



COVID-19 and Headaches

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OHSU Headache Center
April 9th, 2021



Overview



- Headaches as presenting symptoms for COVID-19
- Clinical cases
- Post-COVID headache?
- Predictors of long covid syndrome
- Treatment of covid headache
- PPE and headaches
- Summary

COVID-19



- In December 2019, the World Health Organization reported cases of pneumonia associated with a new coronavirus, SARS-CoV-2.
- By March 11, 2020, the World Health Organization declared the pandemic status.

COVID-19



- The major clinical manifestations of the SARS-Cov-2 infection are due to pulmonary complications.
- Although most have mild symptoms, such as fever, headache, cough, dyspnea, myalgia, and anosmia.
- Other develop acute respiratory distress syndrome (ARDS) that can result in death.



Headache and COVID-19



- A meta-analysis inclusive of 61 studies (59,254 patients) reported that headache was present in 12%, representing the fifth clinical feature (after fever, cough, muscle pain and/or fatigue, dyspnea).
- Headache was also reported in the retrospective case series (214 hospitalized patients) from Wuhan with nearly exactly the same prevalence (**13%**).

Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med*. 2020;9(4).

Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020.



However..



- A large, multicenter, prospective European study performed on 1,420 patients with mild to moderate COVID-19 reported a higher **prevalence of headache (70.3%)**.
 - loss of smell (**70.2%**)
 - nasal obstruction (67.8%)
 - cough (**63.2%**)
 - Asthenia/lack of energy (63.3%)
 - myalgia (62.5%)
 - rhinorrhea (60.1%)
 - gustatory dysfunction (54.2%)
 - sore throat (52.9%)
 - Fever (**45.4%**)

In healthcare workers



- Netherlands in March 2020, 803 healthcare workers were tested for COVID-19, 90 were positive.
- Most frequent symptoms reported in COVID positive patients:
 - headache (**71%**)
 - general malaise (63%)
 - muscle ache (63%)
 - extreme tiredness (57%)

2 Clinical Cases: April 2020



- 38 yo woman with history of migraine with visual aura since age 8 presents with worsening of headaches.
- She used to experience 2-3 severe headaches per month but in the last month, headaches have been daily.

Case #1



- Headaches are described a retroorbital pain associated with nausea and light sensitivity.
- She feels “weak” all over, all of her muscles hurt.
- She barely has the energy to leave her bed.
- She has been on medical leave for the last 2 weeks.
- Her symptoms were preceded by diarrhea for a few days.

Case #1



- Workup done by her internist
 - CT brain/CTA- negative
 - ESR/CRP- wnl
 - CBC/CMP, CK, TSH, ANA, RF, anti-CCP,RPR, HIV,UA- wnl
- Social history: married and works as ambulance driver.
- After the visit: COVID-19: positive

Component	Latest Ref Rng & Units	4/27/2020
		3:39 PM
COVID-19, PCR	Not Detected	Detected (AA)



TABLE 2

Univariate associations of early symptoms with SARS-CoV2 PCR positivity among healthcare workers, the Netherlands, March 2020 (n = 803)

Symptom	SARS-CoV2-positive		SARS-CoV2-negative		OR (95% CI)	p value
	n/N	%	n/N	%		
General non-respiratory symptoms						
Anosmia ^a	37/79	46.8	7/190	3.7	23.0 (8.2–64.8)	< 0.001
✓ Muscle ache	57/90	63.3	143/713	20.1	6.9 (4.2–11.3)	< 0.001
✓ Ocular pain	31/90	34.4	75/713	10.5	4.5 (2.7–7.4)	< 0.001
General malaise	57/90	63.3	208/713	29.2	4.2 (2.6–6.7)	< 0.001
✓ Headache	64/90	71.1	296/713	41.5	3.5 (2.1–5.7)	< 0.001
✓ Extreme tiredness ^a	45/79	57.0	61/190	32.1	2.8 (1.6–4.9)	< 0.001
Fever	51/90	56.7	233/713	32.7	2.7 (1.7–4.2)	< 0.001
Respiratory symptoms						
Common cold	50/90	55.6	363/713	50.9	1.2 (0.8–1.9)	0.406
Sneeze	36/90	40.0	253/713	35.5	1.2 (0.8–1.9)	0.401
Cough	53/90	58.9	424/713	59.5	1.0 (0.6–1.5)	0.916
Shortness of breath	20/90	22.2	157/713	22.0	1.0 (0.6–1.7)	0.965
Runny nose	24/90	26.7	231/713	32.4	0.8 (0.5–1.2)	0.271
Sore throat	36/90	40.0	400/713	56.1	0.5 (0.3–0.8)	0.004
Gastrointestinal symptoms						
✓ Nausea ^a	13/79	16.5	17/190	8.9	2.0 (0.9–4.4)	0.075
✓ Diarrhoea ^a	14/79	17.7	20/190	10.5	1.8 (0.9–3.9)	0.106

Case #2: September 2020



- This is a 48 y.o. woman with HTN, HL, DM-2, OSA on CPA, asthma who presents to the Headache Clinic with daily headache.
- Initially, she reports stuffy nose, muscle aches and headaches.
- At first, she thought she had “bad allergies”. She noticed her “breathing was off”.

Case #2



- She called her PCP and reported feeling “short of breath” but denied chest tightness.
- She denied cough or fever.
- Her social history: she is single, lives with her teenage daughter and works for the school district (delivering food).
- Two days after calling her PCP she had a COVID-19 test which came back positive.

Case 2



▼ MISC SPECIAL CHEMISTRY - EXT			
Component Name	7/23/2020	7/23/2020	7/10/2020
SARS-COV-2 (COVID-19)	Not Detected		DETECTED (A)

- She returned to work after her second test was negative but headaches remained.
- She describes pain as “vise in the neck and around the temple”
- She denies any migraineous features (no light/sound sensitivity or nausea)

Case #2



- She uses Excedrin which helps for a few hours but pain keeps coming back.
- She is upset about her headaches as all of her other symptoms have resolved (dyspnea, nasal congestion and muscle aches).

