

Dear friends of clinical journal club - load the file down at <https://www.mdc-berlin.de/cjc>:

The N Engl J Med image of the week concerns a 78-year-old man, who presented to the emergency department with weakness on the left side that had developed 90 minutes earlier. An ischemic stroke in the territory of the right middle cerebral artery was diagnosed, and treatment was initiated. After some time, examination showed the following change in the patient's tongue. What is the most likely diagnosis? You are offered: Tissue plasminogen activator-associated angioedema, Lingual artery thrombosis, Lingual dystonia, Unilateral hypoglossal nerve palsy, and the Melkersson-Rosenthal syndrome. We review the conditions. Last week, we reviewed acute intermittent porphyria, a mutation in the gene encoding uroporphobilinogen deaminase. Up-regulation of hepatic delta-aminolevulinic acid synthase 1 (ALAS1), with resultant accumulation of delta-aminolevulinic acid (ALA) and uroporphobilinogen, is central to the pathogenesis of acute attacks and chronic symptoms in acute hepatic porphyria. Acute intermittent porphyria is the most common form by far. Givosiran, an RNA interference therapy, inhibits ALAS1 expression. In a double-blind, placebo-controlled, phase 3 trial, investigators randomly assigned symptomatic patients with acute hepatic porphyria to receive either subcutaneous givosiran (2.5 mg per kilogram of body weight) or placebo monthly for 6 months. The primary end point was the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria, again the most common subtype of acute hepatic porphyria. Givosiran, a genuine gene therapy, was successful. Incidentally, the conventional treatment (hemin) that costs very little, was discontinued in the patients. During the current worldwide pandemic, coronavirus disease 2019 (Covid-19) was first diagnosed in Iceland at the end of February. However, data are limited on how SARS-CoV-2, the virus that causes Covid-19, enters and spreads in a population (in size about the same as the borough of Spandau in Berlin, ie <300,000 persons). Investigators targeted testing the persons living in Iceland who were at high risk for infection (mainly those who were symptomatic, had recently traveled to high-risk countries, or had contact with infected persons). They also carried out population screening using two strategies: issuing an open invitation to 10,797 persons and sending random invitations to 2283 persons. They then sequenced SARS-CoV-2 from 643 samples. Children under 10 years of age

were less likely to receive a positive result than were persons 10 years of age or older, with percentages of 6.7% and 13.7%, respectively, for targeted testing; in the population screening, no child under 10 years of age had a positive result, as compared with 0.8% of those 10 years of age or older. Fewer females than males received positive results both in targeted testing (11.0% vs. 16.7%) and in population screening (0.6% vs. 0.9%). Randomized trials involving patients with stroke have established that outcomes are improved with the use of thrombectomy for large-vessel occlusion. These trials were performed in high-resource (rich) countries and have had limited effects on medical practice in low- and middle-income countries. Investigators studied the safety and efficacy of thrombectomy in the public health system of Brazil. We learn that thrombectomy also works in Brazil. The next investigators describe a case of life-threatening disseminated coccidioidomycosis in a previously healthy child. Like most patients with disseminated coccidioidomycosis, this child had no genomic evidence of any known, rare immune disease. However, comprehensive immunologic testing showed exaggerated production of interleukin-4 and reduced production of interferon- γ . Supplementation of antifungal agents with interferon- γ treatment slowed disease progression, and the addition of interleukin-4 and interleukin-13 blockade with dupilumab resulted in rapid resolution of the patient's clinical symptoms. The report shows that blocking of type 2 immune responses can treat infection. The N Engl J Med review is on trisomy 21 or Down's syndrome. The patient of the week is a 73 year-old Covid-19 sufferer who develops electrocardiographic changes and poor cardiac function. We next review 2 Nature papers showing how the anti-contagion policies in the Covid-19 epidemic saved lives. The first group of epidemiologists claimed that 62 million confirmed cases were delayed or avoided. The second group published similar assumptions. Lynch syndrome is a Mendelian inherited form of colon cancer involving faulty DNA repair genes. In the Lancet, we learn that two US aspirin tablets per day substantially reduced the cancer rate in persons harboring such mutations. We next inspect a trial of atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable malignant melanoma featuring the BRAF v600 mutation. Next, we are informed of the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5-vectored Covid-19 vaccine. The results look quite promising. The Lancet review is on meningococcal disease spread by sexual transmission, an evolving health

problem. Finally, you are probably wondering, “whatever happened to the Diamond Princess?” The outbreak of coronavirus disease 2019 (Covid-19) on the cruise ship Diamond Princess led to 712 persons being infected with SARS-CoV-2 among the 3711 passengers and crew members, and 410 (58%) of these infected persons were asymptomatic at the time of testing. Investigators now report on the natural history of asymptomatic SARS-CoV-2 infection in part of this cruise-ship cohort. A total of 96 persons infected with SARS-CoV-2 who were asymptomatic at the time of testing, along with their 32 cabinmates who tested negative on the ship, were then transferred from the Diamond Princess to a hospital in central Japan between February 19 and February 26 for continued observation. Clinical signs and symptoms of Covid-19 subsequently developed in 11 of these 96 persons, a median of 4 days (interquartile range, 3 to 5; range, 3 to 7) after the first positive polymerase-chain-reaction (PCR) test, which meant that they had been presymptomatic rather than asymptomatic. We close with a 51 year-old patient with sleep apnea. He has a systolic murmur. When treated with CPAP, he becomes hypoxemic when the positive pressure is increased. The oral presentations will be in Wednesday at 16.00 English and 17.00 German. Incidentally, the 75 year-old demonstrator from last week who was thrown to the ground and had blood coming out of his ear indeed had a basilar skull fracture. He survived but is now unable to walk.

Yours,

Fred Luft (Check out the file pdf at <https://www.mdc-berlin.de/cjc>)