Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Isolated bulbar palsy after SARS-CoV-2 infection

We read with interest the Article by Matschke and colleagues,[1] who detected inflammatory infiltration, predominantly in the brainstem, and proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the lower cranial nerves of patients who died from COVID-19. Clinical correlates of these neuropathological findings are largely unknown. Indeed, only few studies have reported cranial nerve involvement in COVID-19—namely, ophthalmoplegia and facial nerve palsy in Miller Fisher syndrome,[2] isolated ophthalmoplegia,[2,3] acute vestibular dysfunction,[4] and unilateral Tapia's syndrome.[5]

Between March and April 2020, we assessed four individuals who presented with fever, hyposmia, hypogeusia, and cough (three at IRCCS Mondino Foundation in Pavia, Italy, and one at ASST Bergamo Ovest in Romano di Lombardia, Italy). Within 2 weeks, they developed respiratory failure, which required hospital admission. Their nasopharyngeal swab tests were positive for SARS-CoV-2 RNA and chest CT showed lung ground-glass opacities in all patients. Within few weeks of hospitalisation, these patients needed invasive mechanical ventilation and tracheostomy in the local intensive care unit. When respiratory distress improved, and after weaning from respiratory support and tracheostomy removal, the patients had hoarseness, dysphagia, and tongue deviation. Brain MRI after gadolinium administration and CSF analyses, including isoelectric focusing, showed no abnormalities. Serological assays for anti-ganglioside antibodies and antibodies against Epstein-Barr virus, cytomegalovirus, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, and *Campylobacter jejuni* were negative. At about 20 weeks after the onset of respiratory symptoms, neurological examination showed a breathy voice, left-sided tongue deviation on protrusion, and unilateral or bilateral weakness of the soft palate, trapezius, and sternocleidomastoid in all patients. Pharyngeal sensation tested by means of a stick was preserved. The clinical course for each patient is reported in the appendix (pp 1–2). Electromyography of the muscles innervated by the pharyngeal, superior laryngeal, and recurrent laryngeal branches of the vagus nerve, and by the accessory and hypoglossal nerves, showed asymmetric patterns of acute or chronic neurogenic damage, or both. A hypoglossal nerve conduction study disclosed abnormalities consistent with the electromyography findings. Limb electroneurography, blink reflex, and facial nerve conduction studies were normal in all patients (appendix pp 2–3). At 3 months of follow-up, neurological symptoms were still present. Dysphagia and weakness of the soft palate, trapezius, and sternocleidomastoid improved in patients 3 and 4, and breathy voice and tongue deviation improved in patients 2 and 4. Electromyography showed unchanged chronic neurogenic impairment without evidence of acute denervation, which had been previously observed. The hypoglossal nerve conduction study showed only mild improvement.

Our patients with COVID-19 developed an isolated bulbar palsy, characterised by asymmetric selective involvement of the vagus, accessory, and hypoglossal nerves. This neurological condition might stem from a motor neuronopathy of medullary cranial nerve nuclei or from a lower cranial multiple neuropathy. The neuropathological evidence by Matschke and colleagues supports the involvement of the medulla oblongata,[1] which could have also contributed to the severe respiratory distress. Whether these findings reflect the direct (viral) or indirect (immune-mediated) effect of SARS-CoV-2 remains to be established. Notably, there was no clinical or electrophysiological worsening in our patients, and this finding argues against a progressive motor neuron disease, which could have been potentially triggered by chronic neuroinflammation. Isolated bulbar palsy might be a regional variant of Guillain-Barré syndrome associated with SARS-CoV-2 infection. Alternatively, a severe compression neuropathy of the lower cranial nerves might derive from abnormal head posture during a prone position manoeuvre, malposition or displacement of the tube, and overinflation of the cuff after airway manipulation during orotracheal intubation or tracheostomy. Finally, central and peripheral neurological involvement might coexist, as the damage of a neuronal soma can increase susceptibility to peripheral injury of the downstream axon.

See **Online** for appendix

The ongoing SARS-CoV-2 infection might increase the incidence of isolated bulbar palsy worldwide soon. These cases showed that isolated cranial nerve palsy can be encountered in patients with SARS-CoV-2 infection after intensive care. Long-term follow-up will provide further insights into the final prognosis in patients with this severe neurological complication.

We declare no competing interests.

*Massimiliano Todisco, *Enrico Alfonsi, Sebastiano Arceri, Giulia Bertino, Carlo Robotti, Michele Albergati, Matteo Gastaldi, Cristina Tassorelli, Giuseppe Cosentino*
enrico.alfonsi@mondino.it

Clinical Neurophysiology Unit, IRCCS Mondino Foundation, 27100 Pavia, Italy (MT, EA, SA, GC); Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy (MT, CT, GC); Department of Otolaryngology Head and Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy (GB, CR); Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy (CR); Rehabilitation Unit, ASST Bergamo Ovest, Romano di Lombardia, Italy (MA); Neurorehabilitation Unit (CT) and Neuroimmunology Laboratory (MG), IRCCS Mondino Foundation, Pavia, Italy

1 Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020; **19:** 919–29.

