Neuro-ophthalmological manifestations of diabetes mellitus during COVID-19-related lockdown in India

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Purpose: The coronavirus disease 19 (COVID-19) pandemic has resulted in a huge impact on the health care system. Diversion of health care workforce toward management of a high number of COVID-19 cases and lockdown restrictions have affected the follow-up of patients. The objective of this study was to analyze the impact of this situation on the control of diabetes, eventually resulting in related neuro-ophthalmological complications. Methods: This retrospective case series included diabetic patients visiting the neuro-ophthalmology clinic at a tertiary care eye center in India from 25 March 2020 to 25 September 2020 during the lockdown. The incidence of diabetes-related neuro-ophthalmological complications, including third, fourth, sixth nerve palsies and non-arteritic anterior ischemic optic neuropathy (NAION) was evaluated and compared with that of the same period during 2019. Results: Overall disease incidence rate was significantly higher in the year 2020 (60.2%) compared to the previous year of 2019 (29.8%). The proportion of third nerve palsy (4.8% vs 16.3%, \( P < 0.001 \)) and NAION (0.3% vs 14.3%, \( P < 0.001 \)) had increased. Even though the percentage of sixth nerve palsy was 25% in 2020, this was not significantly different from 2019. There was a reduction in the percentage of fourth nerve palsy cases from the year 2019 to 2020. Conclusion: There was a significant increase in diabetes-related neuro-ophthalmic complications during the COVID-19 lockdown. This can possibly be attributed to worsening of glycemic control in diabetic patients.

Key words: COVID-19, diabetes mellitus, lockdown, naion, sixth nerve, third nerve palsy

The COVID-19 outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a public health emergency of international concern by the World Health Organization (WHO) on 30 January 2020.[1] As cases increased, social distancing measures were introduced followed by state-wise lockdowns and eventually a nation-wide 21-day lockdown from 25 March 2020. The lockdown was subsequently extended till 31 May of the same year.[2] This was followed by lifting of lockdown restrictions in a phased manner. The lockdown restrictions, including travel restriction and curbing of non-urgent medical services, largely affected the accessibility to health care services negatively.[3,4]

Diabetes mellitus encompasses heterogenous metabolic conditions resulting in the common phenotype of hyperglycemia.[5] Chronic hyperglycemia often results in damage, dysfunction and failure of various organs because of microvascular and macrovascular complications.[6] In the eye, it can cause retinopathy, cataract, glaucoma, and neuro-ophthalmic manifestations.[7] The most common neuro-ophthalmological manifestations of diabetes are non-arteritic anterior ischemic optic neuropathy (NAION) and ocular motor disorders resulting from third, sixth or fourth cranial nerve palsies.[8] In the elderly, NAION is the leading cause of acute optic nerve disease, often resulting in severe visual loss.[9] The incidence of ocular nerve palsies in diabetics has been reported to be 0.4%–14%, being seven to eight times commoner than in non-diabetics.[10,11]

Several studies have evaluated the effect of the lockdown on the control of diabetes. Studies have also assessed the impact of lockdown on ocular diseases and their management. This study was performed to specifically evaluate the effect of the lockdown on diabetes-related neuro-ophthalamic complications.

Methods

This retrospective study was conducted at a tertiary eye care hospital in southern India. The electronic medical records of the patients were obtained and evaluated. Patients with a known history of diabetes mellitus (DM) visiting the neuro-ophthalmology department were included in matching timelines in the years 2019 and 2020 to represent pre-COVID and COVID-groups. Pre-COVID group included patients presenting between 25 March 2019 and 25 September 2019 (period 1). COVID group included patients presenting during the identical terms.

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between 25 March 2020 and 25 September 2020 (period 2). Patients with uncontrolled hypertension and review cases with pre-existing neuro-ophthalmic pathology were excluded from the study.

The records of the two groups were scanned for cases with uncontrolled DM complicated by fresh onset of NAION, pupil sparing third nerve palsy, pupil involving third nerve palsy with normal neuroimaging, fourth nerve palsy or sixth nerve palsy. The incidence of these complications was calculated and compared between the two groups.

Uncontrolled DM was defined as either a fasting blood glucose level or post prandial blood glucose level of more than 140 mg/dl and 200 mg/dl, respectively.

