2 disease, loss of smell, has been acknowledged by clinicians and the public globally. A recent clinical study described that smell and taste impairments were

Abbreviations
ACE2, angiotensin-converting enzyme 2.

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RHINOLOGY

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

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Abstract

Objective To investigate the occurrence of olfactory and gustatory dysfunctions in patients with laboratory-confirmed COVID-19 infection.

Methods Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. The following epidemiological and clinical outcomes have been studied: age, sex, ethnicity, comorbidities, and general and otolaryngological symptoms. Patients completed olfactory and gustatory questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

Results A total of 417 mild-to-moderate COVID-19 patients completed the study (263 females). The most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The sQO-NS scores were significantly lower in patients with anosmia compared with normosmic or hyposmic individuals ($p = 0.001$). Among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$).

Conclusion Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection.

Keywords Coronavirus · COVID · COVID-19 · SARS-CoV-2 · Anosmia · Smell · Hyposmia · Dysgeusia · Taste · Loss · Gustatory · Olfactory · Olfaction · Infection · ENT

Jerome R. Lechien and Carlos M. Chiesa-Estomba have equally contributed to this work and should be regarded as joint first authors.

Tareck Ayad and Sven Saussez have equally contributed to this work and should be regarded as joint senior authors.

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Extended author information available on the last page of the article

Introduction

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic that emerged from East Asia and quickly spread to the rest of the world [1]. This infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is so far responsible for more than 15,000 deaths worldwide [2]. Human-to-human transmission is characterized by a troubling exponential rate, which

blood Perspective

COVID-19 and its implications for thrombosis and anticoagulation

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Severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019 (COVID-19)-induced infection can be associated with a coagulopathy, findings consistent with infection-induced inflammatory changes as observed in patients with disseminated intravascular coagulopathy (DIC). The lack of prior immunity to COVID-19 has resulted in large numbers of infected patients across the globe and uncertainty regarding management of the complications that arise in the course of this viral illness. The lungs are the target organ for COVID-19; patients develop acute lung injury that can progress to respiratory failure, although multiorgan failure can also occur. The initial coagulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen-degradation products, whereas abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations. Coagulation test screening, including the measurement of D-dimer and fibrinogen levels, is suggested. COVID-19–associated coagulopathy should be managed as it would be for any critically ill patient, following the established practice of using thromboembolic prophylaxis for critically ill hospitalized patients, and standard supportive care measures for those with sepsis-induced coagulopathy or DIC. Although D-dimer, sepsis physiology, and consumptive coagulopathy are indicators of mortality, current data do not suggest the use of full-intensity anticoagulation doses unless otherwise clinically indicated. Even though there is an associated coagulopathy with COVID-19, bleeding manifestations, even in those with DIC, have not been reported. If bleeding does occur, standard guidelines for the management of DIC and bleeding should be followed. (*Blood*. 2020;135(23):2033-2040)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has besieged us with its relentless worldwide march and high morbidity and mortality. Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) is a coronavirus with human infection designated as COVID-19 by the World Health Organization. Bats and birds serve as the typical coronavirus hosts, with zoonotic spread and a long-documented history of animal-animal-human transmission.[1] In December 2019, an outbreak of a new type of coronavirus was noted with a novel member of the coronavirus genera. The viral reservoir may be bats, given the high homology of SARS-CoV-2 to other SARS-like viruses found in bats.[2]

SARS-CoV-2 is like SARS and Middle East respiratory syndrome viruses in the *Coronaviridae* family, with its positive-sense single-stranded RNA genome containing a surface glycoprotein that studs the viral envelope, giving it the characteristic corona on electron microscopic imaging.[3] These peplomers are known as spike proteins, or S protein, and are thought to be responsible for the tropism it displays as they engage only with specific receptors on the cell surfaces of target organisms.[4] SARS-CoV-2 appears to preferentially target respiratory epithelium where it enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, similar to SARS-CoV.[4,5]

Initial reporting of findings from China have helped inform and guide the world. Dissemination of information is important, yet within quick succession of the findings, the time needed to interpret and apply the information by frontline workers is nonexistent, as hospitals and staff become overwhelmed with the rapid influx of COVID-19 patients. Guidance from subspecialists is critically important to help clinicians engaged in COVID-19 patient care, especially as multiple specialties are needed for patient management in intensive care unit (ICU) and non-ICU settings.

In this *Perspective*, we will review data for coagulation abnormalities that occur in association with COVID-19, and the clinical management questions likely to arise. Approaches to management will be discussed in the context of past management strategies and the unique issues of COVID-19. Our considerations are based on evolving data and consensus, and are for coagulopathy management in disseminated intravascular coagulopathy (DIC) applied to COVID-19 patients.

little use in comparing therapeutic efficacies across trials with different study designs.

The (often erratic) variability of symptom patterns over time in patients who have IBS has become a familiar occurrence to all health-care professionals involved in a patient's long-term care, and thus we do not find it unusual that a "change in direction of symptom improvement after week 5" occurred. Contrary to Enck and colleagues' comments, it should be pointed out that patient instructions remained unaltered during the entire study.

We concur with Enck and colleagues that the study treatment markedly improved almost all relevant IBS symptoms; however, we are somewhat puzzled that they should find this observation so surprising. Rather, we consider this observation unsurprising because several defined pharmacological and non-pharmacological therapeutic interventions have been shown to be effective for different symptoms; and within the complex pathogenic framework of IBS, identical patho-mechanisms have been shown across widely different clinical symptom patterns. For example, impairment of epithelial barrier function has been established as a crucial defect in all IBS subtypes, and thus has been shown to be independent of individual predominant symptoms, such as diarrhoea or constipation.[4] Convincing evidence was presented by Bühner and colleagues,[5] who showed that pathological activation of enteric neurons occurs in people with IBS. In this landmark study, patients with IBS were purposefully selected to represent all relevant IBS subtypes; aberrant neuronal responses and responsible intermediary mechanisms were almost identical in all symptom subgroups, and thus not associated with IBS subtype.[5]

Hence, if we can assume that an individual pathomechanism can be causative for triggering or enhancing the entire IBS symptom spectrum, we can assume inversely that therapeutic attenuation of such a mechanism by a single approach can induce amelioration of different symptoms, as observed in our study.

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Gastrointestinal and liver involvement in patients with COVID-19

Gastrointestinal symptoms and liver injury are not uncommon in patients with COVID-19, as stated in the systematic review and meta-analysis reported by Ren Mao and colleagues.[1] However, we have some concerns about the study.

First, when doing pooled analyses of the overall prevalence of abnormal liver chemistry and liver injury, it would be more appropriate to analyse the data stratified by the severity of COVID-19. As stated by the investigators, patients with severe COVID-19 have a greater risk of liver injury than do patients with non-severe COVID-19. Hence, the overall prevalence of increased aminotransferases and liver injury is influenced by the proportion of patients with severe COVID-19 included; the more studies enrolling patients with severe COVID-19 in the meta-analysis, the higher the prevalence of increased amino-transferases and liver injury is likely to be. Consequently, a subgroup analysis based on the severity of COVID-19 is more valuable to assess the prevalence of liver injury than is a pooled analysis.

Second, not all abnormal liver function tests mean that patients with COVID-19 have liver injury.[2,3] Elevated aminotransferases might partly result from myocardial injury and muscle injury.[2,3] Some of the studies included in Mao and colleagues' meta-analysis[1] only reported data for hypertransaminaemia.[4–6] When doing their pooled analysis of the prevalence of liver injury, Mao and colleagues[1] considered hypertransaminaemia as liver injury. We do not think this is appropriate. As a result, the prevalence of liver injury might be overestimated in patients with COVID-19.

We declare no competing interests. YX and PL contributed equally to this Correspondence.

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1 Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 667–78.

BRIEF REPORT

First Case of 2019 Novel Coronavirus in the United States

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SUMMARY

An outbreak of novel coronavirus (2019-nCoV) that began in Wuhan, China, has spread rapidly, with cases now confirmed in multiple countries. We report the first case of 2019-nCoV infection confirmed in the United States and describe the identification, diagnosis, clinical course, and management of the case, including the patient's initial mild symptoms at presentation with progression to pneumonia on day 9 of illness. This case highlights the importance of close coordination between clinicians and public health authorities at the local, state, and federal levels, as well as the need for rapid dissemination of clinical information related to the care of patients with this emerging infection.

From the Epidemic Intelligence Service (M.L.H.), the National Center for Immunizations and Respiratory Diseases (A.C., L.F., A.P.), the Division of Viral Diseases (S.I.G., L.K., S.T., X.L., S. Lindstrom, M.A.P., W.C.W., H.M.B.), the Influenza Division (T.M.U.), and the Division of Preparedness and Emerging Infections (S.K.P.), Centers for Disease Control and Prevention, Atlanta; and the Washington State Department of Health, Shoreline (M.L.H., C.D., S. Lindquist, K.H.L., J.W.), Snohomish Health District (H.B., C.S.), Providence Medical Group (K.E.), and Providence Regional Medical Center (S.W., A.T., G.D.), Everett, and Department of Medicine, University of Washington School of Medicine, Seattle (C.S.) — all in Washington. Address reprint requests to Ms. Holshue at the Washington State Department of Health Public Health Laboratories, 1610 NE 150th St., Shoreline, WA 98155, or at michelle.holshue@doh.wa.gov.

*A full list of the members of the Washington State 2019-nCoV Case Investigation Team is provided in the Supplementary Appendix, available at NEJM.org.

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On December 31, 2019, China reported a cluster of cases of pneumonia in people associated with the Huanan Seafood Wholesale Market in Wuhan, Hubei Province.[1] On January 7, 2020, Chinese health authorities confirmed that this cluster was associated with a novel coronavirus, 2019-nCoV.[2] Although cases were originally reported to be associated with exposure to the seafood market in Wuhan, current epidemiologic data indicate that person-to-person transmission of 2019-nCoV is occurring.[3-6] As of January 30, 2020, a total of 9976 cases had been reported in at least 21 countries,[7] including the first confirmed case of 2019-nCoV infection in the United States, reported on January 20, 2020. Investigations are under way worldwide to better understand transmission dynamics and the spectrum of clinical illness. This report describes the epidemiologic and clinical features of the first case of 2019-nCoV infection confirmed in the United States.

