



Management of Patients with Cerebellar Ataxia During the COVID-19 Pandemic: Current Concerns and Future Implications

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Abstract

The current worldwide severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that causes coronavirus disease 2019 (COVID-19) has brought some medical systems to the brink of collapse. This crisis is also negatively impacting the care of patients with non-COVID-19 conditions, including those with cerebellar ataxia (CA). Older patients with CA and those with immune-mediated ataxias on immunosuppressive medication are potentially at high risk of developing serious complications of the infection, although it is also possible that immunosuppressive agents may provide a defense against cytokine storm. This has implications for even greater attention to preventing contracting the disease through physical distancing and/or isolation. The CA patient population is also at higher risk because of the neurological complexities of their underlying disorder and the comorbid medical illnesses that often accompany the genetic ataxias. As the disruption of social patterns and healthcare delivery in response to the crisis continues, interruption of rehabilitation, speech and language therapy, and face-to-face consultations threatens to have a negative impact on the course and well-being of CA patients. Mental and physical health is also potentially at greater risk because the prevailing uncertainty and anxiety may be superimposed upon cerebellum-specific neuropsychological challenges. We identify and review some of the short- and long-term consequences of this global pandemic for the community of ataxia patients and their families and for the clinical and academic neurologists/ataxiologists caring for these patients. This includes the recognition that telemedicine has emerged as a principle means of caregiver-patient contact and that neurological manifestations of COVID-19 including those specific to cerebellar neurobiology are increasingly recognized and will require close surveillance and monitoring. This COVID-19 Cerebellum Task Force consensus provides some guidance on how we may approach this uncertain time and consider preparing for the new realities we face in CA patient care once this acute crisis has passed.

Keywords SARS-CoV-2 · COVID-19 · Cerebellar ataxia · Cerebellum

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A highly infectious and pathogenic novel zoonotic corona virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has caused a global pandemic, Corona virus disease 2019 (COVID-19), presenting predominantly with severe pulmonary disease leading to acute respiratory failure, multisystem failure, and mortality of between 1 and 10% depending on environmental circumstances [1, 2]. Neurological manifestations occur in about one third of hospitalized patients, involving both the central nervous system (dizziness, headache, impaired consciousness, acute cerebrovascular events, ataxia, seizure), the peripheral nervous system (loss of smell and taste, neuropathic pain, variants of Guillain-Barré syndrome), and skeletal muscle injury [3]. Neurological manifestations occur in particular in patients with severe infection. SARS-CoV2 requires the angiotensin-converting enzyme 2 (ACE2) to enter cells. This receptor is expressed in endothelial cells and neurons, which indicates that it has neuroinvasive potential [4].

The exponential increase in the number of affected patients with COVID-19 requiring inpatient care has exceeded the capacity of medical services in several countries because of the unprecedented surge in patients requiring ventilatory support and multiorgan management in intensive care units (ICU). In addition, the pandemic is jeopardizing healthcare delivery for non-COVID-19 patients [5, 6]. The European Stroke Organization has already documented the reallocation of stroke resources and reduction of hospital staff due to quarantine or infection [5, 6]. Neurologists and trainees are being redeployed to the frontlines of COVID-19 care, either in the emergency department or within the ICU, while others are in self-isolation. Concern has been raised regarding discontinuation of disease-modifying therapies, such as immunosuppressive therapies, for major neurological conditions such as multiple sclerosis, with potentially irreversible consequences [6].

There are currently no data regarding the direct effect of COVID-19 on patients with cerebellar ataxia (CA), but the crisis nevertheless does appear to be likely negatively affecting their health and well-being. There are disease-specific issues that CA patients face that potentially place them at high risk of greater complications should they contract the disease. For those CA patients presently unaffected by COVID-19 infection, reduction of medical support negatively impacts their daily lives, and their social and psychological situation is further complicated by the difficulties they encounter accessing vital shopping and delivery services due to their physical handicap. Their reliance on caregivers potentially increases their risk of exposure to the virus. At the same time, diminished care by service providers no longer coming to their homes or available to them in the outpatient clinic limits their access to medical care and much-needed social interactions.