2 Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020; **95:** e601-5.
3 Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* 2020; **95:** 221–23.
4 Escalada Pellitero S, Garriga Ferrer-Bergua L. Report of a patient with neurological symptoms as the sole manifestation of SARS-CoV-2 infection. *Neurologia* 2020; **35:** 271–72.
5 Decavel P, Petit C, Tatu L. Tapia syndrome at the time of the COVID-19 pandemic: lower cranial neuropathy following prolonged intubation. *Neurology* 2020; **95:** 312–13.

Advanced consent for acute stroke trials

As described by Erwin J O Kompanje and colleagues in their Personal View,[1] consent for enrollment into acute stroke trials is challenging because enrollment must happen quickly; however, patients are frequently incapacitated and are rarely accompanied by a proxy decision maker. We would like to propose advanced consent as a novel strategy to address these limitations: patients at risk for stroke could be asked to provide consent for a trial, should they become eligible for enrollment in the future.[2] Advanced consent is allowed under many research guidelines[3,4] and has been used for research in dementia, but has not been investigated for acute stroke trials.[5]

We envision a system in which patients at risk are identified through stroke prevention clinics, where they can get informed about ongoing trials and invited to consent; decisions would then be documented in the electronic medical record. Advanced consent would supplement standard recruitment efforts, and patients not seen in a stroke clinic would still be eligible for enrollment into the same trials.

Advanced consent would ensure that patients' wishes regarding trial participation are respected, even if they are incapacitated at the time of enrollment. Advanced consent could also help address the under-representation of women in stroke trials,[6] which might, in part, reflect the fact that women are excluded from trials because they are older[7] and more likely to be living alone when presenting with stroke,[8] and therefore are less likely to have a proxy decision maker available to consent on their behalf.[9] By providing their own advanced consent, women would have a greater opportunity to be enrolled into acute stroke trials, increasing their fairness and generalisability.

Data from our tertiary care academic centre in Ottawa (Ontario, Canada) support the feasibility of advanced consent. More than two thirds of patients seen in our stroke clinic are open to being approached about research. By our estimates, 5–7% of patients seen in our stroke prevention clinic with minor stroke or transient ischaemic attack present to the emergency department with an acute stroke within 1 year of their clinic appointment, reflecting 100–150 potential trial candidates annually. Applied more broadly, the potential for advanced consent is more apparent: in 2018, more than 1500 patients presented to our emergency department with ischaemic stroke, intracerebral haemorrhage, seizure, or status epilepticus. Of these, 56% had been assessed in any outpatient clinic in the preceding 2 years. We are eager to explore the potential of advanced consent for acute stroke trials and anticipate expanding this approach to other emergency conditions.

We declare no competing interests.

*Michel Shamy, *Brian Dewar, Naomi Niznick, Stuart Nicholls, Dar Dowlatshahi*
bdewar@ohri.ca

Department of Medicine, Neurology (MS, NN,DD), Ottawa Hospital Research Institute (BD, SN),Ottawa, ON K1Y 4E9, Canada

1 Kompanje EJO, Dijck JTJM van, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. *Lancet Neurol* 2020; **19:** 1033–42.
2 Niznick N, Lun R, Dewar B, Dowlatshahi D, Shamy M. Advanced consent for participation in acute care randomised control trials: protocol for a scoping review. *BMJ Open* 2020; **10:** e039172.
3 Government of Canada. Tri-council policy statement on ethical conduct for research involving humans. Feb 5, 2016. https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2018.html (accessed July 9, 2019).
4 US Food and Drug Administration. Protection of human subjects: informed consent and waiver of consent requirements in certain emergency research; final rules. 1996; **61:** 51497–531.
5 Largent EA, Wendler D, Emanuel E, Miller FG. Is emergency research without initial consent justified? The consent substitute model. *Arch Intern Med* 2010; **170:** 668–74.
6 Tsivouglis G, Katsanos AH, Caso V. Under-representation of women in stroke randomized controlled trials: inadvertent selection bias leading to suboptimal conclusions. *Ther Adv Neurol Disord* 2017; **10:** 241–44.
7 Lai SM, Duncan PW, Dew P, Keighley J. Sex differences in stroke recovery. *Prev Chronic Dis* 2005; **2:** A13
8 Glader EL, Stegmayr B, Norrving B, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke* 2003; **34:** 1970–75.
9 Burke JF, Brown DL, Lisabeth LD, Sanchez BN, Morgenstern LB. Enrollment of women and minorities in NINDS trials. *Neurology* 2011; **76:** 354–60.

Authors' reply

Michel Shamy and colleagues propose an advanced consent procedure as a solution for challenges encountered in obtaining informed consent in acute stroke trials. Available informed consent alternatives, such as deferred consent or exception from consent, are well established methods that allow acute stroke trials to be done despite these challenges.[1] We don't think that another procedure is required.

The proposed procedure seems a laudable effort to honour patient autonomy in emergency research. It allows individuals to pre-record their preferences regarding trial participation before becoming eligible and guarantees that these preferences are complied with in acute medical situations. This procedure would be seemingly an improvement, compared with current consent alternatives in which patient or proxy consent is obtained as soon as possible, usually after study intervention. The importance of honouring patient autonomy should not be underestimated, but there are some important limitations.

First, obtaining valid advanced consent for ongoing studies investigating