CASE REPORT

On January 19, 2020, a 35-year-old man presented to an urgent care clinic in Snohomish County, Washington, with a 4-day history of cough and subjective fever. On checking into the clinic, the patient put on a mask in the waiting room. After waiting approximately 20 minutes, he was taken into an examination room and underwent evaluation by a provider. He disclosed that he had returned to Washington State on January 15 after traveling to visit family in Wuhan, China. The patient stated that he had seen a health alert from the U.S. Centers for Disease Control and

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19*

ABSTRACT

BACKGROUND

Since December 2019, when coronavirus disease 2019 (Covid-19) emerged in Wuhan city and rapidly spread throughout China, data have been needed on the clinical characteristics of the affected patients.

METHODS

We extracted data regarding 1099 patients with laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020. The primary composite end point was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death.

RESULTS

The median age of the patients was 47 years; 41.9% of the patients were female. The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. Only 1.9% of the patients had a history of direct contact with wildlife. Among nonresidents of Wuhan, 72.3% had contact with residents of Wuhan, including 31.3% who had visited the city. The most common symptoms were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality was found in 157 of 877 patients (17.9%) with nonsevere disease and in 5 of 173 patients (2.9%) with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission.

CONCLUSIONS

During the first 2 months of the current outbreak, Covid-19 spread rapidly throughout China and caused varying degrees of illness. Patients often presented without fever, and many did not have abnormal radiologic findings. (Funded by the National Health Commission of China and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Zhong at the State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Rd., Guangzhou, Guangdong, China, or at nanshan@vip.163.com.

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SARS-Associated Viral Hepatitis Caused by a Novel Coronavirus: Report of Three Cases

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Liver impairment is commonly reported in up to 60% of patients who suffer from severe acute respiratory syndrome (SARS). Here we report the clinical course and liver pathology in three SARS patients with liver impairment. Three patients who fulfilled the World Health Organization case definition of probable SARS and developed marked elevation of alanine aminotransferase were included. Percutaneous liver biopsies were performed. Liver specimens were examined by light and electron microscopy, and immunohistochemistry. Reverse-transcriptase polymerase chain reaction (RT-PCR) using enhanced real-time PCR was applied to look for evidence of SARS-associated coronavirus infection. Marked accumulation of cells in mitosis was observed in two patients and apoptosis was observed in all three patients. Other common pathologic features included ballooning of hepatocytes and mild to moderate lobular lymphocytic infiltration. No eosinophilic infiltration, granuloma, cholestasis, fibrosis, or fibrin deposition was noted. Immunohistochemical studies revealed 0.5% to 11.4% of nuclei were positive for proliferative antigen Ki-67. RT-PCR showed evidence of SARS-associated coronavirus in the liver tissues, but not in the sera of all 3 patients. However, electron microscopy could not identify viral particles. No giant mitochondria, micro- or macro-vesicular steatosis was observed. In conclusion, hepatic impairment in patients with SARS is due to SARS-associated coronavirus infection of the liver. The prominence of mitotic activity of hepatocytes is unique and may be due to a hyperproliferative state with or without disruption of cell cycle by the coronavirus. With better knowledge of pathogenesis, specific therapy may be targeted to reduce viral replication and modify the disease course. (HEPATOLOGY 2004;39:302–310.)

Coronaviruses are enveloped viruses with single-stranded, positive-sense RNA that is 5′ capped and 3′ polyadenylated and replicates in the cytoplasm of infected cells.[1] They include a large number of viruses that infect different animal species. The predominant diseases associated with these viruses are respiratory and enteric infections, although hepatic and neurologic diseases also occur. Severe acute respiratory syndrome–associated coronavirus (SARS-CoV) is a novel virus that has been found to be a causative agent of a recently described atypical pneumonia.[2,3] The disease may progress rapidly, resulting in acute respiratory distress syndrome. At the time of writing, more than 8,221 individuals were affected worldwide and 735 patients had succumbed to the illness, which the World Health Organization (WHO) has termed *severe acute respiratory syndrome* (SARS).

Liver impairment is common and has been reported in up to 60% of patients suffering from SARS.[2,4,5] The majority of these patients have been treated with antibiotics, antiviral medications, and steroids, which are potentially hepatotoxic. Hence, whether or not SARS-CoV infection can lead to liver damage *per se* remains unknown. Here we report the clinical course and liver pathology in three SARS patients with liver impairment.

Methods

Patients

Three patients who fulfilled the WHO case definition of probable SARS[6] and developed liver derangement were

Abbreviations: SARS, severe acute respiratory syndrome; WHO, World Health Organization; RT-PCR, reverse-transcriptase polymerase chain reaction; PCR, polymerase chain reaction; SARS-CoV, SARS-associated coronavirus; CMV, cytomegalovirus; ALT, alanine aminotransferase.

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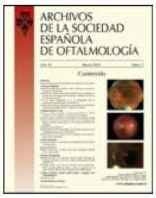

Revisión

Manifestaciones oftalmológicas del SARS-CoV-2: Revisión de la literatura

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RESUMEN

En esta revisión resumimos las principales publicaciones que informan sobre las potenciales manifestaciones oculares de la enfermedad por el nuevo coronavirus (COVID-19). La evidencia científica se basa en cartas al editor, casos clínicos aislados y series de casos, principalmente de corte transversal. Hasta la fecha, incluimos la conjuntivitis viral, una conjuntivitis inmunomediada y parálisis oculomotoras (POM). Se discute la posibilidad de retinopatía. La conjuntivitis viral puede aparecer aislada o asociada al cuadro sistémico, principalmente pulmonar, antes o después del inicio de los síntomas respiratorios. Puede ser tanto unilateral como bilateral, es típica la presencia de folículos, y presenta una duración variable entre 5 y 20 días. La conjuntivitis inmunomediada consiste en un enrojecimiento ocular acompañada de eritrodermia y febrícula. Aparece más frecuentemente en los niños y se ha asociado a un cuadro «Kawasaki-like» y síndrome del shock tóxico. Las POM pueden presentarse de forma aislada, o formando parte de un síndrome de Miller-Fisher, junto con ataxia e hiporreflexia. Los oftalmólogos presentamos un riesgo considerable de contraer la COVID-19 debido a un contacto estrecho con el paciente, exposición a las lágrimas y a las secreciones oculares y al uso de multitud de equipos y aparatos susceptibles de contaminarse.

Ocular manifestations of SARS-CoV-2: Literature review

Keywords:
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ABSTRACT

In this review, a summary is presented of the main reports regarding the potential ocular manifestations of the new coronavirus disease (COVID-19). Scientific evidence is based on letters to the editor, clinical cases and case series, cross-sectional, and a few longitudinal studies. To date, it includes viral conjunctivitis, immune conjunctivitis, and oculomotor palsies (OCP) due to the novel coronavirus. Retinopathy is discussed. A viral conjunctivitis outbreak can be isolated or associated with the systemic picture, mainly pulmonary, before

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viruses

MDPI

Review

Virology, Epidemiology, Pathogenesis, and Control of COVID-19

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Abstract: The outbreak of emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) in China has been brought to global attention and declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Scientific advancements since the pandemic of severe acute respiratory syndrome (SARS) in 2002~2003 and Middle East respiratory syndrome (MERS) in 2012 have accelerated our understanding of the epidemiology and pathogenesis of SARS-CoV-2 and the development of therapeutics to treat viral infection. As no specific therapeutics and vaccines are available for disease control, the epidemic of COVID-19 is posing a great threat for global public health. To provide a comprehensive summary to public health authorities and potential readers worldwide, we detail the present understanding of COVID-19 and introduce the current state of development of measures in this review.

Keywords: SARS-CoV-2; COVID-19; epidemiology; pathogenesis; therapeutics

1. Introduction

At the end of 2019, a cluster of pneumonia patients with an unidentified cause emerged in Wuhan, Hubei Province, China [1]. Since then, outbreaks and sporadic human infections have resulted in more than 80,000 laboratory confirmed cases (update on March 23, 2020) across mainland China. Through the analysis of sequence, this unidentified pneumonia was considered to be caused by a novel coronavirus (CoV) named 2019-nCoV [2]. Subsequently, the World Health Organization (WHO) announced a standard format of Coronavirus Disease-2019 (COVID-19), according to its nomenclature, for this novel coronavirus pneumonia on February 11, 2020 [3]. On the same day, the International Committee on Taxonomy of Viruses (ICTV) named this novel coronavirus as SARS-CoV-2 [4]. So far, the SARS-CoV-2 infection is still spreading, and this virus poses a serious threat to public health, though joint prevention and quarantine mechanisms in almost all provinces of mainland China have been confirmed to be enacted. Due to a lack of specific antiviral treatments and pressure of clinical treatment, thousands of severe cases have died every day worldwide. In this review, we discuss the virology, clinical and molecular epidemiology, diagnosis, pathogenesis, and potential therapeutics for treatment of this infection.

El COVID-19
EN REPÚBLICA DOMINICANA.
TRATADO POR ESPECIALISTAS DE LA SALUD

DRA. EVANGELINA SOLER
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Case Report

Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department

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ABSTRACT

The 2019 coronavirus disease (COVID-19) has not appeared to affect children as severely as adults. However, approximately 1 month after the COVID-19 peak in New York City in April 2020, cases of children with prolonged fevers abruptly developing inflammatory shock-like states have been reported in Western Europe and the United States.

This case series describes four previously healthy children with COVID-19 infection confirmed by serologic antibody testing, but negative by nasopharyngeal RT-PCR swab, presenting to the Pediatric Emergency Department (PED) with prolonged fever (5 or more days) and abrupt onset of hemodynamic instability with elevated serologic inflammatory markers and cytokine levels (IL-6, IL-8 and TNF-α).