Statistical analysis
The data were entered into REDCap software, version 11.2.6, and statistical analysis was performed using Stata statistical software, version 14.0 (StataCorp, College Station, Texas, USA). Categorical variables were expressed as frequency and percentage. Percentage change was calculated between the categorical variables of the two groups. Chi-squared test or Fisher’s exact test was used to assess the association of categorical variables. A two-tailed P value of 0.05 was taken as the level of statistical significance.

Results
In periods 1 and 2 respectively, a total of 887 and 98 diabetic patients attended the neuro-ophthalmology clinic. The mean age of the patients was 60.00 ± 11.35 years and 59.55 ± 9.89 years in period 1 and period 2, respectively. Both the periods showed a male predominance with period 1 having 577 (65.1%) and the 2 having 68 (69.3%) of the same.

Among the patients visiting during periods 1 and 2, 264 (29.8%) and 59 (60.2%) patients had fresh diabetes-related neuro-ophthalmic manifestations, respectively. None of the included patients for analysis in this study had any history of COVID-19 infection or test positivity prior to their onset of symptoms.

During period 1, among the 887 patients, a majority had sixth nerve palsy (21.1%) followed by third nerve palsy (4.8%), fourth nerve palsy (3.5%) and NAION (0.3%). During period 2, among the 98 patients, 26.5% had sixth nerve palsy followed by third nerve palsy (16.3%), NAION (14.3%) and fourth nerve palsy (3.1%). On comparison of proportion of diabetes-related neuro-ophthalmic manifestations between the two time periods, it was noted that the rate was significantly higher in period 2 (60.2%) compared to period 1 (29.8%) (P < 0.001). The proportion of patients with third nerve palsy increased from 4.8% in period 1 to 16.3% in period 2 (P < 0.001), and rate of NAION increased from 0.3% to 14.3% during period 2 (P < 0.001). The rate of sixth and fourth nerve palsy cases did not show any significant differences; however, both showed a trend toward an increased rate during period 2 [Table 1 and Fig. 1].

Discussion
The aim of the study was to analyze the effect of the COVID-19 lockdown on diabetes-related neuro-ophthalmic manifestations. It was demonstrated that there was an increased incidence of diabetes-related neuro-ophthalmic manifestations except for fourth nerve palsy, when compared to pre-COVID group. As of 2021, 537 million adults (aged 20–79 years) worldwide live with diabetes. The age adjusted prevalence of diabetes in India is 9.6%. With such a high burden of
The COVID-19 pandemic measures and the related lockdown impacted several aspects of health care negatively. This in turn resulted in the worsening of the control of chronic systemic conditions and poor outcomes of several ocular pathologies. Most affected were the conditions where regular follow-ups and interventions formed an important part of the management.

Accessibility to health care was affected for persons with non-communicable diseases in rural India. A study demonstrated that 14% missed their follow-up visit, 13.4% faced difficulties in obtaining medications and 11.6% reported either development of new complaints or worsening of already existing symptoms.[13]

Assessment of the effect of COVID-19 pandemic on the care of patients with kidney diseases showed that 28.2% of patients defaulted one or more dialysis sessions, 2.74% required emergency dialysis sessions, and 104 (4.13%) did not report for dialysis.[15]

A study analyzing the impact of the lockdown on the integrated care for hypertension and HIV concluded that although the HIV medications were universally obtained, there was a worsening of hypertension control and an increase in hypertension-related adverse events. Difficulty in obtaining anti-hypertensive medications was noted due to the lockdown.[16]

Measures related to COVID-19 pandemic were found to have resulted in additional cancer deaths. This was due to a suppressed health-seeking behavior among patients due to the personal risk of severe illness from COVID-19 and decreased accessibility of essential diagnostic and screening services.[17]

The COVID-19 pandemic and the related lockdown had a negative impact on several ocular pathologies as well.

A cessation of continuous patient care in the form of regular follow-up examinations and intravitreal anti-vascular growth factor (anti-VEGF) injections resulted in a deleterious impact on patients with diabetic retinopathy (DR) and neovascular age-related macular degeneration (nvARMD).

