strategy based on the onset time, driving times, likelihood of aLVO, and hospital-specific workflow times. With this model, we showed that a positive predictive value of 0·40 can justify direct transport to an intervention centre in certain regions, as the treatment benefit for patients with aLVO outweighs the harm caused by delaying intravenous thrombolysis in patients with non-aLVO ischaemic stroke.[3] Because the optimal pathway is context-specific, health policy makers should estimate the impact and feasibility of prehospital triage strategies in their region before implementation, preferably using modelling-based approaches. We are currently preparing our prehospital personalised decision model for implementation in a mobile application, which will be evaluated in PRESTO-II. This application incorporates the RACE scale (range 0–9), time since symptom onset, real-time driving times, and hospital-specific workflow times.

Before additional interventions such as mobile stroke units or advanced large-vessel occlusion detection tools are sufficiently substantiated, validated prehospital stroke scales are our best option to improve personalised prehospital triage of patients with ischaemic stroke.

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## Freezing of gait and levodopa

In their Historical Insight, Peter Koehler and colleagues[1] propose that freezing of gait (FOG) in patients with advanced Parkinson's disease is the result of chronic long-term levodopa use. Furthermore, they notice that, if FOG was present in the pre-levodopa era, it expressed itself as akinetic, not as the shuffling and trembling subtypes seen mostly nowadays. Therefore, they conclude that the high-frequency oscillatory features of FOG are probably induced by levodopa. Although we appreciate this thought-provoking hypothesis, we would like to present some observations that refute it.

First, FOG can manifest before levodopa intake. In the Parkinson Progression Marker's Initiative cohort, 23 (5%) of 423 de novo patients had FOG at baseline.[2] Also, five (17%) of 30 drug-naive patients from a cohort in sub-Saharan African had FOG.[3] After 1 year of levodopa treatment, only one patient reported FOG; after 2 years, still only four patients in this cohort reported FOG, with significantly reduced severity when compared with presentation at baseline.

Second, accurate detection of FOG is challenging even with high-resolution cameras and wearable sensors, particularly for discerning small amplitude high-frequency movements during brief episodes. Hence, we suspect that historical cinematography with all its technical limitations was not optimal for the detection of FOG, particularly that of the trembling subtype.

Third, we found two papers from the pre-levodopa era describing FOG episodes along with correlates, in which FOG triggers varied between patients, and visual cues could temporarily overcome the event.[4,5] Also, Koehler and colleagues did not find one film from the pre-levodopa era showing FOG, but FOG does appear to be present in a patient filmed around 1910.[6]

Therefore, given our concern that the Historical Insight might induce unfounded so-called levodopa-phobia in some patients, we urge caution when proposing that FOG has increased after the introduction of levodopa. What the piece by Koehler and colleagues does highlight is the great need for reliable datasets on FOG to enable in-depth characterisation of its phenotypes. Longitudinal studies are needed to determine how evolving pathology and dopaminergic therapy interrelate and affect the emergence of FOG as a graded phenomenon reflecting motor and non-motor circuit failure.

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## Could SARS-CoV-2 cause tauopathy?

A large cohort study on the neurological sequelae of COVID-19 found that approximately 34% of patients received a psychiatric or neurological diagnosis within 6 months of SARS-CoV-2 infection.[1] Some of these diagnoses are indicative of acute or subacute changes to the CNS. Although the long-term consequences of these changes are unknown, viral infection in a subset of patients might promote chronic neuroinflammation and, over a period of years, lead to tau aggregation and neurodegeneration.

Tauopathies are characterised by the deposition of insoluble aggregated tau in neurons and, occasionally, glial cells. Tauopathies are classified as either primary, in which tau is thought to be the driver of disease, or secondary, in which tau aggregation is downstream of another insult. Secondary tauopathies can have a wide range of causes, from extracellular accumulation of amyloid β to repetitive head trauma. Although the exact mechanism for how these diverse insults lead to tau aggregation and neurodegeneration is still poorly understood, secondary tauopathies are associated with neuroinflammation. In particular, activation of the NLRP3 inflammasome can promote tau hyperphosphorylation and the formation of neurofibrillary tangles.[2] The activation of the NLRP3 inflammasome, triggered during SARS-CoV-2 infection, could lead to downstream tau aggregation and neurodegeneration.

SARS-CoV-2 might cross the blood–brain barrier and directly infect neurons or the surrounding vasculature, as shown in non-human primates.[3] Once inside cells, SARS-CoV-2 can directly activate the NLRP3 inflammasome[2] and induce tau mislocalisation[4] in human cells in vitro.

A second possible mechanism by which SARS-CoV-2 could affect the CNS is through inducing a widespread systemic inflammatory response. For example, cytokines released in systemic inflammation can activate glial cells. The increase in cytokine levels during SARS-CoV-2 infection, including interleukin (IL)-18 and IL-1β, can also lead to activation of the NLRP3 inflammasome.[2] Activation of NLRP3 by these cytokines has been observed in the brain in murine models.

Accumulated exposures to pathogens that contribute to neuroinflammation might increase the risk of developing a tauopathy. For example, the subacute sclerosing panencephalitis and postencephalitic parkinsonism tauopathies have been suggested to be triggered by viral infections. These diseases share the neuropathological hallmarks of hyperphosphorylated tau, neurofibrillary tangles, and neurodegeneration.[5] In post-mortem samples from individuals with subacute sclerosing panencephalitis, measles virus has been detected in neurons and glial cells that contain tau neurofibrillary tangles.[5] Postencephalitic parkinsonism is thought to be a long-term sequela of encephalitis lethargica that occurred during and after the 1918 influenza pandemic. Subacute sclerosing panencephalitis is diagnosed 3–34 years (median 9–10 years) after measles infection, whereas postencephalitic parkinsonism was generally diagnosed 1–5 years after encephalitis lethargica.[6]

Only 0·01–0·1% of measles infections lead to subacute sclerosing panencephalitis.[5] If a COVID-19-induced tauopathy develops at a similar rate, there could be 10 000–100 000 cases for every 100 million people infected with SARS-CoV-2. However, the proportion of individuals infected with SARS-CoV-2 who have substantial neuroinflammation, and who are therefore potentially at a higher risk of developing secondary tauopathy, is unknown. It is also important to note that no direct causal link between COVID-19 and neurological or psychiatric sequelae has been found, and some complications—including anxiety disorders—might be due to the stress and trauma associated with social factors (eg, isolation) and treatment options (eg, intubation).[1]

We believe that follow-up studies of neurological dysfunction in survivors of COVID-19 should be done, particularly in people who showed acute or subacute neurological symptoms. Such studies should persist for at least a decade and focus on young individuals (ie, those aged 30–40 years), to reduce the proportion of participants who will develop tauopathies because of old age. These studies should also investigate tau in blood or CSF, and tau aggregation by use of PET tracers.

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