Emergency physicians must maintain a high clinical suspicion for this COVID-19 associated post-infectious cytokine release syndrome, with features that overlap with Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS) in children with recent or current COVID-19 infection, as patients can decompensate quickly.

1. Introduction

The 2019 coronavirus disease (COVID-19) caused by SARS-CoV-2 was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. Although children of all ages are susceptible to COVID-19, clinical manifestations have generally been reported as less severe than in adults [1]. As of May 2 2020, the U.S. CDC reported 17,982 confirmed cases of COVID-19 in American children <18 years old with at least 3 deaths in children <15 years old.

It is speculated that children have had milder illness for several reasons. First, ACE2, which is the likely cell receptor of SARS-CoV-2, may be less developed leading to decreased ability of the virus to bind in children [2]. Additionally, children may have cross-immunity from other viral infections, and/or their developing immune systems may respond to SARS-CoV-2 differently [1].

On April 26, 2020, the Pediatric Intensive Care Society in the United Kingdom issued an alert that children of all ages are presenting with a multi-system inflammatory state requiring intensive care across their region. They describe children with overlapping features of Toxic Shock Syndrome (TSS) and atypical Kawasaki Disease (KD) with blood parameters consistent with severe COVID-19 in children. They have observed this in children with confirmed RT-PCR positive SARS-CoV-2 infection as well as children who are RT-PCR negative.

Below, we describe four similar COVID-19 serology positive, RT-PCR negative patients who presented to our New York City Pediatric Emergency Department (PED) approximately 1 month from the peak of 6207 new COVID-19 cases reported on April 6, 2020. All four patients developed a similar multi-system, inflammatory state requiring admission to the Pediatric Intensive Care Unit (PICU).

2. Case reports

2.1. Case 1

A 13-year-old male with hypothyroidism was brought to the ED by his father for 1 day of rash, and 6 days of fever, cough, fatigue and myalgias. On the sixth day of illness, he developed bilateral conjunctivitis, a truncal rash, and redness of his palms. He had a few days of abdominal discomfort and loose stools with several isolated episodes of nonbloody, nonbilious emesis over this time period. He also endorsed a mild intermittent frontal headache. The patient denied shortness of breath or sore throat. His father had suspected COVID-19 infection one month prior, with the patient being asymptomatic at the time of the father's illness.

Abbreviations: COVID-19, 2019 coronavirus disease; KD, Kawasaki Disease; TSS, Toxic Shock Syndrome; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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Manifestaciones orales y maxilofaciales asociadas a la COVID-19. Revisión de la literatura

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Claudia Patricia Peña–Vega 3
Andrés Rueda–Jiménez 4

Oral and maxillofacial manifestations associated with COVID-19. Literature review

RESUMEN

Objetivo: realizar una revisión, descripción y análisis de los estudios y reportes de casos con información sobre la posible relación existente entre las manifestaciones orales y maxilofaciales reportadas y la COVID-19. **Métodos:** se revisaron 16 publicaciones realizadas en bases de datos de Pubmed, SciencedDirect, Google Académico, ProQuest, Medline Complete y Nature. Los términos de búsqueda empleados fueron ***COVID-19 y oral manifestations***, relacionados en la ecuación de búsqueda con el conector booleano "AND". **Resultados:** 22 casos de pacientes que presentaron manifestaciones orofaciales asociadas a la COVID-19. La distribución entre mujeres y hombres fue similar con porcentajes de 45,5% y 54,5%, respectivamente. Diagnóstico de la COVID-19 positivo en un 86,4% y sospechoso de infección en un 13,6%. La ubicación más frecuente de lesiones fue en mucosa masticatoria (31,3%), mucosa de revestimiento (28,1%) y lengua (15,6%). A nivel facial, 25% de los reportes evaluados informaron lesiones. El edema retromandibular, en el 23,8 % de los casos evaluados, y las úlceras en mucosa oral, en el 28,6%, fueron el tipo más frecuente de lesiones. **Conclusiones:** las manifestaciones orales y maxilofaciales en pacientes con COVID-19 han sido reportadas en algunas publicaciones; las más frecuentes han sido las relacionadas con edema retromandibular (parotiditis) y úlceras. Se sugiere una posible asociación de dichas manifestaciones con la infección por SARS-CoV-2 o con coinfecciones o comorbilidades del paciente, administración de medicamentos, estancia hospitalaria en UCI o ventilación mecánica. Aunque los reportes son pocos, estos pueden servir como pauta para futuros estudios que permitan esclarecer esta relación.

Palabras clave: COVID-19; manifestacion; oral; maxilofacial; síntomas.

ABSTRACT

Objective: to carry out a review, description and analysis of the studies and case reports with information on the possible relationship between reported oral and maxillofacial manifestations and COVID-19. **Methods:** 16 publications made in databases of Pubmed, SciencedDirect, Google Scholar, ProQuest, Medline Complete and Nature were reviewed. The search terms used were COVID-19 and oral manifestations, related in the search equation with the Boolean connector "AND". **Results:** 22 cases of patients who presented orofacial manifestations associated with COVID-19. The distribution between women and men was similar with percentages of 45.5% and 54.5%, respectively. COVID-19 diagnosis positive in 86.4% and suspected of infection in 13.6%. The most frequent location of lesions was masticatory mucosa (31.3%), lining mucosa (28.1%) and tongue (15.6%). At the facial level, 25% of the evaluated reports reported injuries. Retromandibular edema in 23.8% of the cases evaluated and ulcers in the oral mucosa in 28.6% were the most frequent type of lesions. **Conclusions:** oral and maxillofacial manifestations in patients with COVID-19 have been reported in some publications; the most frequent have been those related to retromandibular edema (parotitis) and ulcers. A possible association of these manifestations with SARS-CoV-2 infection or with co-infections or comorbidities of the patient, administration of medications, hospital stay in ICU or mechanical ventilation is suggested. Although the reports are few, they can serve as a guideline for future studies to clarify this relationship.

Key words: COVID-19; manifestation; oral; maxillofacial; symptoms.

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CRITICAL REVIEW

Salivary Glands, Saliva and Oral Findings in COVID-19 Infection

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Abstract

The world is under the threat of the novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite several efforts to contain the disease spread, it still constitutes a public health emergency of international concern. Several published reports in the scientific literature called attention of the oral cavity as the potential route of infection, the implications for dental practice and the use of saliva in the diagnose of the COVID-19. The aim of this article is to provide an overview of the literature on the salivary glands and saliva in the context of SARS-CoV-2 infection. A brief discussion of taste disturbances and oral findings in COVID-19 patients is also presented. The literature shows that SARS-CoV-2 could infect the salivary glands. It is not possible, however, to make speculations regarding them as reservoirs for the SARS-CoV-2. In addition, patients with COVID-19 presented several oral repercussions, including hyposalivation and taste disturbances. A few reports showed oral ulcers and blisters associated with SARS-CoV-2 infection. However, it remains not fully understood and might lead to erroneous assumptions. Overall, further studies are necessary to understand the real role of salivary glands and saliva in the context of SARS-CoV-2 infection.

Keywords: Infections; Severe Acute Respiratory Syndrome; Salivary Glands; Saliva; Oral Manifestations.

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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Oral manifestations of COVID-19 disease: A review article

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Abstract

Dysgeusia is the first recognized oral symptom of novel coronavirus disease (COVID-19). In this review article, we described oral lesions of COVID-19 patients. We searched PubMed library and Google Scholar for published literature since December 2019 until September 2020. Finally, we selected 35 articles including case reports, case series and letters to editor. Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), and palate (22%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. Oral lesions were symptomatic in 68% of the cases. Oral lesions were nearly equal in both genders (49% female and 51% male). Patients with older age and higher severity of COVID-19 disease had more widespread and sever oral lesions. Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients.

KEYWORDS
aphthous, COVID-19, gingivostomatitis, manifestation, oral

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-chain RNA virus that is the cause of novel coronavirus disease known as COVID-19. The most common clinical symptoms are fever, headache, sore throat, dyspnea, dry cough, abdominal pain, vomiting, and diarrhea. Angiotensin converting enzyme 2 (ACE 2) receptor is a known receptor for SARS-CoV-2 that is found in the lung, liver, kidney, gastrointestinal (GI) and even on the epithelial surfaces of sweet glands and on the endothelia of dermal papillary vessels. Todate, various cutaneous manifestations of COVID-19 disease have been described including varicelliform lesions, pseudochilblain, erythema multiforme (EM)-liker lesions, urticaria form, maculopapular, petechiae and purpura, mottling, and livedo reticularis-like lesions.[1,2]

At the beginning of COVID-19 pandemic, it was assumed that lack of oral involvement is a differentiating feature of COVID-19 exanthema relative to other viral exanthemas. Recently, SARS-CoV-2 has been detected from saliva of the patients and it has been demonstrated that reverse transcriptase-polymerase chain reaction (RT-PCR) from saliva can even be a more sensitive test in comparison with nasopharyngeal test. Furthermore, ACE2 has been found in oral mucosa, especially with more density on dorsum of tongue and salivary glands relative to buccal mucosa or palates. To date, there is only one systematic review that described oral manifestations of COVID-19 disease; however, it mostly focused on impairment of taste. Dysgeusia is the first recognized oral symptom of COVID-19 reported in 38% of patients, mostly in North Americans and Europeans, females, and patients with mild-moderate disease severity.[1] In this review article, we described oral lesions of COVID-19 patients.

International Journal of Dermatology

Correspondence

Oral vesicles and acral erythema: report of a cutaneous manifestation of COVID-19

Dear Editor,

Dermatologic manifestations of COVID-19 are emerging, which include a wide range of presentations from exanthema, urticaria, livedo, and petechiae to vasculitis and vasculopathic skin eruptions. Acro-ischemic, pernio-like eruptions have been reported in children and adolescents. Herein, we report a 9-year-old girl presenting with fever, a vesicular oral eruption, and acral erythematous papules and plaques preceding the development of respiratory symptoms of COVID-19. The pneumonia and skin eruption favorably improved over the course of a few weeks with supportive therapy. Clinicians should consider COVID-19 within the differential of oral vesicular eruptions, especially in children.