Overview 2 cases with COVID-19



Case 1

- History of migraine
- Worsening of HA-migraine like
- Diarrhea first symptoms
- Extreme fatigue
- Front line worker

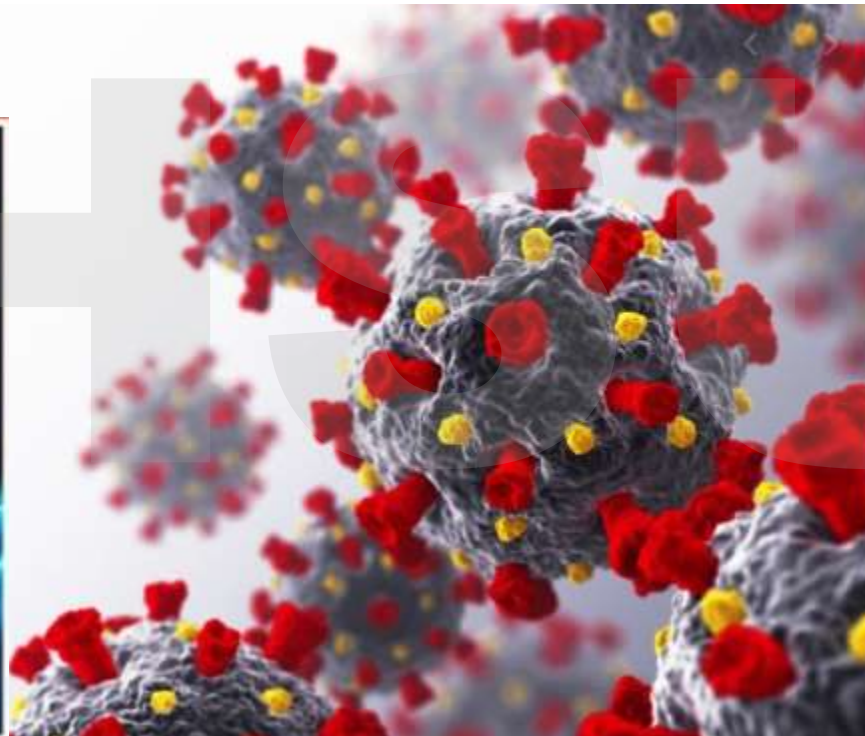
Did not want headache medication.
Believes we are ignoring
“covid headache”

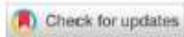
Case 2

- No history of migraine/headache
- New onset HA-tension like
- Dyspnea
- Myalgia
- Essential employee

Headaches have started to respond
to Amitriptyline

COVID headache?





ICHD-3

Cephalalgia
An International Journal of Headache



International
Headache Society

Cephalalgia

2018, Vol. 38(1) 1–211

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 SAGE

**Headache Classification Committee of the International Headache
Society (IHS)**

**The International Classification of Headache Disorders,
3rd edition**





9. Headache attributed to infection

- 9.1 Headache attributed to intracranial infection
 - 9.1.1 Headache attributed to bacterial meningitis or meningoencephalitis
 - 9.1.1.1 Acute headache attributed to bacterial meningitis or meningoencephalitis
 - 9.1.1.2 Chronic headache attributed to bacterial meningitis or meningoencephalitis
 - 9.1.1.3 Persistent headache attributed to past bacterial meningitis or meningoencephalitis
 - 9.1.2 Headache attributed to viral meningitis or encephalitis
 - 9.1.2.1 Headache attributed to viral meningitis
 - 9.1.2.2 Headache attributed to viral encephalitis
 - 9.1.3 Headache attributed to intracranial fungal or other parasitic infection
 - 9.1.3.1 Acute headache attributed to intracranial fungal or other parasitic infection
 - 9.1.3.2 Chronic headache attributed to intracranial fungal or other parasitic infection
 - 9.1.4 Headache attributed to localized brain infection
- 9.2 Headache attributed to systemic infection
 - 9.2.1 Headache attributed to systemic bacterial infection
 - 9.2.1.1 Acute headache attributed to systemic bacterial infection
 - 9.2.1.2 Chronic headache attributed to systemic bacterial infection
 - 9.2.2 Headache attributed to systemic viral infection
 - 9.2.2.1 Acute headache attributed to systemic viral infection
 - 9.2.2.2 Chronic headache attributed to systemic viral infection
 - 9.2.3 Headache attributed to other systemic infection
 - 9.2.3.1 Acute headache attributed to other systemic infection
 - 9.2.3.2 Chronic headache attributed to other systemic infection

9.2.2 Headache attributed to systemic viral infection

Description: Headache caused by and occurring in association with other symptoms and/or clinical signs of a systemic viral infection, in the absence of meningitis or encephalitis.

Diagnostic criteria:

- A. Headache of any duration fulfilling criterion C
- B. Both of the following:
 - 1. systemic viral infection has been diagnosed
 - 2. no evidence of meningitic or encephalitic involvement
- C. Evidence of causation demonstrated by at least two of the following:
 - 1. headache has developed in temporal relation to onset of the systemic viral infection
 - 2. headache has significantly worsened in parallel with worsening of the systemic viral infection
 - 3. headache has significantly improved or resolved in parallel with improvement in or resolution of the systemic viral infection
 - 4. headache has either or both of the following characteristics:
 - a) diffuse pain
 - b) moderate or severe intensity
- D. Not better accounted for by another ICHD-3 diagnosis.

New Daily Persistent Headache



- Headache begins one day and does not remit (for at least 3 months).
- Patients can pinpoint the exact date their headache started.
- 20-30% of patients recall infection or flu-like illness triggering the headache.
- Can present with tension-type phenotype or migraine-type phenotype.

Rozen TD. Triggering Events and New Daily Persistent Headache. *Headache*. 2016;56(1):164

Li D, Rozen TD. The clinical characteristics of new daily persistent headache. *Cephalalgia*. 2002;22(1):66–69.



COVID Pathway to headache

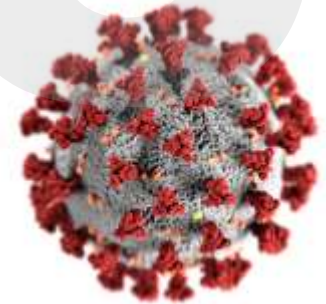


- Hypoxia
- Dehydration
- Fever
- Systemic inflammation
 - Activation of inflammatory mediators:
 - cytokines
 - glutamate
 - NO system
 - Cyclooxygenase-2/Prostaglandin E2 system
- Direct effects of virus-target cells