The Risks of COVID-19 for CA Patients

Risk of complications from COVID-19 increases markedly with age, commencing in the 60s and accelerating in the 70s, 80s, and above. Neurodegenerative disorders, including the CA disorders, often strike in midlife, increasing through the decades, and therefore, many patients with CA will be in their 7th decade and above and at greater risk of morbidity and mortality. Severe outcome is not confined to older populations, however, and whereas underlying disease predisposes to more severe outcome, there are now increasing reports of previously robust individuals succumbing to the illness in their 20s and 30s.

Premorbid conditions increase the risk for worse outcome. These include cardiovascular disease, diabetes, hypertension and history of smoking, and male sex for reasons related to different innate immunity, steroid hormones, and sex chromosomes [7]. What has not to our knowledge been specifically stated in publications to date is the heightened risk of neuromuscular diseases and disorders of respiration that are a consistent concern in patients with CA. Ataxic respiration, maintenance of airway protection, and the presence of aspiration pneumonia are a constant threat, increasing the potential for pulmonary complications in CA patients from COVID-19 in which shortness of breath and cough are usually heralding manifestations. Fatigue, anorexia, weight loss, and general debility from persistent high fever of COVID-19 are also expected to place a further burden on patients with the underlying neurodegenerative disorders that characterize the CA patient population.

Superimposed upon this baseline increased potential risk of greater morbidity and mortality is the awareness of immune compromise as a risk for more severe disease. Patients with immune ataxia are in this category, such as gluten ataxia, post-infectious, paraneoplastic, and unidentified immune ataxias, as they are treated with immune-modulating agents including rituximab, mycophenolate, prednisone, and others.

In addition, many genetic ataxias include cardiac and other diseases as integral components of the presentation. Most notably this includes Friedreich's ataxia with its cardiomyopathy, cardiac conduction defects, and diabetes.

Immediate Consequences of this Heightened Risk of COVID-19 for CA Patients

Populations across the globe are increasingly subject to stay-at-home restrictions, curfews, and frequent reminders to take preventive measures including hand washing, avoiding touching the face, wearing masks, and scrupulous environmental hygiene because of concern about droplets and aerosol spread of the virus. Not everybody is paying such close attention. Because of the heightened risk of the complications of

COVID-19 inherent in the disorders that produce cerebellar ataxia, our patients need to adhere to these preventive measures and heed all precautionary warnings. The most urgent recommendation therefore is to not get the infection by staying at home and avoiding contact with people who may harbor the virus. This has inescapable consequences, which in turn carry the risk of a deleterious impact on patients.

An unresolved issue specific to patients with the immune ataxias is whether their therapies should be stopped, including intravenous immunoglobulin (IVIg), corticosteroids, plasma exchange, mycophenolate, and rituximab. There is currently no internationally accepted recommendation for patients with immune ataxias. There is no evidence to suggest that IVIg, corticosteroids, or plasma exchange carry an additional risk of contracting COVID-19 [8]. Thus, any decision should be based on the individual's potential risks (age, associated diseases, severity of the immune ataxia), and the patient should be involved in decision-making. The recommendation in the UK, which we endorse, is that these patients should continue their treatment but be considered high risk, necessitating shielding, a step beyond physical isolation. In the event the patient develops symptoms suggestive of infection, they are instructed to stop the immunosuppressive drug until they have fully recovered from the infection, as a common general rule. Further problems arise from the inability to perform the usual monitoring of hematologic parameters, as well as the current inability to administer these medications in outpatient infusion therapy centers. Similarly, there is no consensus about starting immunotherapies. It will be better if at all possible to delay the immunotherapy. Clinicians should also, however, recognize the risk of not starting immunotherapies particularly in cases of rapidly progressive immune-mediated ataxias. There is preliminary evidence that the inflammatory cytokines IL-1 and IL-6 are elevated in patients with coronavirus infection and that low-dose prednisolone and tacrolimus might have beneficial effects on COVID-19 critically unwell patients [9]. Notably, COVID-19 elicits cytokine storm syndrome, which might be controlled by immunotherapies including IVIG, corticosteroids, and selective cytokine blockade [10]. However, until we have clear evidence that immunotherapy may be of benefit for COVID-19-positive patients, current best practice suggests the approach outlined above.