A 9-year-old previously healthy girl, from Qom, Iran, presented with profound weakness, loss of appetite, high fever (maximum temperature of 39.6 °C), abdominal pain, diarrhea, and skin eruption. Her parents denied use of medications other than acetaminophen for pain and fever relief. There was a family history of COVID-19 infection in her aunt about 1 month before presentation; our patient had multiple close contact interactions with her aunt over the preceding weeks. On skin examination, she was noted to have vesicles and erosions involving the lips, anterior tongue, and buccal mucosa (Fig. 1). She had deep red, edematous papules and plaques involving the dorsal hands and feet (Fig. 2). Three days later, she developed dry cough, shortness of breath with tachypnea (respiratory rate: 60/minute), hypoxia (O_2 saturation: 88%), and somnolence. A chest x-ray showed ground glass densities involving bilateral lungs. Nasopharyngeal swab RT-PCR was positive for COVID-19 virus. She was treated conservatively with hydration, supplemental oxygen therapy as needed at home. Her symptoms gradually improved over the course of a few weeks, and mucocutaneous eruption resolved in about a week.

Reports regarding the cutaneous manifestations of a novel coronavirus infection, COVID-19, are on the rise. The initial report from Italian dermatologists described skin manifestations in 20% of affected patients; 44% of these patients had skin eruption at disease onset.[1] Cutaneous manifestations of COVID-19 are polymorphic and most commonly include exanthematous and urticarial eruptions, followed by livedoid, petechial, vesicular eruptions, and cutaneous vasculitis.[2,3] An acro-ischemic, pernio-like eruption has been reported in asymptomatic or mildly affected children and adolescents.[4] Histopathologic evaluation of COVID-19 skin lesions may show vascular microthrombi and lymphocytic vasculitis.[5]

We report a child with a vesicular/herpetiform oral eruption and acral erythematous papules and plaques as initial manifestation of COVID-19. At presentation, the differential diagnosis

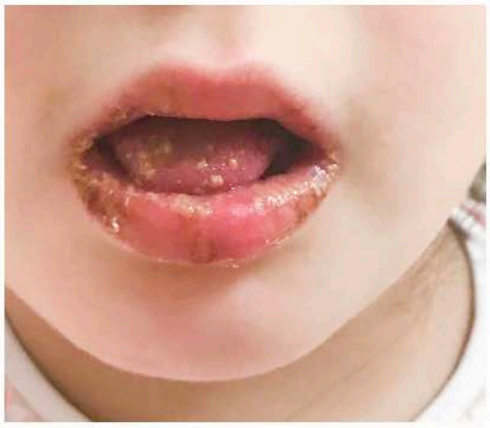

Figure 1 Vesicles and erosions involving the lips and anterior tongue in a grouped distribution

Figure 2 Deeply erythematous to violaceous papules and plaques involving the dorsal and plantar feet

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Article type : Research Letter

Prevalence of mucocutaneous manifestations, oral and palmoplantar findings in 666 patients with COVID-19 in a field hospital in Spain

Dear Editor:

Coronavirus disease 2019 (Covid-2019) has been associated with several cutaneous manifestations(1–3). A temporary field hospital was implemented during the pandemic peak in Madrid, Spain, to attend COVID-19 patients with mild to moderate pneumonia.

A team of dermatologists working as medical volunteers performed a cross-sectional study between April 10 and April 25, 2020 to evaluate cutaneous findings of such patients.

A total of 666 COVID-19 patients fulfilled the inclusion criteria (either positive RT-PCR testing for SARS-CoV-2 or bilateral pneumonia). The mean age was 55.67 years; with a slight female predominance (58%). Remarkably, 47.1% were from-Latin America.

Globally, 304 (45.65%) of our patients presented one or more mucocutaneous manifestations. Oral cavity findings were seen in 78 (25.65%) cases, including transient lingual papillitis (11.5%), glossitis with lateral indentations (6.6%)(Figure 1A), aphthous stomatitis (6.9%), glossitis with patchy depapillation (3.9%) (Figure 1B) and mucositis (3.9%). Burning sensation was reported in 5.3% of patients and taste disturbances (dysgeusia) was commonly associated.

Palmoplantar involvement was observed in 121 patients (39.8%) and included diffuse desquamation in 77 patients (25.3%), often favouring the weight bearing areas and reddish-to-brown acral macules on palms and soles in 46 (15.1%)(Figure 1C and 1D). Mild pruritus was occasionally reported. Fungal cultures of plantar desquamation performed in 9 patients ruled out superficial mycoses. Histological study from the acral macules was performed in 4 patients, showing a mild to moderate lymphocytic infiltrate surrounding the blood vessels and the eccrine

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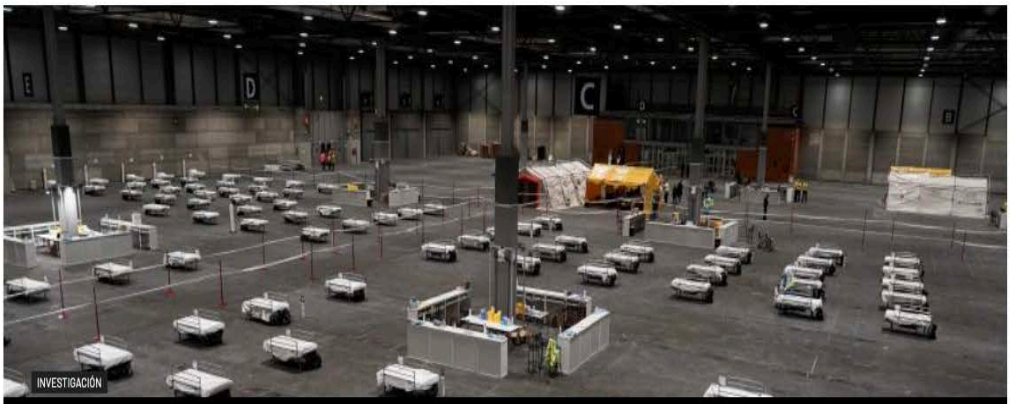
GACETA MÉDICA 20 años



INVESTIGACIÓN

Un estudio español revela alteraciones en la lengua como un nuevo síntoma de COVID-19

La investigación se ha desarrollado con pacientes ingresados durante el mes de abril en el Hospital de la Comunidad de Madrid en IFEMA

Por **Gaceta Médica** - 26 enero 2021

Un estudio español liderado por el **Hospital Universitario La Paz y de Atención Primaria del Servicio Madrileño de Salud (SERMAS) de la Comunidad de Madrid** ha revelados nuevos síntomas asociados al SARS-CoV-2, entre ellas, la lengua COVID-19.

La investigación, que se ha desarrollado con pacientes ingresados durante el mes de abril en el

CORONAVIRUS ◇ INFORMACIÓN

El nuevo síntoma es la lengua Covid

escrito por WebSalud | 18 enero 2021

Compartir en:

El coronavirus sigue sorprendiendo. Cada vez aparecen más consecuencias, más señales de que el patógeno está en nuestro cuerpo. **El nuevo síntoma es la lengua Covid**. Así lo ha alertado Tim Spector, profesor de epidemiología genética en el King's College de Londres, en su cuenta de Twitter. El SARS-CoV-2 no sólo puede provocar síntomas desconocidos hasta ahora, sino que **una de cada cinco personas con el virus sufre síntomas menos comunes** que ni siquiera están recogidos en los Sistemas de Salud. Uno de ellos es el citado de la lengua, igual que lo son las erupciones cutáneas.

En el caso de la lengua covid, estamos ante **una de las señales que todavía pasan desapercibidas** para que cada

LO + VISTO

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28 octubre 2020

2 Embarazo: cuánto mide y pesa el feto cada semana
17 diciembre 2019

3 La vacuna Hipra que puede salvar a España del Covid-19
18 abril 2021

4 ¿Qué es la hipoestesia?
18 mayo 2020

5 Piden retirar esta mascarilla FFP2 por dañar los pulmones
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21 abril 2021

Última hora sobre la

Journal of the Pediatric Infectious Diseases Society

CASE REPORT

Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series

Kathleen Chiotos,[1,2,3] Hamid Bassiri,[2,3] Edward M. Behrens,[4] Allison M. Blatz,[2] Joyce Chang,[3,4] Caroline Diorio,[5] Julie C. Fitzgerald,[1,3] Alexis Topjian,[1,3] and Audrey R. Odom John[2,3]

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We present a series of 6 critically ill children with multisystem inflammatory syndrome in children. Key findings of this syndrome include fever, diarrhea, shock, and variable presence of rash, conjunctivitis, extremity edema, and mucous membrane changes.

Keywords. COVID-19; Kawasaki disease, multisystem inflammatory syndrome in children; SARS-CoV-2.

On 27 April 2020, the United Kingdom National Health Service issued an alert highlighting a multisystem inflammatory syndrome increasingly observed across the United Kingdom, citing a possible link to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19). On 6 May 2020, authors from London, England, reported clinical and laboratory features of a cluster of 8 children with hyperinflammatory shock, all of whom tested positive for SARS-CoV-2 antibodies [1]. Clinical characteristics of these cases share features with toxic shock syndrome, Kawasaki disease, and Kawasaki disease shock syndrome, including fever, shock, and variably rash, conjunctivitis, extremity edema, and gastrointestinal symptoms. On 5 May, the New York City Department of Health issued a health alert including 15 similar cases [2]. Most recently, on14 May, the Centers for Disease Control and Prevention issued a public health advisory and case definition for this hyperinflammatory syndrome, termed multisystem inflammatory syndrome in children (MIS-C) [3]. Here, we describe the clinical features, laboratory findings, and therapies for a cohort of 6 children with MIS-C cared for in our tertiary pediatric intensive care unit (PICU).