Pathway to headaches



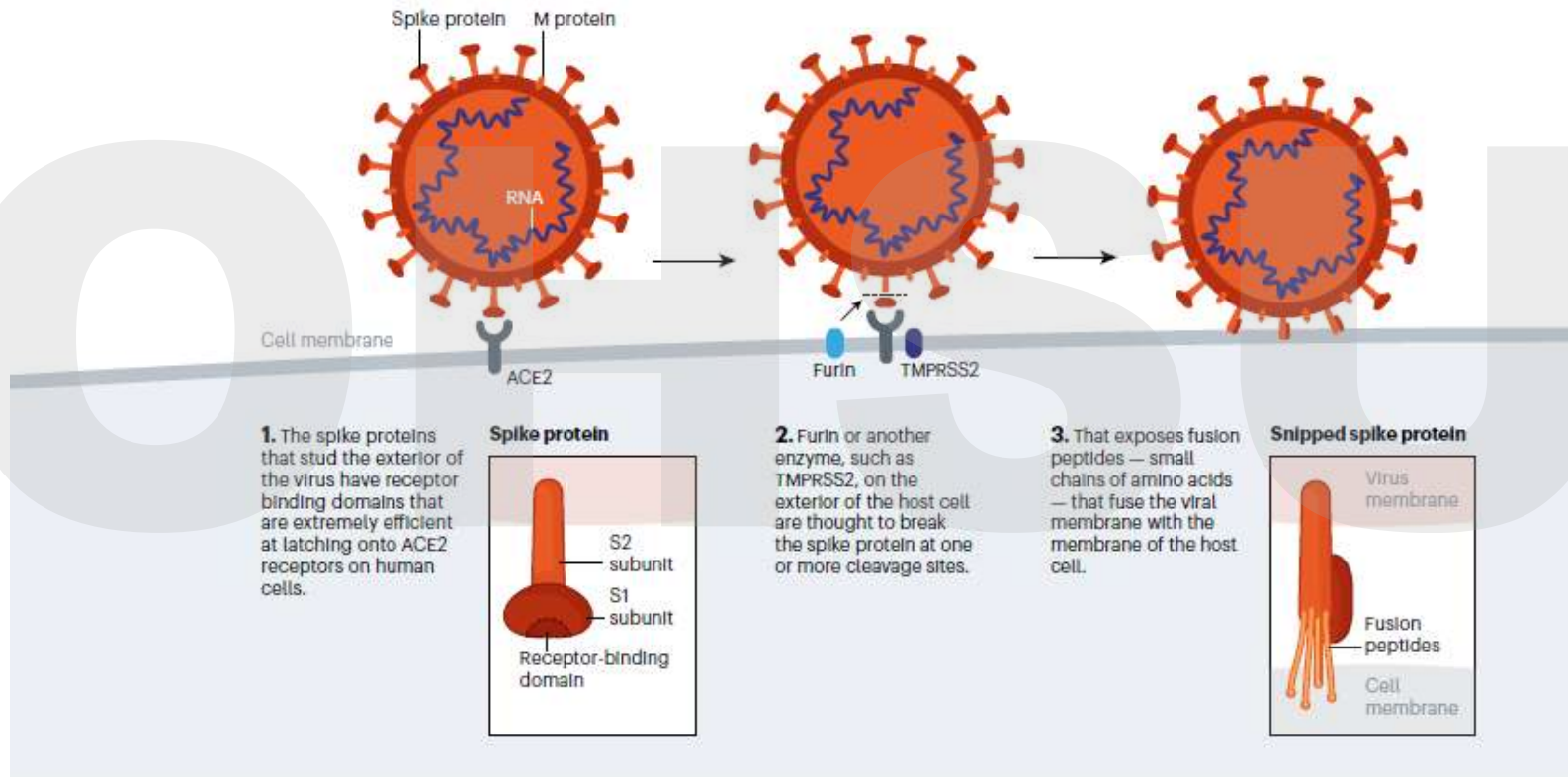
- The SARS-related coronaviruses are covered by spike proteins.
- SARS-CoV2 binds to angiotensin-converting enzyme 2 (ACE2) receptors to enter cells.
- ACE2 receptors are found
 - on alveolar epithelial cells
 - intestinal enterocytes
 - arterial and venous endothelial cells

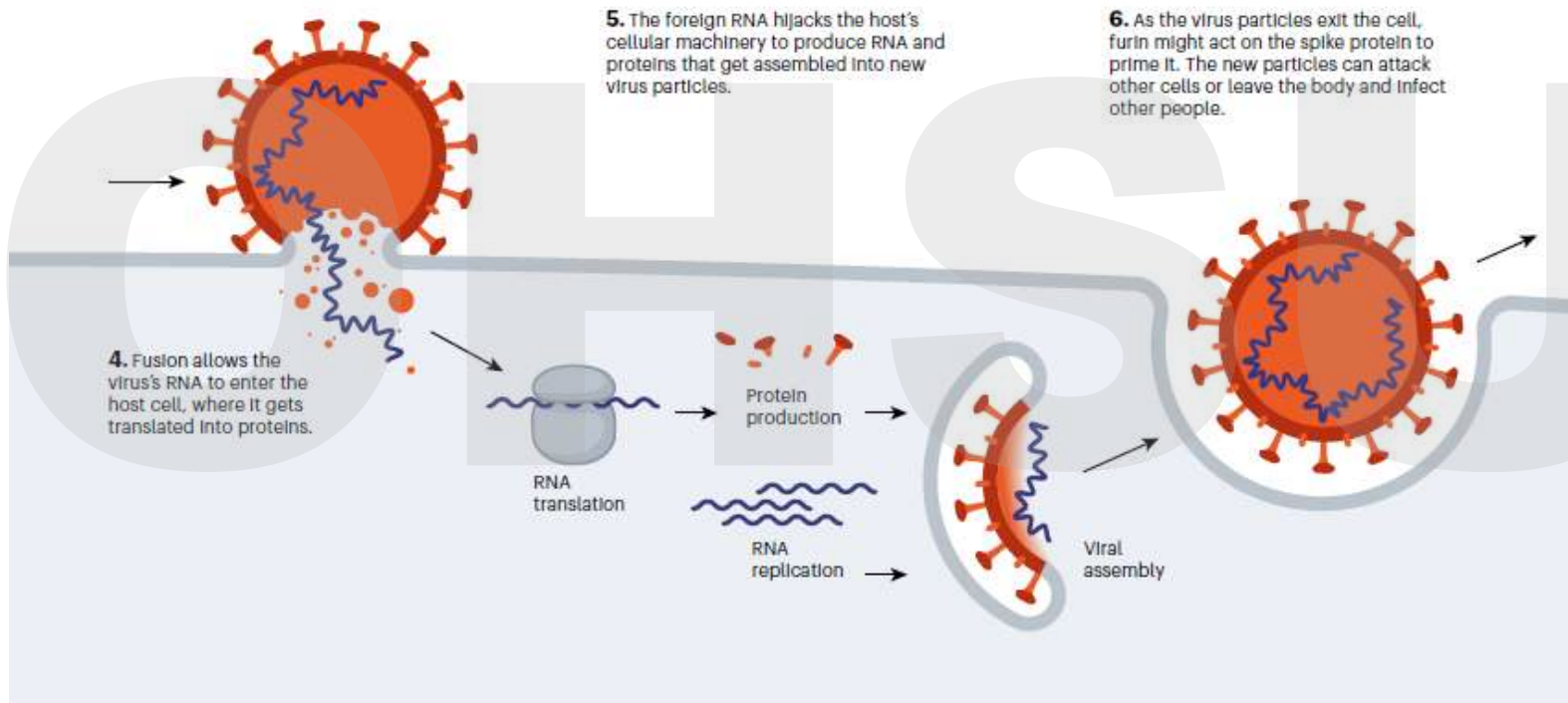


Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11:995-998.