For those patients with CA who become ill with COVID-19 and who require intensive care, there is an additional important consideration. Decisions about escalation to intensive care are likely to be made by intensivists and/or internists without the input of the neurologist who normally cares for CA patients. These decisions are fraught with difficulty and have led to algorithms in some countries, exemplified by the use in the UK of the Clinical Frailty Scale (CFS) score [11]. Current recommendations are that for patients over 65 with CFS scores of 5 or greater; discussions should be held in advance about the suitability of critical care should their

condition deteriorate. Such discussions are unlikely to involve the neurologist who cares for the patient. Most patients with CA over the age of 65 are likely to be in that ≥ 5 category. (“Mildly Frail – These people often have more evident slowing and need help in high order instrumental activities of daily living such as finances, transportation, heavy housework, medications. Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.”)

The intense pressure on limited numbers of intensive care beds during the pandemic is therefore at risk of placing the CA patient population at a disadvantage if the details of the CA are not known to the primary care/intensive care teams who may lump all ataxia patients together, despite large variation in severity and long-term outlook of the underlying diseases. Neurologists, and specifically ataxiologists, should be alerted to this possibility and maintain open dialog with their patients and their fellow practitioners about the optimal approach to rational, equitable, and evidence-based decision-making in these difficult scenarios.

Ambulatory Visits

Current Challenges

The closure of ambulatory care clinics except in urgent circumstances is perhaps the most pressing issue affecting the delivery of care to patients with chronic neurological conditions. As ambulatory visits are suspended in many countries, patients are unable to see their doctors in person unless there are true medical emergencies. This has the downside of potentially delaying or preventing care, compounding the burden of disease to the point that it may require inpatient admission, placing these chronically ill patients at risk of acquiring infections, and further burdening the already strained healthcare system. Postponing all visits to after the COVID-19 pandemic is not a viable option, because patients need care in real-time now, and the backlog of cases to be seen at some later point in time would be untenable. It is also unclear precisely when that time would come.

We expect that as the pandemic resolves, healthcare providers will need to plan for different phases of return to normalcy. That would introduce different sets of challenges such as patients being fearful of traveling outside their restricted zone and the strain on existing medical systems of an expected backlog of new patient referrals. Those issues, problematic as they may be, would likely be welcomed as a marker of the crisis having receded.

For the present though, it has become apparent that novel practice patterns that are safe and effective need to be implemented now to provide appropriate care and prevent complications of the underlying CA disease.

Strategies for Intervention

The virtual visit platform for patient care has come to the rescue. Many institutions have already implemented telehealth/telemedicine, and this has rapidly become standard practice for many neurologists. Available programs such as Zoom, Doxy.Me, Cisco Jabber, WhatsApp, and FaceTime are used for healthcare visits if a patient agrees and contacts the doctor first, and while recent security breaches have been recognized, they are in the process of being repaired. These telemedicine platforms are efficient and practical. In our experience, they are appreciated by patients and have demonstrable positive impacts on patient sense of well-being and confidence that they have access to care providers to address concerns either related to our independent of the current pandemic. These virtual platforms make it possible to maintain contact with patients; review interim history and medications; and identify new, active, or potentially resolving issues. They keep the flow of conversation open and allow care providers to have meaningful dialog with patients in real-time. Virtual video-assisted platforms are well suited to performing some of the core elements of the neurology clinic visit including assessing overall mental state, selected eye movements, speech, examination of hyperkinetic movement disorders, ataxia, dexterity, gait (if caregiver is also present), and power (if caregiver can assist). We need to acknowledge, though, that while the virtual visit platform is a powerful and useful tool, it cannot fully replace the in-person encounter. Assessment of movement disorders such as tremor is not optimal using these video-assisted platforms. The oscillating nature of the movements is not always adequately captured in two dimensions, the quality of the video feed may be poor, and technical sophistication may be limited not only on the part of the patients and their families but also the physicians new to this platform. Further, for those patients with accompanying Parkinsonism, dystonia, or hyperkinesias, it is not possible to assess rigidity remotely. Finally, virtual interaction may be more difficult for CA patients because of the flat two-dimensional virtual environment and technical issues related to the audio component of the interaction. Delayed timing of speech and limitations of the visual platform might disproportionately burden CA patients because their automatized social models of timing and sequencing might be weaker and/or less flexible. There are no data on this topic to our knowledge, which makes this a potential fruitful area for future research.