CASE PRESENTATIONS

Case 1

A 14-year-old female with no chronic medical conditions presented with a 5-day history of fever; headache; diarrhea; a diffuse, erythematous rash; and a 1-day history of dyspnea. Her lowest documented blood pressure within 24 hours of admission was 79/39 mm Hg. Notable laboratory findings on admission included elevated inflammatory markers, hyperferritinemia, hyponatremia, and acute kidney injury. Nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) testing was negative (Table 1). Chest radiography demonstrated bilateral pulmonary infiltrates, and bedside cardiac ultrasound demonstrated moderately diminished left ventricular (LV) function (Table 2). She was emergently intubated and started on vasoactive infusions. SARS-CoV-2 PCR testing from tracheal aspirates were negative on 2 repeat samples. Vancomycin, cefepime, clindamycin, and doxycycline were started empirically for concern of toxic shock syndrome or rickettsial disease. Over the first 5 hospital days (HD), she had intermittent fevers and developed thrombocytopenia, mild coagulopathy, hypoalbuminemia, and leukocytosis. To evaluate for incomplete Kawasaki disease/Kawasaki disease shock syndrome, an echocardiogram was performed on HD 6 that demonstrated normal biventricular systolic function (shortening fraction [SF], 38%; normal, 28%–45%) but identified right coronary artery dilation (Boston *z* score, 3.15). She was then treated with intravenous immunoglobulin (IVIG) 2 g/kg, methylprednisolone 2 mg/kg/day, and low-dose aspirin. Her fever resolved on HD 6. She was weaned off vasoactive infusions by HD 5 and was extubated on HD 6. She was transferred out of the PICU on HD 8, discharged to acute rehabilitation on HD 14, and discharged home HD 17. Her final echocardiogram on HD 13 demonstrated normal biventricular systolic function (SF, 37%) and similar right coronary artery dilation (Boston *z* score, 3.32). SARS-CoV-2 immunoglobulin G (IgG) testing collected on HD 17 was positive.

Case 2

A 12-year-old male with no chronic medical conditions presented to an outside facility with a 6-day history of fever,

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LETTER TO THE EDITOR

A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis

Ping Wu[1] · Liang Liang[1] · ChunBao Chen[2] · ShengQiong Nie[1]

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Dear Editor,

As we all know, the 2019 novel coronavirus disease (COVID-19) infected by SARS-CoV-2 are spreading worldwide. It was reported that there were different clinical features between pediatric and adult patients with COVID-19 [1]. Our previous study had shown that conjunctivitis symptoms were found in a minority of adult patients confirmed COVID-19, with positive results of viral nucleic acid in conjunctival swab samples [2]. Nevertheless, there are no reports in the medical literature at this time, to our knowledge, on children infected by SARS-CoV-2 with ocular abnormalities. Here we firstly report an infected boy characterized by conjunctivitis and eyelid dermatitis without any other symptom.

The child, 2 years and 10 months old, was detected and confirmed through community screening with positive result of SARS-Cov-2 nucleic acid in his nasopharyngeal swabs on February 17, 2020. He likely acquired SARS-CoV-2 infection from his household member because of his father and grandma diagnosed before. He was quarantined at a government designated hotel with his mother, for being asymptomatic initially. On day 7 of confinement, the child presented with conjunctivitis and eyelid dermatitis (Fig. 1), and was referred to our hospital subsequently. Admission tests reconfirmed the SARS-CoV-2 infection by RT-PCR, meanwhile revealed myocardial damage and atypical change in lymphocyte count (Table 1), with normal chest CT. After treatment depending on the national protocol in China [3], conjunctivitis and eyelid dermatitis gradually disappeared 5 days later. From days 10 to 12 of admission, negative results of viral nucleic acid twice in 48 h, with positive IgG but negative IgM of the virus in serum, indicated that the virus had been cleared [4]. The child left hospital on March 7, 2020, with no respiratory and other systemic symptoms until now.

Our child was found muscle enzyme elevation unintentionally; meanwhile, the trend of recovery was not clear when leaving hospital (Table 1). It indicated that we should closely track the blood indexes of child patients as soon as earlier to know the condition of myocardium and whole system after diagnosed even though without any clinical manifestation.

Lymphocyte count usually decreased in the early stage of most adult cases [5], while that of this child was slightly higher than normal in admission tests. To some extent, it was related to that the count and proportion of lymphocytes in children under 5 years old are higher than those in adults in the general population. Therefore, the significance of this test for early diagnosis of COVID-19 should be combined with age and need to be confirmed by large sample data.

Studies had shown that ACE2 is a receptor of SARS-CoV-2 to invasion [6]. ACE2 is expressed not only in human type II alveolar epithelial cells, but also in cornea and conjunctiva [7], suggesting that ocular surface tissue may also be a potential target tissue infected by SARS-CoV-2. Our previous report had shown that conjunctivitis symptoms were found in a small number of adult patients confirmed COVID-19 [2]. However, so far, there has been no report on infected children with eye symptoms. This case showed a child involved conjunctivitis and eyelid dermatitis on day 7 of COVID-19 confirmed. It may be caused by virus infection, or by secondary bacterial infection with poor body resistance after systemic virus infection.

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JAMA Ophthalmology | Original Investigation

Ocular Manifestations and Clinical Characteristics of Children With Laboratory-Confirmed COVID-19 in Wuhan, China

Nan Ma, MD; Ping Li, MD; Xinghua Wang, MD, PhD; Yueqi Yu, MD; Xuan Tan, BS; Peng Chen, MD; Shilian Li, MD; Fagang Jiang, MD, PhD

IMPORTANCE Ocular manifestations and outcomes in children with confirmed coronavirus disease 2019 (COVID-19), relevant affecting factors, and differences in ocular disease between children and adults have yet to be fully understood.

OBJECTIVE To investigate ocular manifestations and clinical characteristics of children with laboratory-confirmed COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study was conducted at Wuhan Children's Hospital in Wuhan, China. Children with COVID-19 confirmed by severe acute respiratory syndrome coronavirus disease 2 nucleic acid tests of upper respiratory tract specimens between January 26 and March 18, 2020, were included.

MAIN OUTCOMES AND MEASURES Onset clinical symptoms and duration, ocular symptoms, and needs for medication.

RESULTS A total of 216 pediatric patients were included, among whom 134 (62%) were boys, with a median (interquartile range) age of 7.25 (2.6-11.6) years. Based on the exposure history, 193 children (89.4%) had a confirmed (173 [80.1%]) or suspected (20 [9.3%]) family member with COVID-19 infection. The most common symptoms among symptomatic children were fever (81 [37.5%]) and cough (79 [36.6%]). Of 216 children, 93 (43.1%) had no systemic or respiratory symptoms. All children with mild (101 [46.8%]) or moderate (115 [53.2%]) symptoms recovered without reported death. Forty-nine children (22.7%) showed various ocular manifestations, of which 9 had ocular complaints being the initial manifestations of COVID-19. The common ocular manifestations were conjunctival discharge (27 [55.1%]), eye rubbing (19 [38.8%]), and conjunctival congestion (5 [10.2%]). Children with systemic symptoms (29.3% vs 14.0%; difference, 15.3%; 95% CI, 9.8%-20.7%; $P = .008$) or with cough (31.6% vs 17.5%; difference, 14.1%; 95% CI, 8.0%-20.3%; $P = .02$) were more likely to develop ocular symptoms. Ocular symptoms were typically mild, and children recovered or improved.

CONCLUSIONS AND RELEVANCE In this cross-sectional study, children hospitalized with COVID-19 in Wuhan, China, presented with a series of onset symptoms including fever, cough, and ocular manifestations, such as conjunctival discharge, eye rubbing, and conjunctival congestion. Patients' systemic clinical symptoms or cough were associated with ocular symptoms. Ocular symptoms recovered or improved eventually.

CME Quiz at jamacmelookup.com and CME Questions page 1112

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Paris, le 15 avril 2020

COVID-19 ET LÉSIONS CUTANÉES
POINT D'ÉTAPE DE L'ENQUÊTE COVIDSKIN DE LA SOCIÉTÉ FRANÇAISE DE DERMATOLOGIE

Comme indiqué précédemment, des **signes cutanés ont été récemment rapportés comme possiblement associés au COVID-19.** Ceci a amené la Société Française de Dermatologie à lancer un appel à cas national **afin de confirmer ou non cette association ou lien éventuel,** en documentant précisément ces cas (recueil du contexte, de l'histoire de la maladie, des signes cliniques et de leur évolution, photos et éventuellement biopsies et exploration virologique des cas soit atypiques cliniquement, soit avec notion de contage ou signes associés).
Voici le premier point d'étape à partir des 113 cas rapportés avec une fiche d'information détaillée, principalement par des dermatologues, mais aussi des généralistes, que nous remercions.