Progression to active proliferative diabetic retinopathy (PDR) was observed in 30% of patients from non-proliferative diabetic retinopathy (NPDR) and in 8.3% of patients from stable PDR. A worsening of best-corrected visual acuity (BCVA) and central subfield retinal thickness (CSRT) was also observed in patients with diabetic macular edema.[18] There was a statistically significant worsening of BCVA and macular neovascular exudation in patients with nvARMD.[19]

A significant worsening of corneal ulcer cases was noted. This was attributed to the delay in initial presentation and lack of follow-up. Corneal scrapings were performed by a reduced number of ophthalmologists due to the risk of disease transmission and suspended routine microbiological services. There was a limited availability of essentials required to manage corneal ulcers. Lack of donor tissue due to decline in eye donation and retrieval severely affected corneal transplant services.[20,21]

The proportion of patients presenting with higher grade of cataract increased significantly during and after the lockdown, which included total, brunescent, black, or morgagnian cataracts; phacomorphic or phacolytic glaucoma; and one-eyed patients with cataract. Economic constraints, suspension of elective procedures, and transport restrictions resulted in a delayed presentation.[22]

In our hospital, a study showed that 88.21% of glaucoma patients missed their follow-up and 57.3% were non-adherent to medication.[23] Another study revealed that several patients could not undergo urgent treatment due to logistical and financial issues directly related to the lockdown.[24]

Diabetes care was also one of the several aspects of health care that was affected. According to the type of diabetes, the impact of the lockdown was different. A systematic review and meta-analysis of 33 studies revealed that a majority of type one diabetic (T1D) patients showed improvement in glycemic control. On the contrary, type two diabetic (T2D) patients showed deterioration in glycemic control.[25] Since more than 95% of the diabetic patients have type two diabetes,[26] the negative impact of the lockdown was magnified.

Improvement in the glycemic control of T1D patients has been hypothesized to be due to various reasons. Due to the lockdown, more time was available for self-care and to prioritize T1D management. Balance between diet, exercise, and insulin requirements was achieved which allowed to negate the effect of the lockdown. The lockdown also allowed for a more regular daily routine which included scheduled meals. Digital treatments such as continuous glucose monitoring, flash glucose monitoring and hybrid closed-loop system were found to have a positive impact on T1D. Medication compliance, which is the main determinant in the management of T1D, was better achieved during the lockdown.[28] Contradictory to this, one study from India showed worsening of glycemic control in T1D due to non-availability of insulin and glucostrips during lockdown.[26]

On the contrary, worsening of glycemic control for T2D resulted from lifestyle changes including alterations in diet, decreased physical activity, more screen time and weight gain. Physical inactivity increased during the lockdown due to home confinement. Other causes included inadequate sleep, socioeconomic difficulties affecting healthy nutrition, inability
to visit hospitals or pharmacies and stress.[29]

A majority of the population aged between 30 and 65 years were affected by the lockdown, 63% of them being diabetics.[3] The mean age of onset of NAION (55 ± 9 years) and cranial nerve palsies associated with diabetes (58.5 ± 11.9 years) also lie in the same age bracket.

In our study, there was a significant increase in the incidence of NAION and third nerve palsy. There was an increase in the number of cases of sixth nerve palsy, but it was not statistically significant. Diabetes has been found to be a predominant cause for these conditions.[10,28] Considering the strong causal association between diabetes and these entities, the significant increase in their incidence during the lockdown period reflects the possibility of an overall lack of control of diabetes and systemic disease in these patients. The reduction in the incidence of fourth nerve palsy during the lockdown can be explained by the decrease in the rate of injuries. There was a significant decrease in the number of road traffic accidents.[29] Fourth nerve palsies are predominantly caused by trauma rather than diabetes-related microangiopathy.[30]

COVID-19, secondary to its aggressive neurotropism and neuro-invasion, has been reported to result in cranial nerve involvement.[31] However, the prevalence of the same has not been reported in the literature yet. In this study, we excluded patients having any prior history of COVID-19.

Thaller et al.[32] reported a negative impact of COVID-19-related lockdown on papilledema and idiopathic intracranial hypertension (IIH). They reported a 367% increase in CSF diversion surgery in their center following lockdown. This was attributed to the impaired access to care and weight gain resulting from lifestyle changes.