We expect the virtual visit platform will have long-term consequences that will improve the overall quality of healthcare and patient access. Many of the clinic visits, even after COVID-19 is resolved, could be performed using this telemedicine approach which has already been used in many networks, for instance, for stroke. The virtual visit can lessen the patient's need to come in to the office in person for every visit, relieving the burden of the time and practical challenges

inherent in traveling sometimes far distances, incurring expenses to get to the clinic, and requiring the assistance or family members who must take time off from work to accompany them. The era of ambulatory clinical medicine that existed before COVID-19 is thus likely to be transformed in a positive way, at least in part, by the experience of care during this pandemic. This development may represent a silver lining of this catastrophe and an opportunity for scientists and healthcare providers to invest in remote data collection to build on this potentially efficient approach to evaluating disease and monitoring progression in the clinical environment and in clinical trials.

Rehabilitation Issues

Current Challenges

Ambulatory care services have dramatically decreased their activities in countries considered epicenters of the pandemic. As a result, patients with CA are already reporting from phone interviews a worsening of balance and falls. Patients with spasticity in the context of spinocerebellar ataxias complain of increased muscle spasms. The benefits of rehabilitation therapy reported for stroke patients are also applicable to patients with CA [12]. A 4-week intensive rehabilitation program (1 h × 3 sessions per week) improved balance, gait, and limb coordination based on the Scale for Assessment and Rating of Ataxia. Importantly, the retention of beneficial effects of such programs depends on continuous training. Long-term programs that include daily 1-h training sessions at home are associated with 1-year benefits, despite gradual decline in motor performance associated with natural progression of the disease. These results highlight the long-term benefits of intensive rehabilitation therapy in CAs, especially when combined with home rehabilitation. Thus, discontinuation of rehabilitation could exacerbate symptoms and worsen the clinical condition. Speech therapists are particularly exposed to viral infections due to the nature of their work, and many of them have stopped visiting patients at home or in residential homes. Patients are now reporting greater difficulties not only for oral communication but also more dysphagia. This is a worrisome development because of the greater incidence of potentially life-threatening aspiration pneumonia. Novel treatments under investigation such as transcranial direct current stimulation have also been discontinued.

Strategies for Intervention

Dynamic strategic planning is necessary at institutional levels, and changes must adapt to lessons learnt from other colleagues, sub-specialties and disease categories, institutions, and countries. For example, home-based therapy for

Parkinson's disease patients is freely available through the American Parkinson's Disease Association webpage. Some institutions are offering in-house online video tutorials for physical therapy. Balance therapy can be practiced remotely by following online tutorials of Tai-Chi or Yoga, frequently practiced measures at baseline. Similar online modules can be developed for speech therapy. Expert panels on cerebellar disorders are positioned to offer additional guidelines, generating the virtual means of telemedicine rehabilitation that patients can practice remotely. These measures, at a minimum, may keep patients with CA physically active and engaged, prevent decompensation, address anxiety, and prepare patients for the eventual resumption of their regular routines once the crisis has passed.