Le groupe le plus important est celui des patients présentant des lésions à type d'engelures avec 84 patients, 36 hommes, 48 femmes, âgés de 9 à 67 ans (moyenne d'âge 30 ans). Dix-sept ont déjà eu des engelures ou un syndrome de Raynaud précédemment et dans seulement 6 cas, on trouve une exposition au froid dans les jours précédents. Un peu moins de la moitié de ces patients n'ont eu aucun signe associé. Pour les 45 autres, les signes associés étaient non graves (aucune hospitalisation), et dans la majorité des cas, il s'agissait de signes isolés (asthénie et/ou toux le plus souvent, ou fièvre, myalgies). Un seul patient a présenté une anosmie. Ces signes étaient dans la majorité des cas antérieurs à la survenue des lésions à type d'engelures (8 à 15 jours auparavant) et avaient alors le plus souvent régressé ou étaient en voie de régression. Dix patients rapportaient un contage COVID possible ou probable dans les 15 jours-trois semaines auparavant. Nous ne disposons pas encore du recul sur l'évolution de ces lésions à type d'engelure, mais pour plusieurs patients, l'évolution a été favorable soit spontanément, soit avec application de topiques cicatrisants ou de dermocorticoïdes.
Chez 32 patients, une PCR nasopharyngée a été réalisée (chez les patients avec signes cliniques) dont les résultats, disponibles à ce jour pour 18, sont tous négatifs. Ces patients ont eu pour certains une biopsie cutanée, une exploration immunologique et un bilan sérologique complémentaire (hors COVID). Les résultats de ces examens seront analysés secondairement, et présentés dans un prochain point. Il a été prévu lorsque les tests seront disponibles et validés de proposer de réaliser une sérologie COVID pour ces patients.
Au total, une manifestation inhabituellement fréquente en cette saison, non associée à une sévérité particulière, et pouvant parfois faire suite à des signes de type infectieux minimes, avec pour les cas explorés une PCR négative, ce qui n'exclut pas une possible infection COVID antérieure, mais ne permet pas non plus à ce stade de l'affirmer. Les études en cours devront le démontrer et le cas échéant préciser le mécanisme physiopathologique. Ces données ne montrent aucun argument en faveur d'une contagiosité potentielle de ces patients, message important pour les patients et leur entourage.
À noter que des travaux récemment menés par l'équipe du Pr JOLY à Rouen, actuellement soumis à publication, suggèrent de façon très convaincante sur 33 patients, l'absence de relation entre ces lésions cutanées et l'infection par le COVID-19.

Les autres patients présentaient des manifestations très variées, survenant soit sans contexte associé, soit associés à des signes infectieux, soit encore chez des patients hospitalisés y compris en réanimation pour un COVID et 8 pneumopathies. Il s'agissait d'éruptions érythémateuses du visage (les plus fréquentes) ou encore d'urticaires, d'exanthèmes maculopapuleux, d'œdèmes du dos des mains, d'érythème noueux, de livédo ou de présentation à type de pityriasis rosé de Gibert. Dans ce groupe hétérogène, une PCR était effectuée chez 16 patients et était positive dans 6 cas avec des signes infectieux généraux au premier plan et où l'atteinte cutanée n'était pas révélatrice. Des biopsies cutanées et bilan complémentaire notamment immunologique ont là aussi été effectués pour plusieurs patients.
Au total, des signes hétérogènes avec, pour ceux associés (sous réserve des résultats en cours) à une PCR positive surtout un érythème du visage ou un livédo et une infection COVID déjà connue ou suspectée.

Pr Marie BEYLOT-BARRY, Présidente de la SFD.
Dr Laurence LE CLEACH, Coordonnatrice COVIDSKIN.

Perspectiva de la dermatología y COVID-19

Natalia Calvache[1]; Juan Carlos Jaimes[2]; Paula Candelo[3]; Christian Prada[4]; Yurani Pineda[5]; Erika Peña[6]; Eduardo Fierro[7]

RESUMEN

La evidencia científica sobre manifestaciones cutáneas producidas por el nuevo coronavirus SARS-CoV-2 (COVID-19) cada vez es mayor. La exacerbación de enfermedades cutáneas preexistentes y las lesiones por uso prolongado de elementos de protección personal son emergentes. Los especialistas en dermatología deben conocerlas, orientar en su prevención y tratamiento.

En este artículo se revisan las manifestaciones cutáneas en pacientes con COVID-19, las lesiones en piel que han surgido en trabajadores de la salud, la perspectiva de la teledermatología como herramienta para combatir la pandemia, algunas consideraciones especiales y protección de la piel y membranas mucosas.

PALABRAS CLAVE: infecciones por coronavirus; manifestaciones cutáneas; pandemias; personal de salud; dermatología; teledermatología.

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Review article

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Skin manifestations of COVID-19 in children: Part 1

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Summary

The current COVID-19 pandemic is caused by the SARS-CoV-2 coronavirus. The initial recognized symptoms were respiratory, sometimes culminating in severe respiratory distress requiring ventilation, and causing death in a percentage of those infected. As time has passed, other symptoms have been recognized. The initial reports of cutaneous manifestations were from Italian dermatologists, probably because Italy was the first European country to be heavily affected by the pandemic. The overall clinical presentation, course and outcome of SARS-CoV-2 infection in children differ from those in adults as do the cutaneous manifestations of childhood. In this review, we summarize the current knowledge on the cutaneous manifestations of COVID-19 in children after thorough and critical review of articles published in the literature and from the personal experience of a large panel of paediatric dermatologists in Europe. In Part 1, we discuss one of the first and most widespread cutaneous manifestation of COVID-19, chilblain-like lesions. In Part 2, we review other manifestations, including erythema multiforme, urticaria and Kawasaki disease-like inflammatory multisystemic syndrome, while in Part 3, we discuss the histological findings of COVID-19 manifestations, and the testing and management of infected children, for both COVID-19 and any other pre-existing conditions.

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Skin manifestations of COVID-19 in children: Part 2

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Summary

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(**Figure 1**). Their HAP scores gradually increased, and the hypotrichosis in the patient with TRPS1 did not improve (**Figure 2**A). Hair shaft diameters were increased in every participant with *LIPH* pathogenic variants (Figure 2B and C). There were no serious adverse events, but some mild adverse events were reported (dry skin on the scalp, trichiasis, and mild hypertrichosis on the entire body).

Discussion | Lysophosphatidic acids bind the P2Y5 receptor in the hair follicle epithelium and activate hair growth.[5] In ARWH due to *LIPH* pathogenic variants, loss-of-function variants in *LIPH* lead to a deficiency of lysophosphatidic acids and insufficient activation of P2Y5. The present prospective interventional study suggests that minoxidil could be associated with improvements in hypotrichosis in ARWH owing to *LIPH* pathogenic variants. There appears to be a binary response to minoxidil, with one group responding better than the other. The data on causative pathogenic variants suggest that it is unrelated to the *LIPH* pathogenic variants. Among the 8 patients with ARWH due to *LIPH* pathogenic variants, 5 patients were unrelated, and the other 3 were from 1 family. All 3 members of the family were in the group responding better. Thus, we cannot exclude the possibility that the family had an unknown genetic modifying factor affecting the efficacy of minoxidil. We need to know more about the follicular pathology to understand the pharmacologic response to minoxidil.

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Enanthem in Patients With COVID-19 and Skin Rash

Recalcati[1] recently reported skin manifestations in 18 patients in Italy with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or coronavirus disease 2019 (COVID-19), describing "erythematous rash," "widespread urticaria," and "chickenpox-like vesicles." Additional reports have described other rashes, including petechial and purpuric changes,[2] transient livedo reticularis,[3] and acro-ischemic lesions.[4] Whether these manifestations are directly related to COVID-19 remains unclear, since both viral infections and adverse drug reactions are frequent causes of exanthems. An important clue to distinguish between both entities is the presence of enanthem (oral cavity lesions).[5] However, owing to safety concerns, many patients with suspected or confirmed COVID-19 do not have their oral cavity examined. Herein we describe variants of enanthem in a series of patients with COVID-19.

Methods | We included 21 consecutive patients from a tertiary care hospital who had skin rash and COVID-19, confirmed by real-time reverse transcriptase–polymerase chain reaction from a nasopharyngeal swab, and who required dermatology consultation from March 30 to April 8, 2020. The oral cavities of patients presenting with skin rash were systematically examined. Enanthems were classified into 4 categories: petechial, macular, macular with petechiae, or erythematovesicular.[5] This study was approved by the institutional review board of Ramon y Cajal University Hospital in Madrid. Accordingly, informed consent was obtained verbally from all patients before examination, and they have been deidentified through omission of individual age and sex.

Results | Of 21 patients with COVID-19 and skin rash, 6 patients (29%) had enanthem. The age range of these patients was between 40 and 69 years, and 4 of the 6 (66%) were women. The morphology of the skin rash was papulovesicular, purpuric periflexural, and erythema multiforme–like in 1, 2, and 3 patients, respectively. The clinical and histologic findings of the erythema multiforme–like exanthem have been reported

Covid-19, una mirada desde la pediatría

Covid-19, a look from pediatrics

Giuseppe Grandy [a,1,2], *Carlos G. Terán* [b,3], *Alejandro Martínez* [c,4], *Anna Volz* [d,2]

Resumen

El COVID-19 fue predominantemente más prevalente entre adultos mayores de 15 años en las primeras etapas del brote y la proporción de casos confirmados entre niños fue relativamente menor. Sin embargo, debido a la creciente propagación mundial del SARS-CoV-2, tenemos nuevos desafíos para la prevención y el control de la epidemia de COVID-19 entre los niños. Ya que en los más pequeños no se pueden emplear medidas de prevención (barbijos), la clínica inespecífica que presentan, las dificultades para el diagnóstico, la deficiente comunicación entre médico-paciente y familiar que han contribuido al desafío de desarrollar medidas para proteger a esta población, al igual que al personal de salud que manejan casos pediátricos. Al mismo tiempo, los niños con comorbilidades, s on vulnerables a la infección por SARS-CoV-2. La presente revisión intenta mostrar esta enfermedad desde el punto de vista pediátrico, para orientar en su diagnóstico y manejo.

Palabras clave: coronavirus, Covid-19, pediatría, pandemia, SARS-CoV-2

Abstract

COVID-19 was predominantly more prevalent among adults over the age of 15 in the early stages of the outbreak, and the proportion of confirmed cases among children was relatively lower. However, because younger children cannot wear chinstraps and no other preventive measures have been taken in this group. Children have certain peculiarities and we cannot clearly demonstrate their state of health, which has contributed to the serious challenge of protecting, diagnosing and treating this population. Due to the increasing worldwide spread of SARS-CoV-2, we have new challenges for the prevention and control of the COVID-19 epidemic among children. At the same time, children with comorbidities are vulnerable to SARS-CoV-2 infection. The present review tries to show this disease from the pediatric point of view, to guide its diagnosis and management.