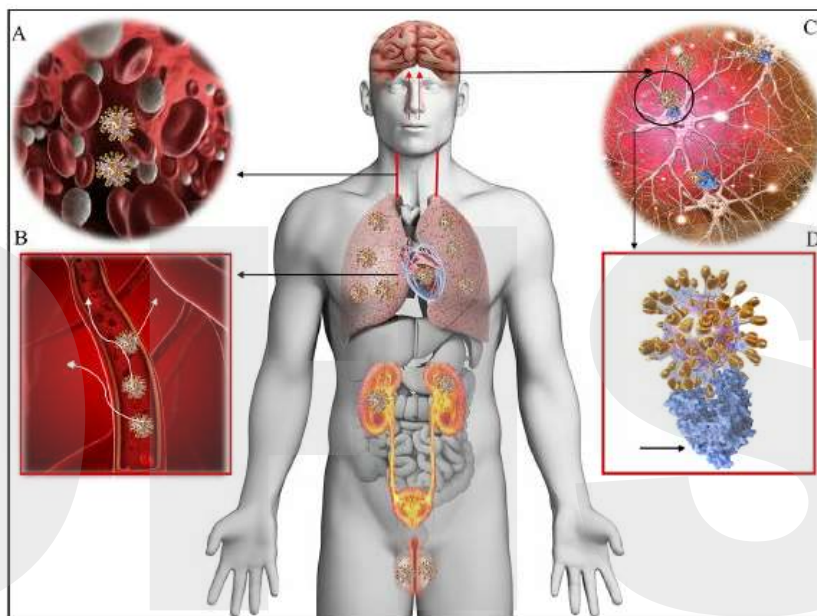
Manji H, Carr AS, Brownlee WJ, et al. Neurology in the time of COVID-19. *J Neurol Neurosurg Psychiatry*. 2020;91:568-570.

Pathway to headaches





Pathway to headaches



- Presence of COVID-19 virus in blood-sluggish flow, facilitate interaction between spike protein and ACE2 receptor on capillary endothelium.
- Budding of viral particle from capillary endothelium can cause endothelial lining damage and allow for viral access to the brain (where it can bind glial cells/neurons).
- Another pathway may be through olfactory epithelium which also express ACE2 receptors. Entry can happen across the cribriform plate of the ethmoid bone.
- Or via sensory fibers of the vagus nerve (change in taste), may enter the medulla via jugular foramen.

Other Neurological symptoms?



- Meningitis/encephalitis
- Cerebrovascular disease: hypercoaguable state, ischemic stroke, cerebral hemorrhage
- Myelitis/rhabdomyolysis
- ADEM(acute disseminated encephalomyelitis)
- Neuropathy including a post-infectious Guillain-Barre syndrome

Red flags to be aware of?






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Research Submission

Frequency and Type of Red Flags in Patients With Covid-19 and Headache: A Series of 104 Hospitalized Patients

David García-Azorín, MD ; Javier Trigo, MD; Blanca Talavera, MD; Enrique Martínez-Pías, MD ;
Álvaro Sierra, MSci; Jesús Porta-Etessam, MD, PhD ; Juan F. Arenillas, MD, PhD;
Ángel L. Guerrero, MD, PhD

Study from Spain, 576 patients with COVID
95% had pneumonia
22% presented with headaches
13 patients died