Psychological and Emotional Health

Current Challenges

It is now established that the clinical complex of neurocognitive and behavioral-affective symptoms in CA is caused in part by disruptions of the neural connections between the cerebellum and the limbic circuitry as well as the prefrontal, temporal, and parietal association cortices [9, 10]. The clinical features vary but include impaired executive function, visuospatial cognition, and personality changes with blunting of affect or abnormal behavior [13, 14]. Patients with spinocerebellar ataxia types 1 and 2 (SCA1 and SCA2) develop severe depression and negative symptoms, particularly apathy [15]. Thus, it is reasonable to expect that these patients may be more vulnerable to a psychological crisis such as we are seeing with COVID-19. In addition to their cerebellar disease, CA patients are chronically ill, which predisposes them to greater anxiety and depression. The altered structure of life around them, social isolation, and fear of acquiring the infection may exacerbate these tendencies. Compounding this psychological vulnerability is the reality that providers may have fewer resources available to offer. General practitioners are overwhelmed by the pandemic and less able to commit time and effort to the daily care of patients with chronic neurological conditions such as CA, and in-person psychology or therapy visits have ceased in most countries. In the present stressful climate, it is important to emphasize the need for assessment and monitoring of patients' emotional health.

Strategies for Intervention

Virtual online platforms have proven to be vital, efficient, practical, and impactful ways to address the needs of patients and their families. We recommend that patients connect with their behavioral therapists, psychologists, and psychiatrists using virtual visits. The present reality has

prompted healthcare providers and insurance companies to recognize these virtual services, which have now become billable. It is our experience already that these communication systems and online programs help provide opportunities to lessen anxieties and enable caregivers to assess their patients while providing timely and necessary support, counsel, and therapeutic intervention. This was shown empirically in a trial in Shanghai which described the benefits of interventions designed to cope with psychological crises among affected populations [16]. The authors utilized on-site psychological services to patients with COVID-19 as well as telephone and the Internet interactions to provide systematic psychological support to family members, friends, and/or colleagues, as well as people living in the neighborhood. The physical isolation required to flatten the curve of transmission has the potential negative consequence of true social isolation, with loss of in-person interactions with the support systems and society at large. Online platforms organizing virtual support group meetings can be instrumental in breaking the social deprivation. Local support group leadership should be encouraged to host such endeavors, supported by ataxia specialists who can address questions and issues raised by members of the support groups.

The Advent of Testing

The challenges of in-home therapy raise the concern about providers coming in direct and close contact with the patient, when the providers themselves may be asymptomatic or pre-symptomatic carriers of the virus. This adds to the burden of the psychological and emotional well-being of patients and their families. The rapidly evolving state of the field may provide the solution to this dilemma.

The powerful information available from the results of tests for the presence of infection with SARS-CoV-2 fundamentally changes the equation about the risks of exposure to people who are asymptomatic carriers. The development of rapid turnaround tests is expected to expedite the ability of society to grapple with the uncertainty of not knowing whether a person has been exposed to the virus and could be an asymptomatic carrier/spreader. Similarly, the development of a definitive serum test for the presence of antibody response to prior infection will enable more informed and rational decision-making about optimal approaches to a person entering the home of a patient to provide care or caregivers returning to work and to what we regarded as normal life just a few months ago. Data on body site-specific virus replication, immunity, and infectivity are critical to establish strategies of decontamination [17]. When a vaccine eventually becomes available, it will transform COVID-19 into another form of preventable influenza, but that is some way off.

Education and Dissemination of Knowledge

Current Challenges

The uncertainty surrounding all aspects of teaching and research impacts the future care of patients with CA.

The COVID-19 pandemic has led to cancellation of in-person instruction for all ages at educational institutions across the world, including doctoral programs which have been placed on hold. This has had a dramatic impact on the means of fulfilling educational curricula and the dissemination of knowledge. In addition to the termination of regular teaching courses, all local, regional, national, and international conferences of any kind have been canceled.