Keywords: coronavirus, Covid-19, pediatrics, pandemic, SARS-CoV-2

Los coronavirus es una amplia familia de virus RNA (39 especies) que afectan a mamíferos y aves y capaces de producir enfermedades en humanos que van desde el resfrió común (10%) hasta enfermedades severas. Hasta la fecha se han reconocidos[6] virus como agentes causantes de una gama de infecciones de las vías respiratorias, incluidos HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV (síndrome respiratorio agudo severo) y MERS-CoV (Síndrome Respiratorio del Medio Oriente). El SARS-CoV se describió en 2003 en un epidemia única en China, que causó más de 700 muertos con un 20-30% precisando ventilación mecánica y con una letalidad del 10%, especialmente elevada en pacientes con comorbilidades. El MERS-CoV se detectó por primera vez en 2012 originando un cuadro clínico similar, pero con una mayor letalidad (36%). Esta infección no se ha extinguido y persisten casos esporádicos. Ambas son zoonosis transmitidas al hombre, la primera a través de murciélagos y la segunda originada en dromedarios.

En diciembre de 2019, un nuevo tipo de infección por coronavirus apareció en Wuhan (provincia de Hubei), China, y se ha extendido rápidamente. Hasta la fecha, la epidemia de la enfermedad causada por este virus se ha extendido a todas partes de China y en aproximadamente 197 países. El 10 de enero de 2020, se logra la secuenciación del genoma del virus aislado del tracto respiratorio inferior de un paciente y se confirmó que se trataba de un nuevo tipo de coronavirus. Dos días después, la Organización Mundial de la Salud (OMS) denominó a este patógeno "nuevo coronavirus 2019 (2019-nCoV)". El 20 de enero de 2020, la Comisión Nacional de Salud de la República Popular de China (RPC) incorporó formalmente la enfermedad causada por el virus, conocido como COVID-19. Adoptó medidas para la prevención y el control de enfermedades infecciosas de clase A. El 7 de febrero de 2020, la Comisión Nacional de Salud de la RPC nombró el último tipo de neumonía infectada por coronavirus como "Nueva neumonía por coronavirus". El 11 de febrero de 2020, el Grupo de Estudio de Coronavirus de la Comisión Internacional de Clasificación de Virus nombró al nuevo coronavirus como "Síndrome Respiratorio Agudo Severo por coronavirus 2 (SARS-CoV-2)". El mismo día, la OMS nombró la enfermedad causada por el nuevo coronavirus como enfermedad por coronavirus-2019 (COVID-19). Después de la evaluación, el 12 de marzo de 2020, la OMS anunció que COVID-19 había alcanzado el estado de pandemia.

Las investigaciones actuales han determinado que el SARS-CoV-2 pertenece a un nuevo tipo de familia de coronavirus, a saber, del género β. Sus características genéticas son claramente diferentes de las del coronavirus del síndrome

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Manifestaciones clínicas no respiratorias, secundarias a infección por SARS-CoV-2 en niños

Non-respiratory clinical manifestations, secondary to SARS-CoV-2 infection in children

Armando Reyes-Cadena

Los coronavirus son importantes patógenos humanos y animales. A finales de 2019 se identificó un nuevo coronavirus causante de neumonía, en un grupo de casos, en Wuhan, China. En febrero 2020 la OMS designó a la enfermedad COVID-19, que significa enfermedad por coronavirus 2019. El virus que causa COVID-19 se denomina síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2). El 11 de marzo de 2020 la OMS declaró pandemia al COVID-19.[1]

Los coronavirus pertenecen a la familia Coronaviridae, integrada por dos subtipos: Coronavirinae y Torovirinae. Son virus ARN con una cubierta de glicoproteínas en forma de espiga, envoltura y proteínas de la membrana, tienen forma esférica y miden de 70 a 120 nm de diámetro, con cuatro proteínas estructurales. Las proteínas espigadas ayudan al virus a entrar a las células del huésped. El virus invade múltiples tipos de células epiteliales respiratorias, macrófagos alveolares y monocitos, utilizando los receptores ACE2.[1] **Figura 1**

El COVID-19 parece ser más leve en niños, que en adultos, y sus síntomas pueden pasar inadvertidos antes del diagnóstico, aunque se han informado casos graves. De los 69,703 casos de COVID19 confirmados por laboratorio en menores de 20 años, notificados a los Centros para el Control y la Prevención de Enfermedades (CDC) de Estados Unidos al 30 de mayo 2020, los niños y las niñas se vieron igualmente afectados.[1]

Si bien los hallazgos clínicos en niños con COVID-19 son diversos, la fiebre y la tos son los síntomas notificados con más frecuencia. En la vigilancia de casos en Estados Unidos (hasta el 30 de mayo 2020), la

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Oral manifestations of COVID-2019–related multisystem inflammatory syndrome in children: a review of 47 pediatric patients

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ABSTRACT

Background. Although much is still unknown about the full effects of COVID-19, literature from the early stages of the COVID-19 pandemic (spring and summer 2020) supports a postviral immunologic reaction resulting in a multisystem inflammatory syndrome in children (MIS-C). The purpose of this study was to report the rates of documented oral and oropharyngeal manifestations among these patients and to determine the association of these findings with other MIS-C symptoms.

Methods. The authors conducted a retrospective review of pediatric patients with COVID-19 who were admitted to the Morgan Stanley Children's Hospital of NewYork-Presbyterian. Patients fulfilling the Centers for Disease Control and Prevention criteria for MIS-C were included in this study. The documented signs, symptoms, and laboratory values were collected and compared with the presence of oral or oropharyngeal findings.

Results. The mean (standard deviation) age of MIS-C patients was 9.0 (5.0) years (range, 1.3-20.0 years), and there was no obvious sex difference (51.1% male, 48.9% female). With respect to oral findings, 23 patients (48.9%) had red or swollen lips, whereas only 5 (10.6%) had a strawberry tongue. Oral or oropharyngeal findings were associated significantly with the presence of systemic rash ($P = .04$) and conjunctivitis ($P = .02$).

Conclusions. The presence of oral or oropharyngeal changes may be an early indicator of MIS-C and should be considered suggestive of MIS-C in the setting of COVID-19 infection.

Practical Implications. Dental care providers may play an integral role both in the early detection of oral manifestations of MIS-C and in the identification of oral lesions in hospitalized patients with confirmed MIS-C.

Key Words. COVID-19; MIS-C; multisystem inflammatory syndrome in children; strawberry tongue; Kawasaki disease; pandemic.

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Coronaviruses are enveloped, nonsegmented, positive sense, RNA viruses belonging to the *Coronaviridae* family.[1-3] Although most coronaviruses cause mild cold or flulike symptoms, 2 betacoronaviruses (severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus) have resulted in more serious illnesses in 2002 and 2012, respectively.[4,5] Since December 2019, the novel strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, has caused a global pandemic.[6-8] Whereas older adults and immunocompromised patients have experienced substantial symptoms from this infection, children and adolescents with COVID-19 generally are asymptomatic and experience only mild respiratory symptoms.[9-14] Despite this observation, an alarming new trend in pediatric COVID-19 infections has been reported. A growing body of literature supports the association between COVID-19 and a postviral immunologic reaction resulting in a multisystem inflammatory syndrome in children (MIS-C).[15-20]

The case definition of MIS-C according to the Centers for Disease Control and Prevention (CDC) is a patient younger than 21 years with fever, laboratory evidence of inflammation,

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

ARTÍCULO DE REVISIÓN

INFECCIÓN POR EL NUEVO CORONAVIRUS 2019 EN NIÑOS

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RESUMEN

La enfermedad del coronavirus 2019 (COVID-19) es poco frecuente en niños y su salud se ve poco comprometida en la mayoría de casos. La presentación clínica más común es tos, fiebre y eritema faríngeo, los casos graves suelen presentarse con taquipnea. El curso de la enfermedad es de una a dos semanas. Los hallazgos de laboratorio son inespecíficos, entre ellos, linfopenia, elevación de la proteína C reactiva y la procalcitonina. En fases iniciales, la radiografía torácica es usualmente normal, y los hallazgos tomográficos más comunes son consolidaciones con signo del halo, vidrio esmerilado y nódulos pequeños, que afectan principalmente las zonas subpleurales. El manejo es sintomático y, en los casos graves, debe estar enfocado a brindar soporte respiratorio. Se recomienda que la manipulación de las secreciones respiratorias sea limitada y que se tengan las mismas precauciones para evitar contaminación que en pacientes adultos.

Palabras clave: Coronavirus; Enfermedad por Coronavirus 2019-nCoV; Niño (fuente: DeCS BIREME).

NOVEL 2019 CORONAVIRUS INFECTION IN CHILDREN

ABSTRACT

COVID-19 is rarely reported in children and they are mildly affected in most cases. The most common clinical presentation of COVID-19 is cough, fever and sore throat; severe cases show tachypnea. The course of the disease is from one to two weeks. Laboratory findings are nonspecific; lymphopenia, elevation of C-reactive protein and procalcitonin have been described. Early chest X-ray is usually normal, and the most common tomographic findings are consolidations with halo, ground-glass opacities and tiny nodules which mainly affects subpleural areas. Management of the disease is supportive; in severe cases, it should be focused on respiratory support. It is recommended to limit the handling of respiratory secretions and to follow the same preventive measures provided to adults

Keywords: Coronavirus Infection; 2019 Novel Coronavirus Disease; Child (source: MeSH NLM).

INTRODUCCIÓN

El 11 de marzo de 2020, la Organización Mundial de la Salud (OMS) consideró pandemia la infección por SARS-CoV-2. La enfermedad por coronavirus 2019 (COVID-19, por sus siglas en inglés) fue descrita por primera vez en diciembre de 2019, en la ciudad de Wuhan, provincia de Hubei (China). Para el 26 de abril de 2020, se habían notificado 2 804 796 casos y 193 710 muertes en todo el mundo [1].