Red flags in HA & COVID-19

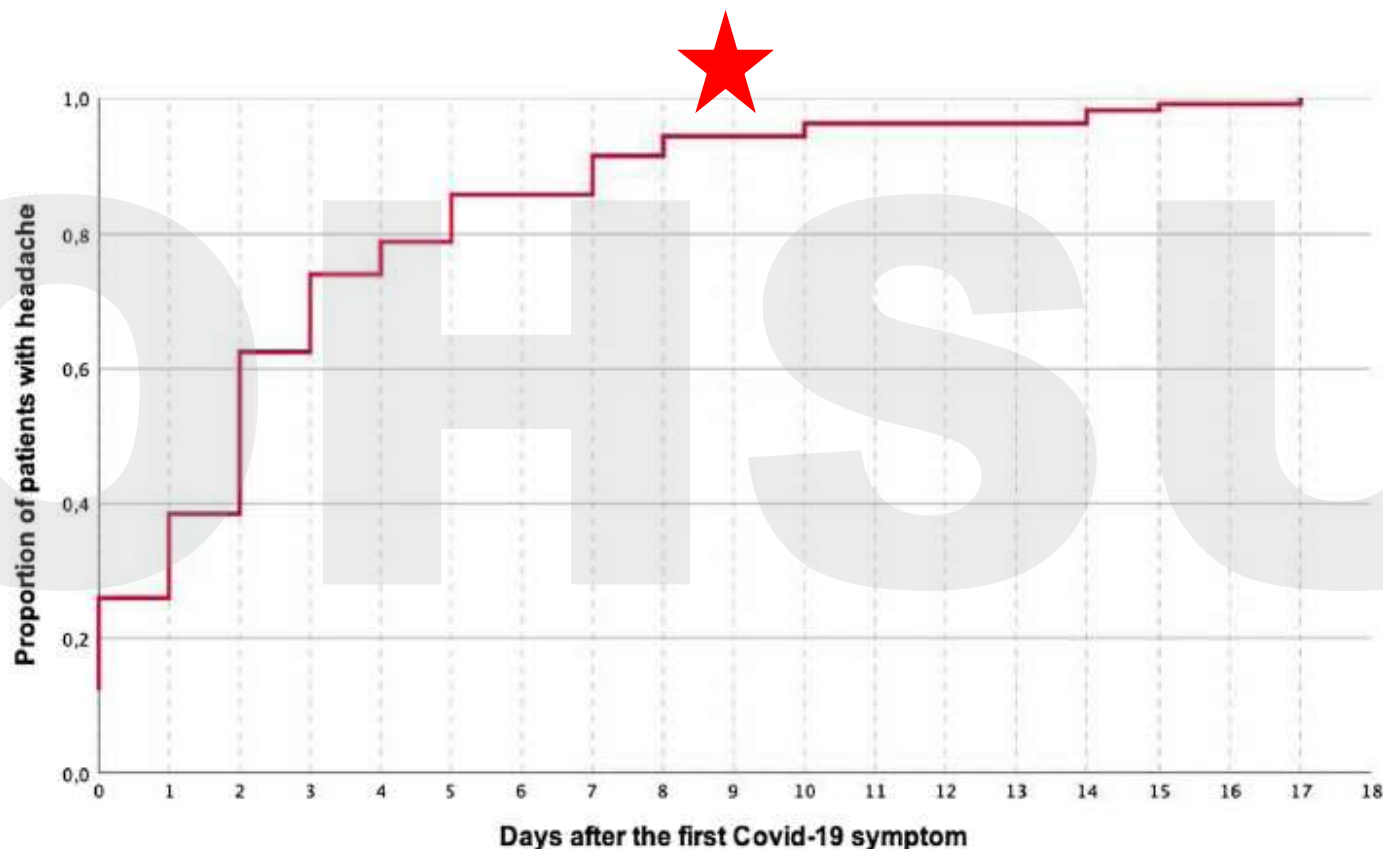


Fig. 1.—Headache onset in the course of Covid-19 disease. Number of days after the first Covid-19 symptom in which headache started. Kaplan-Meier 1-minus survival curve (n = 104). [Color figure can be viewed at wileyonlinelibrary.com]

Mean time between the onset of symptoms and the ED presentation was **8.8 (SD: 6.4) days**.
In 91/104 (**87.5%**) patients, the headache was present at the moment of emergency department visit.

Red flags



1670

September 2020

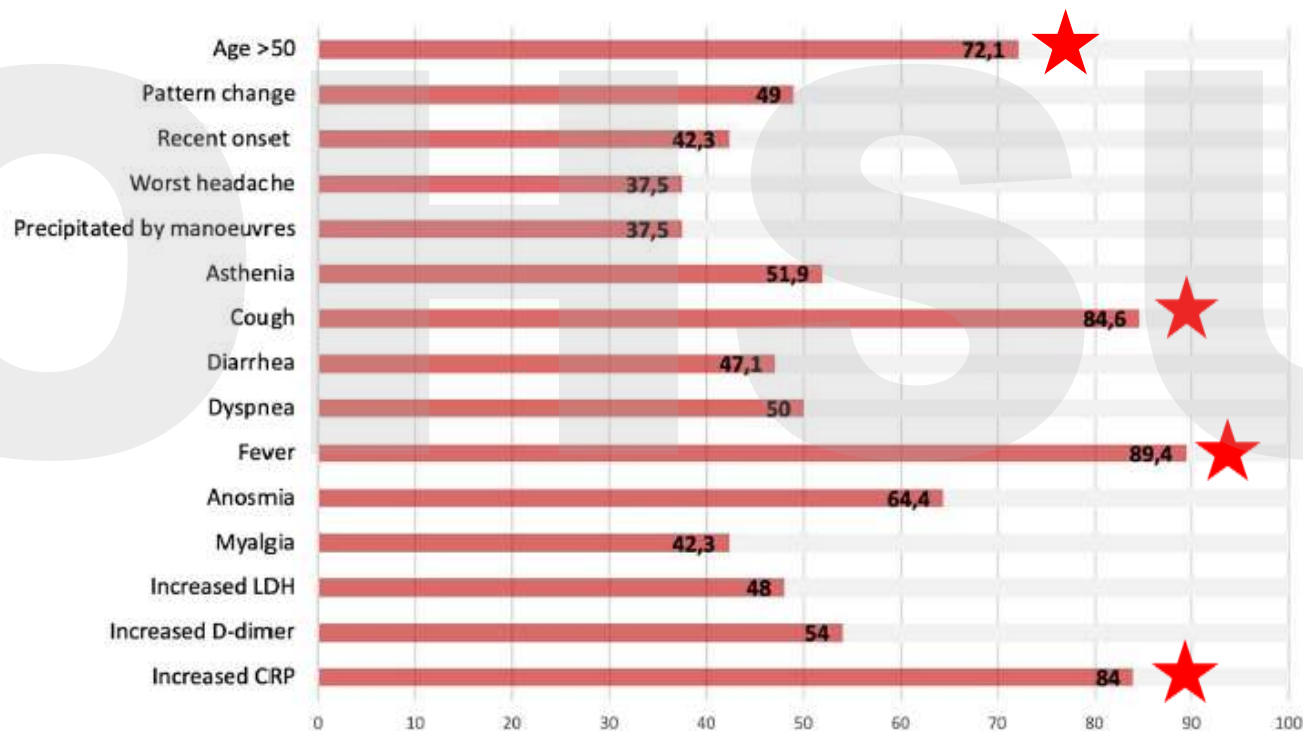


Fig. 2.—Most common red flags in hospitalized patients with Covid-19 disease and headache. [Color figure can be viewed at wileyonlinelibrary.com]

Overview



- Headaches can be a presenting symptoms of COVID-19, generally alongside other symptoms (malaise/fatigue/muscle aches).
- Age older than 50, presence of fever/cough and elevated inflammatory markers are associated with more severe cases of COVID-19.
- Headaches can persist even after testing negative for COVID-19: ?part of long COVID sx vs NDPH

What is Long Covid Syndrome?



- Symptoms >3 weeks= post-Acute COVID
- Symptoms > 12 weeks= chronic COVID= Long COVID syndrome.
- Long Covid estimates ~ 10% (range 0.5-25 %)
- Not limited to elderly or severely ill

Long COVID syndrome



- Affects all systems (CNS, cardiac, GI, renal, pulmonary).
- Covid symptoms study app gathered data:
 - 4182 pts (with + PCR test) in GB, USA and Sweden
 - Top 4 symptoms at 56 days: fatigue, HA, shortness of breath and loss of smell.