To the best of our knowledge, this is the first study evaluating the effects of lockdown on diabetes-related neuro-ophthalmic manifestations. It highlights one of the several aspects of health care affected by the lockdown. Several factors such as transport restriction, limited availability of drugs, outpatient services, diagnostic facilities and deferral of elective procedures have led to worsening of many conditions. Strategies to tackle these barriers need to be devised. There is a need to promote diabetes self-management education where the patient becomes partially free of his dependence on the health care provider. Self–blood glucose monitoring should be encouraged.[33] Weight gain is an important determinant for the development or worsening of metabolic disorders.[33,34] Exercising which can be done at home such as skipping should be prescribed and encouraged for weight management. Stocking of medicines and glucose testing supplies can tackle shortage of supplies. Teleconsultation services should be strengthened to allow continuum of care and help in triaging patients.[33]

A few limitations were identified in our study. There is a possibility that only those diabetic patients who developed symptoms like sudden diminution of vision (NAION) and sudden diplopia (cranial nerve palsies) visited the hospitals during the lockdown and not the diabetics who come for routine fundus evaluations, which might have resulted in an inclusion bias. A detailed set of biochemical tests was not done for the patients. Hence, we cannot directly attribute the rate of neuro-ophthalmic manifestations to poor control of diabetes. We make a conjecture that this may be a possibility.

Conclusion
There was a significant increase in neuro-ophthalmic complications due to diabetes. The worsening of the glycemic control represented just one of several aspects of health care that have been affected by the COVID-19 pandemic. It has highlighted several gaps in the health care system. Although lockdown restrictions have been eased with a drastic decrease in the number of active cases of COVID-19, the constant mutations in the genome of the virus are still of concern, and a future outbreak cannot be ruled out. This time should be utilized for future preparedness to help fight such situations more effectively.

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Conflicts of interest
There are no conflicts of interest.

References
1. COVID-19 Public Health Emergency of International Concern (PHEIC) Global research and innovation forum [Internet]. Available from: https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(phei)-global-research-and-innovation-forum. [Last accessed on 2022 Jan 28].
2. Mazumder A, Arora M, Bharadiya V, Berry P, Agarwal M, Behera P, et al. SARS-CoV-2 epidemic in India: Epidemiological features and in silico analysis of the effect of interventions. F1000Res 2020;9:315.
3. Raman R, Rajalakshmi R, Surya J, Ramakrishnan R, Sivaraprasad S, Conroy D, et al. Impact on health and provision of healthcare services during the COVID-19 lockdown in India: A multicentre cross-sectional study. BMJ Open 2021;11:e043590.
4. Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, Michel J-P, et al. The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: Consequences for healthy ageing. Aging Clin Exp Res 2020;32:1189-94.
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36(Supplement_1):S67-74.
6. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008;88:1254-64.
7. Henriques J, Vaz-Pereira S, Nascimento J, Rosa PC. [Diabetic eye disease]. Acta Med Port 2015;28:107-13.
8. Moster ML. Neuro-ophthalmology of diabetes. Curr Opin Ophthalmol 1999;10:376-81.
9. Hayreh SS. Anterior ischemic optic neuropathy. Arch Neurol 1981;38:675-8.
10. Lajmi H, Hmaied W, Ben Jalel W, Ben Yakhlef A, Ben Zineb F, et al. Oculomotor palsy in diabetics. J Fr Ophtalmol 2018;41:45-9.
11. Watanabe K, Hagura R, Akanuma Y, Takasu T, Kajinuma H, Kuzuya N, et al. Characteristics of cranial nerve palsies in diabetic patients. Diabetes Res Clin Pract 1990;10:19-27.
12. Home, Resources, diabetes L with. Acknowledgement, FAQs, Contact, et al. IDF Diabetes Atlas 10th Edition [Internet]. Available from: https://diabetesatlas.org/. [Last accessed on 2021 Nov 27].
13. Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr 2020;14:2211-7.
14. Gummidi B, John O, Jha V. Continuum of care for non-communicable
diseases during COVID-19 pandemic in rural India: A mixed methods study. J Family Med Prim Care 2020;9:6012-7.