Una revisión de 72 314 casos de infección por SARS-CoV-2 realizada por el Centro Chino para el Control y Prevención de Enfermedades encontró que solo 1% de los casos fueron de niños y adolescentes [2]. El Centro de Control y Prevención de Enfermedades de Corea del Sur, uno de los países que ha realizado más pruebas a su población, informó hasta el 20 de marzo de 2020, que el 1,1% y el 5,2% fueron pacientes de cero a nueve años y de 10 a 19 años, respectivamente [3].

En el Perú, el 5 de marzo de 2020 se confirmó el primer caso importado de COVID-19 y actualmente en los casos registrados no es posible identificar el nexo epidemiológico con algún caso confirmado [4]. Al 26 de abril del año en curso, se habían diagnosticado 27 517 personas con la COVID-19 y reportado 728 fallecimientos [5], de los cuales cuatro eran niños y uno, adolescente [6].

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Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19)

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SUMMARY Drugs that are specifically efficacious against SARS-CoV-2 have yet to be established. Chloroquine and hydroxychloroquine have garnered considerable attention for their potential to treat coronavirus disease 2019 (COVID-19). Increasing evidence obtained from completed clinical studies indicates the prospects for chloroquine/hydroxychloroquine to treat COVID-19. More randomized control clinical studies are warranted to determine the feasibility of these two drugs in treating COVID-19.

Keywords SARS-CoV-2, COVID-19, chloroquine, hydroxychloroquine

Coronavirus disease 2019 (COVID-19) has caused more than 1 million confirmed cases and approximately 70,000 deaths worldwide as of April 6, 2020 (*1*). Drugs that are specifically efficacious against SARS-CoV-2 have yet to be established. Chloroquine and hydroxychloroquine have garnered considerable attention for their potential to treat COVID-19. In China, chloroquine was added to the "Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis, and Management" issued by the National Health Commission on February 18, 2020 (*2*). The U.S. Food and Drug Administration (FDA) issued an emergency use authorization for chloroquine/hydroxychloroquine to treat COVID-19 on March 28, 2020 (*3*). The European Medicines Agency contended that the two drugs should be used in clinical trials or national emergency use programs for the treatment of COVID-19 on April 1, 2020 (*4*). The low cost and easy availability of chloroquine/hydroxychloroquine may help to curb this global public health emergency if their efficacy and safety are ultimately verified in clinical studies.

Chloroquine phosphate is the first drug reported to display efficacy against COVID-19 in early clinical studies in China (*5,6*). Based on this encouraging finding, chloroquine phosphate was added to the Sixth Edition of the Guidance for tentative treatment of COVID-19 (*2*). The Sixth Edition recommended that adult patients in whom chloroquine is not contraindicated should take chloroquine phosphate tablets, 500 mg (300 mg for chloroquine) twice a day for no more than 10 days (*7*). To reduce the risk of adverse effects of chloroquine, the Seventh Edition of the Guidance, issued on March 3, 2020, recommends a reduced dosage and shortened duration of treatment (*8*). Specifically, the dosage of chloroquine phosphate for adult patients (ages 18-65) with a body weight greater than 50 kg is 500 mg twice a day for 7 days and that for adult patients (ages 18-65) with a body weight less than 50 kg is 500 mg twice a day for the first 2 days and 500 mg once a day for the following 3-7 days (*8*). Regarding the treatment strategy, chloroquine and another antiviral favipiravir that also displayed efficacy in clinical trials are highlighted for their use in mild and moderate COVID-19 cases to prevent disease progression (*9*).

In a pilot study (*10*) aiming to evaluate the efficacy and safety of chloroquine in inpatients with COVID-19, 10 patients (3 with severe disease and 7 with moderate disease) received chloroquine phosphate 500 mg orally twice a day for 10 days, and 12 patients (5 with severe disease and 7 with moderate disease) received lopinavir/ritonavir 400/100 mg orally twice a day for 10 days. Chloroquine was slightly superior to lopinavir/ritonavir in terms of virus-negative conversion since the chloroquine group tested negative for SARS-CoV-2 at a slightly higher rate than the control group on day 7, day 10, and day 14 post-treatment (*10*). However, chloroquine was superior to lopinavir/ritonavir in improving the radiological appearance of the lungs and decreasing the duration of hospitalization. Adverse events including vomiting, abdominal pain, nausea, diarrhea, a rash or itch, a cough, and shortness of breath were observed in the chloroquine group, but chloroquine was not discontinued in any of the patients during the treatment period. The efficacy and safety of chloroquine

Organización Mundial de la Salud

Alocución de apertura del Director General de la OMS en la rueda de prensa sobre la COVID-19 celebrada el 11 de marzo de 2020

11 de marzo de 2020

Buenas tardes.

A lo largo de las dos últimas semanas, el número de casos de COVID-19 fuera de China se ha multiplicado por 13, y el número de países afectados se ha triplicado.

En estos momentos hay más de 118 000 casos en 114 países, y 4291 personas han perdido la vida.

Miles de personas más están luchando por sus vidas en los hospitales.

En los días y semanas por venir esperamos que el número de casos, el número de víctimas mortales y el número de países afectados aumenten aún más.

Desde la OMS hemos llevado a cabo una evaluación permanente de este brote y estamos profundamente preocupados tanto por los alarmantes niveles de propagación y gravedad, como por los alarmantes niveles de inacción.

Por estas razones, hemos llegado a la conclusión de que la COVID-19 puede considerarse una pandemia.

«Pandemia» no es una palabra que deba utilizarse a la ligera o de forma imprudente. Es una palabra que, usada de forma inadecuada, puede provocar un miedo irracional o dar pie a la idea injustificada de que la lucha ha terminado, y causar como resultado sufrimientos y muertes innecesarias.

El hecho de describir la situación como una pandemia no cambia la evaluación de la OMS

Protocolo odontológico ante el SARS-CoV2 (COVID-19) en Atención Primaria

2020

CONSEJO
DENTISTAS
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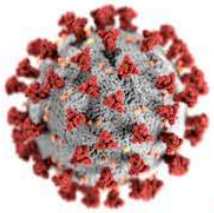
DE DENTISTAS
DE ESPAÑA

PLAN ESTRATÉGICO DE ACCIÓN PARA EL PERIODO POSTERIOR A LA CRISIS CREADA POR EL COVID-19



VERSIÓN 13 DE ABRIL 2020

Clinical Review

COVID-19 Transmission in Dental Practice: Brief Review of Preventive Measures in Italy

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Abstract

The outbreak and diffusion of SARS-CoV-2, responsible for the coronavirus disease (COVID-19), has caused an emergency in the health system worldwide. After a first development in Wuhan, China, the virus spread in other countries, with Italy registering the second highest number of cases in Europe on the 7th of April 2020 (135,586 in total). The World Health Organization declared the pandemic diffusion of COVID-19, and restrictive measures to limit contagion have been taken in several countries. The virus has a predominantly respiratory transmission through aerosol and droplets. The importance of infection control is therefore crucial in limiting the effects of virus diffusion. We aim to discuss the risks related to dental practice and current recommendations for dental practitioners. A literature search was performed to retrieve articles on the management of COVID-19 diffusion in dental practice. The documented clinical experience, the measures of professional prevention, and the actual Italian situation were reported and described. Four articles were retrieved from the literature search. Among the eligible articles, 3 reported measures to contrast COVID-19 diffusion. The infection management protocols suggested were reviewed. Finally, recommendations based on the Italian experience in terms of patient triage, patients' entrance into the practice, dental treatment, and after-treatment management are reported and discussed. COVID-19 is a major emergency worldwide, which should not be underestimated. Due to the rapidly evolving situation, further assessment of the implications of COVID-19 outbreak in dental practice is needed.

Keywords: dental public health, dental education, infection control, practice management, prevention, virology

Introduction

The definition of coronavirus includes a range of respiratory viruses, which can present with mild to severe manifestations and lead to respiratory failure. The name recalls the microscopic appearance of the virus, characterized by the presence of pointed structures on the surface, resembling a crown (Yang, Peng, et al. 2020).

The novel coronavirus was identified in Wuhan, China, in December 2019 in patients presenting with pneumonia of unknown origin. After a rapid escalation, on January 9, 2020, the World Health Organization declared the discovery a new coronavirus, first called 2019-nCoV and then officially named SARS-CoV-2, which had never been identified in humans before. On February 11, the respiratory disease deriving from SARS-CoV-2 infection was named COVID-19 (coronavirus disease; Lu, Zhao, et al. 2020; Mahase 2020).

SARS-CoV-2 has an estimated incubation period of 1 to 14 d, which is also the duration of medical observation and quarantine in exposed patients. Clinical manifestations of COVID-19 include cough, fever, and shortness of breath. Mild respiratory infections occur in about 80% of those infected, though about half will have pneumonia. Another 15% of patients develop severe illness, while 5% need critical care treatment. In rare cases, COVID-19 can lead to severe respiratory problems, kidney failure, or death. However, it is reported that virus spread can happen in the absence of clinical symptoms (Backer et al. 2020; Chan et al. 2020; Del Rio and Malani 2020; Guan et al. 2020; Huang et al. 2020).

Symptoms may vary from the presence of fever and dry cough to nonspecific symptoms such as shortness of breath, conjunctivitis, sore throat, diarrhea, vomiting, fatigue, and muscular pain (Chen et al. 2020; Guan et al. 2020). In patients who develop pneumonia, ground-glass opacity and patchy shadows can be detected on computed tomography (Zhou et al. 2020). Complications include respiratory distress syndrome, arrhythmia, and shock (Chen et al. 2020; Huang et al. 2020; Wang et al. 2020) and are more frequently associated with older age and the presence of comorbidities (Liu, Fang, et al. 2020; Wang et al. 2020; Yang, Lu, et al. 2020).

COVID-19 has seen a violent and fast spread worldwide, which has led to the declaration of a pandemic outbreak of the coronavirus by the World Health Organization.

In particular, Italy has seen a rapid and disruptive diffusion of COVID-19, also related to the relatively easy transmission

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