Attributes and predictors of Long-COVID



fatigue
headache

Loss of smell

Hoarse voice

	Occurrence overall			Occurrence first week			Duration			Number of reports		
	Short	L28	L56	Short	L28	L56	Short	L28	L56	Short	L28	L56
FA	76.1%	97.7%	96.8%	75.9%	89.1%	87.8%	4 [2 ; 6]	33 [25 ; 56]	73 [55.5 ; 110]	4 [2 ; 6]	31.5 [19.5 ; 54.5]	68 [39 ; 118.5]
HA	65.6%	91.2%	93.7%	65.4%	80.6%	81.5%	3 [1 ; 5]	22 [10 ; 42]	56 [22 ; 93]	2.5 [1.5 ; 4]	10 [4.5 ; 19.5]	15 [7 ; 34.5]
SOB	29.4%	70.8%	75.7%	29.2%	48.4%	51.3%	2 [1 ; 5]	24 [8 ; 45]	59 [37 ; 98]	2.5 [1.5 ; 4.5]	15 [5.5 ; 34.5]	41 [15.75 ; 80.25]
LOS	49.2%	72.0%	75.1%	49.0%	56.8%	58.2%	3 [2 ; 5]	24 [11 ; 42.75]	53 [17.5 ; 84.75]	3.5 [2 ; 5]	19.5 [9 ; 34]	35.75 [11.63 ; 68.88]
PC	40.5%	68.6%	62.4%	40.4%	57.0%	52.9%	3 [1 ; 5]	20 [7.5 ; 32]	34 [14 ; 59]	3 [1.5 ; 4.5]	11.5 [4.5 ; 22.5]	19 [7 ; 40.5]
ST	41.2%	67.0%	72.5%	41.2%	53.6%	54.0%	2 [1 ; 4]	15 [3.25 ; 33.75]	33 [4 ; 63]	2.5 [1.5 ; 4]	6 [3 ; 12]	8 [3 ; 17]
FV	36.1%	62.9%	58.7%	36.1%	50.5%	45.5%	2 [1 ; 3]	6 [2 ; 14]	11 [2 ; 51.5]	2 [1.5 ; 3]	4 [2 ; 7.75]	4.5 [2 ; 11.5]
UMP	29.2%	64.0%	64.6%	29.2%	47.5%	43.4%	2 [1 ; 4]	7 [2 ; 25]	30 [4 ; 76.75]	2.5 [1.5 ; 3.5]	5 [2 ; 11]	9.5 [3 ; 30.63]
SM	29.9%	59.5%	66.7%	29.9%	46.6%	52.4%	2 [1 ; 4]	9 [3.75 ; 20]	13 [4 ; 44]	2.5 [1.5 ; 4]	6 [3 ; 14]	8 [3.5 ; 18.88]
CP	28.2%	60.0%	63.0%	28.1%	42.5%	45.0%	2 [1 ; 4]	13 [3 ; 35]	46 [17 ; 78]	2 [1.5 ; 4]	7.5 [2.5 ; 16.5]	16.5 [7.25 ; 42]
DI	20.4%	51.1%	54.5%	20.1%	34.6%	33.3%	2 [1 ; 3]	9 [2 ; 22]	15 [2 ; 46.5]	2 [1 ; 3]	4.5 [2 ; 9]	5 [2 ; 12.25]
HV	23.0%	53.0%	61.4%	22.9%	41.4%	47.6%	2 [1 ; 4]	9 [3 ; 29]	21 [4 ; 61.5]	2.5 [1.5 ; 4]	6 [3 ; 14.5]	7.5 [3.5 ; 20.625]
AP	17.2%	44.1%	49.2%	17.0%	26.0%	22.2%	1 [1 ; 3]	7 [1 ; 23]	13 [1 ; 56]	2 [1 ; 3]	3.5 [1.5 ; 8.5]	4.5 [2 ; 9.5]
DE	11.8%	30.3%	38.6%	11.7%	19.0%	24.3%	2 [1 ; 3]	8 [1 ; 23]	14 [2 ; 56]	2 [1 ; 3.5]	3.5 [1.5 ; 9]	6.5 [2 ; 16.5]

Symptoms most predictive for long COVID



- Symptoms experienced during the 1st week after infection most predictive of Long Covid:
 - fatigue OR=2.83 [2.09; 3.83]
 - headache OR=2.62 [2.04;3.37]
 - dyspnea OR=2.36 [1.91;2.91]
 - hoarse voice OR=2.33 [1.88 - 2.90]
 - myalgia OR=2.22 [1.80;2.73]

Symptoms most predictive for long COVID in older patients



- In adults aged over 70:
 - loss of smell was the most predictive of long-COVID, OR=**7.35** [1.58 - 34.22]
 - fever, OR=5.51 [1.75 - 17.36]
 - hoarse voice, OR=4.03[1.21,13.42]

Questions to add in 1st time visit



- All our new patient have this questions:

Do you think you were exposed to COVID-19 virus?

- ☐ Yes
☐ No

Were you tested for COVID-19?

- ☐ Yes
☐ No

Was your test positive?

- ☐ Yes
☐ No

Some of our follow-up questions:



- If answers yes on covid exposure/test:
- Presence of:
 - Brain fog/difficulty with concentration
 - Fatigue/malaise
 - Dizziness

How to treat post COVID headache?



- Target treatment to phenotype of headache
- Most post-covid headache are either migraine-like or tension-type.
- Migraine: severe, unilateral pain, throbbing, worsens with movement, associated with either nausea/vomiting or light/sound sensitivity.
- Tension: mild to moderate, bilateral, pressure-like, not aggravated by movement and should not be associated with light/sound sensitivity and nausea.

When to consider treatment?



Frequency

Diary

Yes, >2 HA/w or
4 severe per
month

Infrequent
headaches

Already on preventative
agent
- Optimize dose
- May need to add another
agent or change all together

Not on a preventative
agent:
- Time to discuss one
or at least
supplement/vitamins

Counsel on lifestyle
modification
- caffeine, water intake,
regular exercise, regular
healthy meals, sleep hygiene,
trigger awareness

Tension-type: prevention



Usually sedating

- Amitriptyline 30-75 mg at night
- Nortriptyline 30-75 mg at night



Usually activating

- Protriptyline 20-30 mg in the morning
- Venlafaxine 150 mg in the morning



Usually sedating

- Mirtazapine 30 mg at night

** these are not starting doses, but suggested goal doses

Migraine type: prevention



First line treatment

- Topiramate 100-150 mg daily
- Sodium Valproate 500- 1500 mg daily
- Amitriptyline 30-75 mg daily
- Propranolol 80-240 mg daily



Second line treatment

- Venlafaxine ER 150-225 mg daily
- Lisinopril 10-40 mg daily
- Candesartan 16-32 mg daily