In medical school, lectures for the non-clinical grades are provided online, as are discussions and interactions with teachers and fellow students. In the clinical years, the clerkships have been suspended, putting on hold the opportunity for students to experience medicine in person and firsthand. Some nations have expedited medical education so that final-year students can graduate early and engage in the care of patients with COVID-19. The stress and anxiety associated with this pandemic also affect the emotional well-being of our students and colleagues. Against this background, it is remarkable that the medical community at almost all levels of responsibility and seniority and in almost every corner of the globe has demonstrated enormous resolve as well as astounding professionalism and commitment to patient care and continuation of the educational mission.

Clinical trials of promising therapies in the ataxias have been severely restricted, postponing for an unknown period the hope for cures of the most common spinocerebellar ataxias. Patients currently in clinical trials are being monitored remotely for safety concerns, but no new study subjects are being recruited during the pandemic as the sponsors of clinical trials and participating sites around the world adhere to the guidelines set by international regulatory authorities. Reallocation of grant resources are often unclear, and there is trepidation that funding for basic and translational research in neuroscience unrelated directly to COVID-19 may suffer from diminished public and private investment in these efforts, including the search for novel treatments and cures for the CA disorders.

Strategies for Intervention

It is necessary to continue encouraging education through the platforms that technology permits, including tapping into the power of virtual reality for such fields as anatomy and surgery. For those with advanced degrees or for continuing medical education, we encourage virtual webinars and conferences. These will foster ongoing interactions with local, national, and international colleagues promoting the exchange of

research findings and new ideas. Travel restrictions have made it impossible to gather in person for the next few months at least, but our mandate continues unabated to explore and grow scientific knowledge.

It is equally necessary for medical students and clinical trainees to continue their involvement in practical patient care. Students could be invited to participate in telehealth visits and telehealth programs, learning this new approach to healthcare along with their mentors and teachers. Currently available virtual visit interfaces allow involvement of more than two people. In the era before COVID-19, healthcare delivery was mostly in person; the era after COVID-19 is likely to include an emphasis on virtual visits, complementing the in-person experience. This has the potential to be a win-win situation for the provider and the patient, and medical students and trainees should participate in developing these skills.

We hope that the remarkable open access research that is characterizing the international race for effective approaches to SARS-CoV-2 and COVID-19 will pave the way for more open access research and education in the future. We can envisage a shared purpose in which common resources are assembled by universities and other academic institutions around the world to enhance the education of students and promote their knowledge and understanding of diseases, like the ataxias, that may not be well represented in local clinics or geographic regions.

Equanimity

As physicians, healers, and teachers, we strive to follow in a long tradition of maintaining *Aequanimitas* (*Equanimity*), Sir William Osler's (1904) use of the term for maintaining an even keel, remaining steadfast and unperturbable, with clearness of judgment despite the peril, in order to promote the physical and mental well-being of our patients, trainees, and colleagues [18]. One way we can do this is by focusing on the humanity of the care of our patients while at the same time honoring our privilege to foster the academic mission. The practical manifestations of this are to continue our work with the technology of online conferences; giving permission to ourselves and our colleagues to embrace intellectual and emotional space and take a break from the constant terrible news of the pandemic, from our own involvement in the care of COVID-19 patients now or in the imminent future; and finding comfort in thinking about and discussing the topics we care about in cerebellar neurobiology and clinical neurology. Providing some sense of what we used to think of as normal and routine outside of the COVID-19 environment is academically stimulating and important for patient care and for science; it is also, at this troubled time, a balm for the caregiver.

Prospective Evaluation of the Impact of the Pandemic on Cerebellar Neurobiology

The authors plan to evaluate the specific impact of COVID-19 on cerebellar function and its neurological manifestations. We would welcome reports and observations from colleagues, hospitals, patients, caregivers, and patient advocacy groups to help us expedite this data collection process.

Summary and Conclusions

SARS-CoV2 has caused an outbreak with major consequences at a world level. Patients with chronic CA require special attention, particularly if they are elderly and have other comorbidities. Decisions in the ICUs should involve the ataxiologists who often know their patients better than other caregiver. This pandemic is so dramatic that novel practice patterns need to emerge, including the use of telemedicine to provide care for patients with CA.

Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

Ethical Committee Approval Not applicable.

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