

aggregate response to the COVID-19 pandemic. If you are involved with or interested in autopsy and/or decedent management then please join us (email the author at awilliamson@northwell.edu).

Stay safe, and keep fighting the good fight!

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1. Collection and submission of postmortem specimens from deceased persons with known or suspected COVID-19. Centers for Disease Control and Prevention 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-postmortem-specimens.html>. Accessed May 1, 2020.

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Analysis of COVID-19 Transmission: Low Risk of Presymptomatic Spread?

To the Editor.—More than 6 million confirmed cases of coronavirus disease 2019 (COVID-19) have been identified worldwide, and a number of case reports^{1–5} have indicated that COVID-19 has the potential to be transmitted prior to disease onset. Studies have also shown that infectious virus can be isolated from presymptomatic COVID-19 cases,⁶ and although it is unknown what level of infectious virus is needed to confer efficient transmission potential, detection of infectious virus in the upper respiratory tract indicates that presymptomatic transmission of COVID-19 is plausible. Fear of asymptomatic and presymptomatic transmission of COVID-19 has led to considerable concern among public health policymakers, frontline health care workers, and the public in general. In response, many city, state, and federal leaders have

asked for increased testing via reverse transcriptase–polymerase chain reaction and serologic assays in order to identify asymptomatic cases and potential spreaders. Individual case studies are important for bringing attention to this topic, but they do not provide information regarding the overall proportion of transmission events that occur before or after symptom onset. A better understanding of COVID-19 transmission is needed to control this pandemic, and although some recent studies have provided new insight, others have fueled increased concerns.

Recent modeling of 77 transmission pairs indicated that 34 instances of COVID-19 transmission (44%) occurred before symptom onset, with peak transmission at 0.7 days before symptom onset.⁷ This is an unusual outcome because most respiratory viruses, including influenza or severe acute respiratory syndrome coronavirus (SARS-CoV), spread most efficiently at or after symptom onset and not before. There are also several limitations to this study. The model was not based on direct contact tracing but instead relied upon publicly available data sources and news media reports for determining presymptomatic versus postsymptomatic exposures and transmission intervals. The authors noted that they used a previously published estimate of the COVID-19 incubation period that, if overestimated, had the potential to inflate the proportion of presymptomatic transmission. Sensitivity analysis of different incubation periods is currently underway (M.K.S. and L. Gao, unpublished data, June 1, 2020). Regardless of the study, clinical data based on personal recollection may be subject to recall bias. This may be particularly important for COVID-19 transmission models if people are reluctant to admit they were traveling or not following proper precautions while symptomatic because of pandemic-associated societal pressure and fear of condemnation for their actions. Although it is unclear how these various factors may have impacted this particular study, review of other COVID-19 and SARS transmission studies provides an interesting counterpoint.

In contrast to He et al,⁷ a study examining 468 confirmed COVID-19 cases in China indicated that only 59 case reports (12.6%) resulted from presymptomatic transmission.⁸ Al-

though this study was also based on secondary data sources, they obtained reliable information from confirmed cases in online reports from 18 provincial centers for disease control and prevention. Perhaps the most convincing study on presymptomatic transmission of COVID-19 was performed in Singapore.⁹ Direct contact tracing of 157 locally acquired cases indicated that just 10 of the cases (6.4%) occurred through presymptomatic transmission. Together these studies indicate COVID-19 transmission is 10- to 20-fold more efficient after symptom onset.

Asymptomatic transmission raises similar concerns for contact tracing/isolation procedures, but a study of 24 asymptomatic cases of COVID-19 found that only 1 asymptomatic carrier transmitted the virus to another person.¹⁰ Bearing in mind that COVID-19 has a reproductive number (R_0) = 2 to 3 (meaning on average, 1 infected person transmits to 2–3 other people), the spread of virus by asymptomatic carriers appears very inefficient and may have an $R_0 < 0.1$ if this preliminary study is representative of asymptomatic cases among other groups. Similar results were observed with SARS. Of 669 close contacts to symptomatic SARS patients, 101 (15.1%) developed symptoms, whereas when 363 others had close contact to SARS patients during the incubation period (ie, presymptomatic), none developed symptoms.¹¹ Interestingly, most people are not effective at spreading COVID-19. A recent study found that the distribution of individual R_0 values was highly overdispersed, with 80% of infections being caused by ~9% of cases.¹² There are many factors that may impact transmission efficiency, including duration of exposure, type of exposure/environment (indoor versus outdoor, home versus hospital, public transportation, etc), role and timing of social distancing interventions, and age/health status of the infector as well as the infectee. Nevertheless, the various coronavirus studies described here indicate that if we focus on one parameter of transmission (presymptom versus postsymptom onset exposure), we find that although presymptomatic transmission of COVID-19 is possible, it appears inefficient compared with transmission after symptom onset.