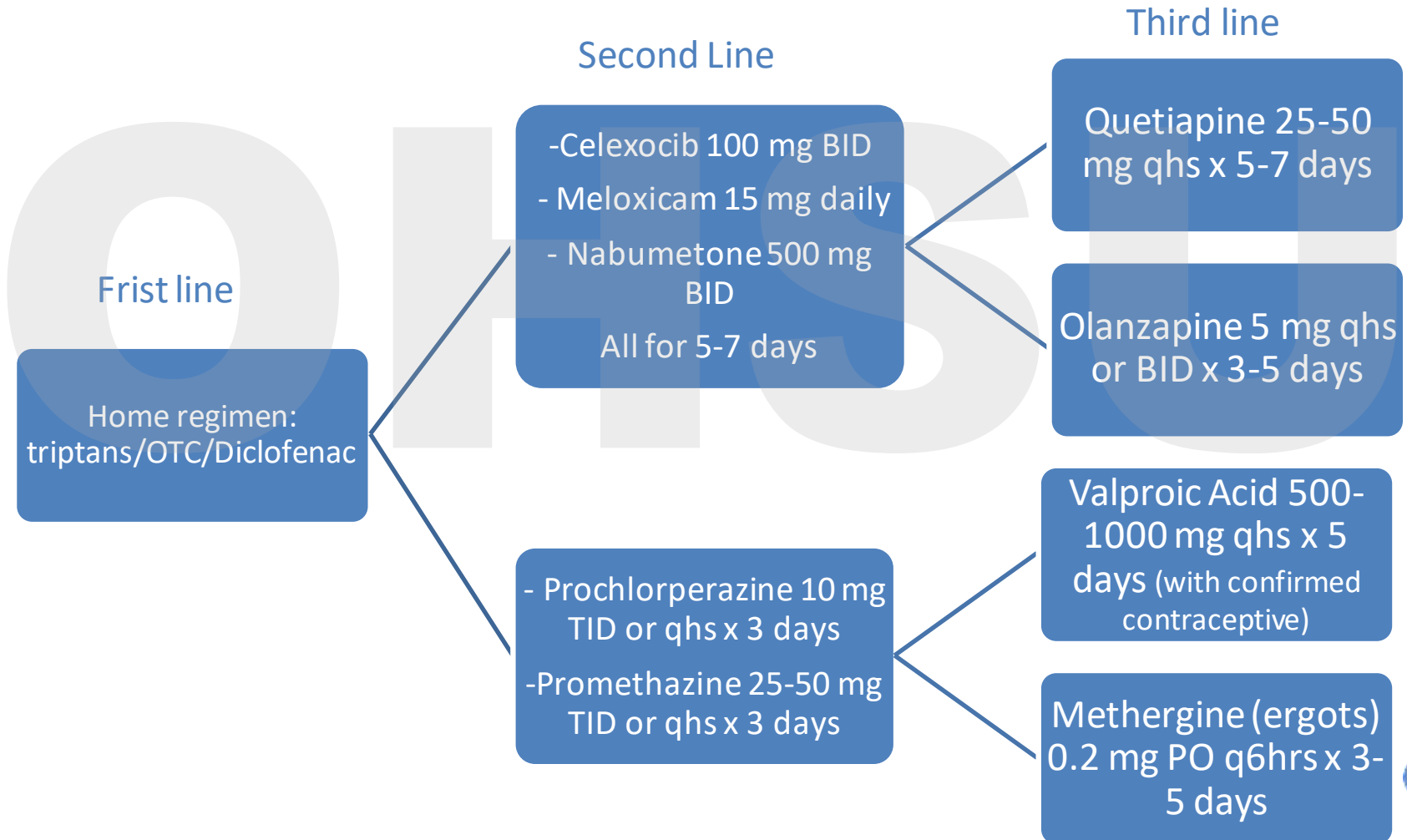


Third line agents

- Botulinum toxin injection
- CGRP monoclonal antibodies- trial should be at least 3-6 months

** these are not starting doses, but goal doses

During pandemic: home treatment for prolonged headaches



Can Personal Protective Equipment cause headaches?



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Research Submissions

Headaches Associated With Personal Protective Equipment – A Cross-Sectional Study Among Frontline Healthcare Workers During COVID-19

Jonathan J.Y. Ong, FRCP; Chandra Bharatendu, MRCP; Yihui Goh, MRCP; Jonathan Z.Y. Tang, MRCEM; Kenneth W.X. Sooi, MRCP; Yi Lin Tan, MBBS; Benjamin Y.Q. Tan, MRCP; Hock-Luen Teoh, MRCP; Shi T. Ong, BSc; David M. Allen, FAMS; Vijay K. Sharma, MRCP

158 healthcare workers were surveyed in Singapore



Can PPE cause headaches?