15. Prasad N, Bhatt M, Agarwal SK, Kohli HS, Gopalakrishnan N, Fernando E, et al. The adverse effect of COVID pandemic on the care of patients with kidney diseases in India. Kidney Int Rep 2020;5:1545-50.

16. Schwartz JI, Muddu M, Kimera I, Mbuliro M, Ssennyonjo R, Ssinabulya I, et al. Impact of a COVID-19 national lockdown on integrated care for hypertension and HIV. Glob Heart 2021;16:9.

17. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: A national, population-based, modelling study. Lancet Oncol 2020;21:1023-34.

18. Chatziralli I, Dimitriou E, Kazantzis D, Machairoudia G, Theodossiadis G, Theodossiadis P. Effect of COVID-19-associated lockdown on patients with diabetic retinopathy. Cureus 2021;13:e14831.

19. Borrelli E, Grosso D, Vella G, Sacconi R, Battista M, Querques L, et al. Short-term outcomes of patients with neovascular exudative AMD: The effect of COVID-19 pandemic. Graefes Arch Clin Exp Ophthalmol 2020;258:2621-8.

20. Raj A, Singh P, Chaudhary N. Online survey on practice patterns in the treatment of corneal ulcer during COVID-19 pandemic. Indian J Ophthalmol 2021;69:2507-10.

21. Christy JS, Mathews P, Rhagavan A, Venugopal A, Manohar D, Janakiraman A, et al. Impact of COVID-19 pandemic on infectious keratitis outcomes: A retrospective multicenter study in tertiary eye hospitals of South India. Cornea [Internet]. 2021 Jul 22; Publish Ahead of Print. Available from: https://journals.lww.com/10.1097/ICO.0000000000002829. [Last accessed on 2022 Feb 28].

22. Bhalerao S, Majji S, Mohamed A, Vuyyuru S, Gogri P, Garg P. Changing trend in the morphology of cataracts at a tertiary eye care centre in South India due to COVID-19-pandemic related national lockdown. Indian J Ophthalmol 2021;69:3643-7.

23. Subathra G, Rajendra babu SR, Senthilkumar VA, Mani I, Udayakumar B. Impact of COVID-19 on follow-up and medication adherence in patients with glaucoma in a tertiary eye care centre in south India. Indian J Ophthalmol 2021;69:1264-70.

24. Babu N, Kohli P, Mishra C, Sen S, Arthur D, Chhablani D, et al. To evaluate the effect of COVID-19 pandemic and national lockdown on patient care at a tertiary-care ophthalmology institute. Indian J Ophthalmol 2021;68:1540-4.

25. Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: A systematic review. Diabetol Metab Syndr 2021;13:95.

26. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol 2016;12:357-70.

27. Reddy D, Rani PK, Jalali S, Rao HL. A study of prevalence and risk factors of diabetic retinopathy in patients with non-arteritic anterior ischemic optic neuropathy (NA-AION). Semin Ophthalmol 2015;30:101-4.

28. Kerr NM, Chew SSSL, Danesh-Meyer HV. Non-arteritic anterior ischemic optic neuropathy: A review and update. J Clin Neurosci 2009;16:994-1000.

29. Yasin YJ, Grivna M, Abu-Zidan FM. Global impact of COVID-19 pandemic on road traffic collisions. World J Emerg Surg 2021;16:51.

30. Keane JR. Fourth nerve palsy: Historical review and study of 215 inpatients. Neurology 1993;43:2439-43.

31. Doblan A, Kaplama ME, Ak S, Basmaci N, Tarini EZ, Göktas ŞE, et al. Cranial nerve involvement in COVID-19. Am J Otolaryngol 2021;42:102999.

32. Thaller M, Tsermoulas G, Sun R, Mollan SP, Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 2021;92:795-7.

33. Tewari A, Tewari V, Tewari J. Effect of COVID 19 lockdown on glycemic parameters in people with type 2 diabetes. J Family Med Prim Care 2021;10:2529-32.

34. Ghosal S, Arora B, Dutta K, Ghosh A, Sinha B, Misra A. Increase in the risk of type 2 diabetes during lockdown for the COVID19 pandemic in India: A cohort analysis. Diabetes Metab Syndr 2020;14:949-52.