A common issue with analysis of COVID-19 transmission rates is the lack of consistent data collection and

differences in symptom definitions. At a minimum, data collection should include symptoms such as fever, cough, sore throat, shortness of breath/difficulty breathing, headache, muscle pain, recent loss of taste or smell, and importantly, recollection of chills or night sweats because some individuals may not have directly measured fever during acute symptom onset. Location of exposure (if known) should also be documented when possible. One formidable challenge has been the lack of consensus on the definition of fever in COVID-19. For instance, the Centers for Disease Control and Prevention defines COVID-19 fever as 38°C/100.4°F, whereas fever was defined as 37.5°C/99.5°F in Wuhan, China.¹³ Thus, an infected individual with a temperature of 37.8°C/100.0°F would be considered asymptomatic in one country and clearly symptomatic in the other. Even within the United States, there is no consensus on the definition for COVID-19 fever. States such as Georgia, Ohio, and Pennsylvania use a cutoff value of 38°C/100.4°F, Texas uses 37.8°C/100°F, and other states, including Minnesota and Delaware, use 37.5°C/99.5°F for routine temperature screening.¹⁴ Although no single definition for fever will be perfect in every circumstance, we propose using 37.5°C/99.5°F to increase the sensitivity for detecting mildly symptomatic COVID-19 cases at the earliest stages of disease onset. Because transient spikes in body temperature can occur for a variety of reasons (environment, physical exertion, etc), specificity for detecting fever may be increased by retesting positive individuals after 20 to 30 minutes of acclimation to confirm an elevated temperature if needed. In summary, coordinated development and standardization of clinical criteria among countries, and even between different states and clinical research groups, will be necessary to reduce confusion in the field and improve the ability to compare and interpret COVID-19 study outcomes in the future.

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1. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382(10):970–971.
2. Yu P, Zhu J, Zhang Z, Han Y. A familial cluster of infection associated with the 2019 novel coronavirus indicating possible person-to-person transmission during the incubation period. *J Infect Dis*. 2020;221(11):1757–1761.
3. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020;323(14):1406–1407.
4. Tong ZD, Tang A, Li KF, et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang Province, China, 2020. *Emerg Infect Dis*. 2020;26(5):1052–1054.
5. Qian G, Yang N, Ma AHY, et al. A COVID-19 transmission within a family cluster by presymptomatic infectors in China [published online ahead of print March 23, 2020]. *Clin Infect Dis*. doi: 10.1093/cid/ciaa316.
6. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility [published online ahead of print April 24, 2020]. *N Engl J Med*. doi: 10.1056/NEJMoa2008457.
7. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672–675.
8. Du Z, Xu X, Wu Y, Wang L, Cowling BJ, Meyers LA. Serial interval of COVID-19 among publicly reported confirmed cases. *Emerg Infect Dis*. 2020;26(6):1341–1343.
9. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):411–415.
10. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci*. 2020;63(5):706–711.
11. Zeng G, Xie SY, Li Q, Ou JM. Infectivity of severe acute respiratory syndrome during its incubation period. *Biomed Environ Sci*. 2009;22(6):502–510.
12. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study [published online ahead of print April 27, 2020]. *Lancet Infect Dis*. doi: 10.1016/S1473-3099(20)30287-5.
13. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
14. Frankel TC. A fever is 100.4 in Ohio; it's 99.5 in Delaware: states, companies write their own rules for temperature screening in a pandemic. *Washington Post*. May 15, 2020. <https://www.washingtonpost.com/business/2020/05/15/fever-screening-coronavirus/>. Accessed June 1, 2020.

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Amyloid Deposition in the Brain

To the Editor.—I read with interest the excellent review of “An Organ System-Based Approach to Differential Diagnosis of Amyloid Type in Surgical Pathology” in the March 2020 issue of the *Archives of Pathology & Laboratory Medicine* by Giannini and Nast.¹ The number of amyloid types and their relevance to diagnostic pathology and patient management will no doubt continue to increase, as they continuously have over the years. Although the review focused specifically on surgical pathology, my experience with cases I see in consultation and discussions with colleagues is that it is not uncommon to see amyloid-related processes in hematoma and brain biopsy specimens handled by surgical pathologists in general practice, even in large medical centers and academic centers where a neuropathologist is not available. As such, I would like to bring to the attention of the readers a few points in this context.

Cerebral amyloidoma is a rare, focal, mass-forming amyloid light chain deposition associated with clonal B-cell population without systemic disease.² Otherwise, beta-amyloid (A β) is the most common type of amyloid seen in the brain.³ Autopsy pathology and detailed discussions aside for the sake of this correspondence on practical diagnostic issues, the typical scenario is the identification of A β in the walls of the blood vessels in the background of blood clot (Figure 1), leading to the diagnosis of A β -cerebral amyloid angiopathy (A β -CAA), the most common type of CAA, originally described as congophilic angiopathy. The hemorrhage is typically lobar/hemispheric, rather than basal ganglionic, thalamic, or pontine hemorrhage of hypertension, and can be multiple metachronously or synchronously, drawing attention to their suspected nature. CAA⁴ is a common cause of cerebral hemorrhage in those older than 60 years of age. Its prevalence increases with age. Rare hereditary forms are also