Headache

867

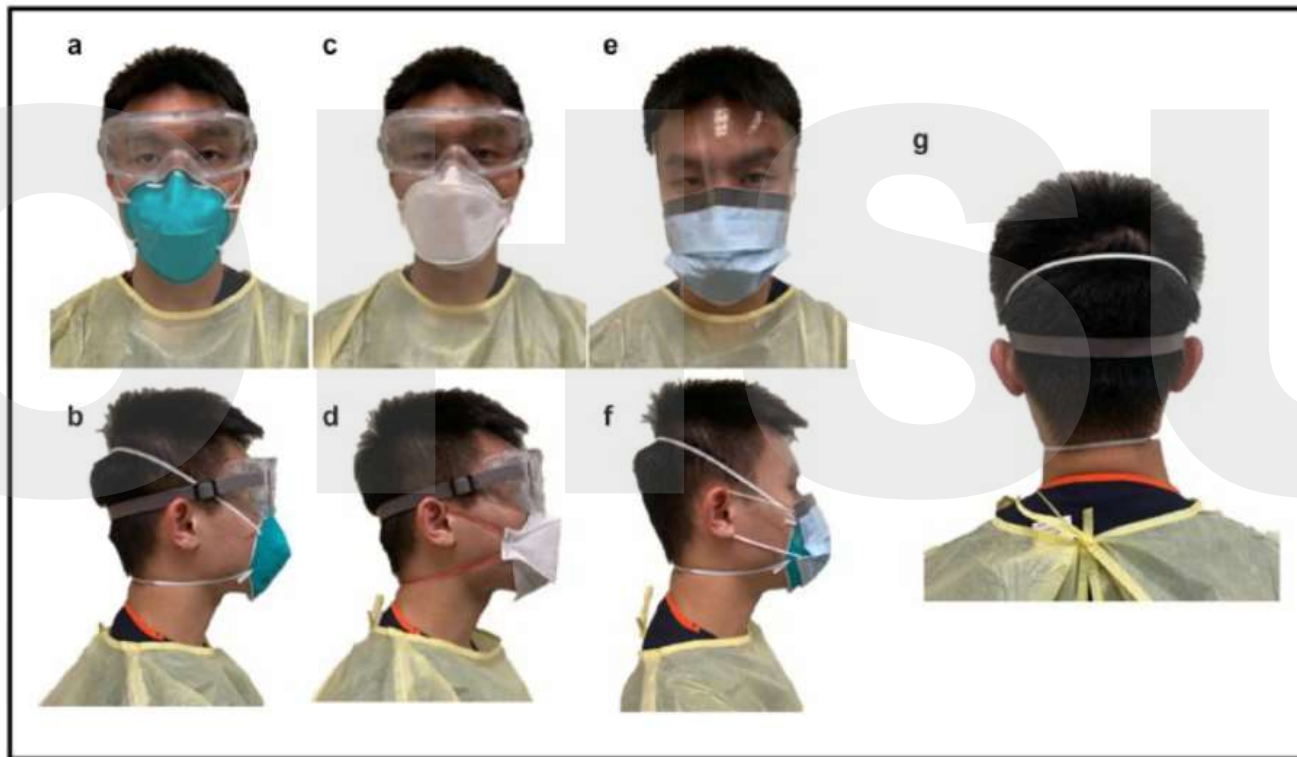


Fig. 1.—Frontal and side profiles of a healthcare worker wearing N95 face mask and protective goggles in combination (a-d). Alternatively, a face-shield or visor may be worn in combination with a N95 face mask (e,f). Posterior profile (g). Note where the edges of the N95 face mask and goggles contact the head (including face). The figure also illustrates the positioning of the various elastic straps from the PPE upon the head (including face) and upper cervical region. [Color figure can be viewed at wileyonlinelibrary.com]

Can PPE cause headaches?



- Of the 158 respondents, 128 (**81.0%**) reported de novo PPE associated headaches.
- Headaches start within 60 minutes of donning either face mask with or without eyewear and resolved within 30 minutes of removing PPE.
- All respondents described the headaches as bilateral in location.

Can PPE cause headaches?

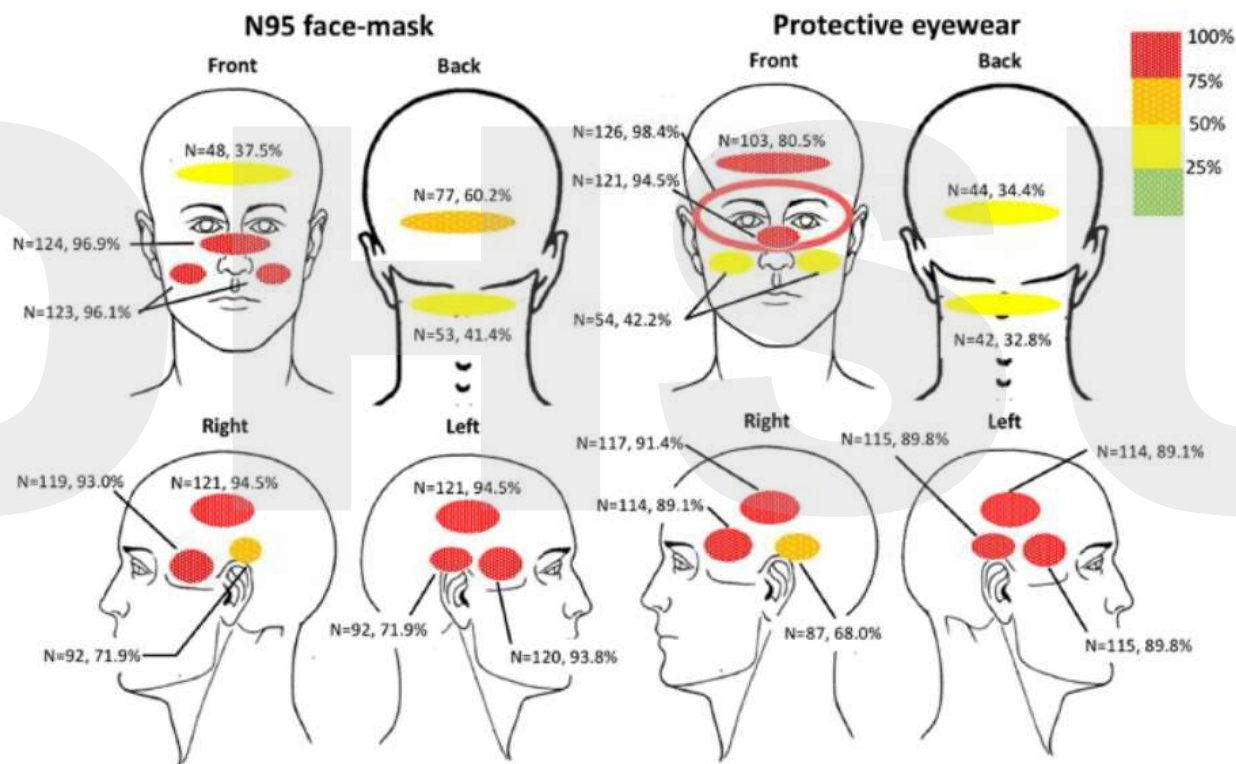


Fig. 3.—Anatomical localization and frequency distribution among 128 respondents who reported de novo PPE-related headaches. All respondents (n = 158) completing the questionnaire were asked to shade the areas where pain, pressure or compression from the respective PPE was experienced if this was present. [Color figure can be viewed at wileyonlinelibrary.com]

Can PPE cause headaches?



- More likely to develop novo PPE-associated headaches if:
 - **Pre-existing** primary headache diagnosis (OR = 3.44, 95%; CI 1.14-10.32; P = .013)
 - Worked in the **emergency department** (OR = 2.39, 95% CI 1.05-5.47; P = .019)
 - Wore combined PPE **more than 4 hours** per day (OR 3.91, 95% CI 1.35-11.31; P = .012)

The International Classification of Headache Disorders, 3rd edition|



4.6.1 External-compression headache

Description: Headache resulting from sustained compression of pericranial soft tissues; for example, by a tight band around the head, hat or helmet, or goggles worn during swimming or diving, without damage to the scalp.

Diagnostic criteria:

- A. At least two episodes of headache fulfilling criteria B–D
- B. Brought on by and occurring within one hour during sustained external compression of the forehead or scalp
- C. Maximal at the site of external compression
- D. Resolving within one hour after external compression is relieved
- E. Not better accounted for by another ICHD-3 diagnosis.

PPE induced headaches



- Multiple requests for accommodation letters:
 - either not use mask in office
 - allow for different position
 - to be exempt to wear masks at all times
- Answer: NO to not wear mask in public/groups but Yes for different position that requires less mask use.

Summary



- Headaches can be a presenting symptoms of COVID-19.
- Both headaches and loss of smell are most common symptoms in mild to moderate COVID.
- Certain red flags (age, fever, cough) are associated with more severe disease.
- PPE can cause de-novo headache and worsen existing headache.
- Treat headaches based on phenotype (tension vs migraine)
- Utilize anti-emetics/neuroleptics/long NSAIDs to break prolonged headaches.



Thank you