



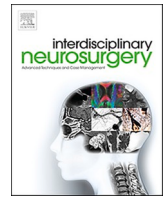
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Changes in stroke presentation in neo-Covid patients: A case study

Anoop Kohli, MD, DM^{a,*}, Charchit Gupta, MD^b, Shvet Dutta, MD^b, Chirag Madaan, MD^c^a Senior Consultant Neurology, Institute of Neurosciences, Indraprastha Apollo Hospitals Delhi, India^b DNB Neurology Resident Institute of Neurosciences, Indraprastha Apollo Hospitals Delhi, India^c Consultant Neurocritical Care, Indraprastha Apollo Hospitals Delhi, India

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ABSTRACT

A 35 year old male had a generalized seizure a week after symptoms of daily fever, rigors, and throat discomfort. He was hospitalized. Magnetic resonance imaging brain showed multiple bilateral scattered infarcts. COVID-19 swab test came positive. An elaborate panel of tests for young strokes, cardiac work-up was normal. At home, he complained of some visual blurring, slowing in thought processing, occasional loss of words. His face became significantly pigmented. A young male, COVID-19 positive, showed multiple scattered infarcts. Exaggerated pro-thrombotic activity of the nature of a cytokine storm, is the probable cause.

1. Commentary

A 35 year old male, had low grade fever with rigors for a week. He had an extreme feeling of weakness throughout. He started tab Hydroxychloroquine (HCQ) twice a day as a precaution. On the advice of his family physician, a swab sample of his throat was sent for Covid testing with results awaited. On the fifth day, he reported increase in frequency of stools. He was given intravenous cefuroxime 500 mg, at home, during which he developed rigidity, followed by tonic-clonic seizures. He was hospitalized and ventilated for a day. We carried out an array of extensive auto-immune tests, coagulation factors, anti-phospholipid antibodies [1]. Complete blood count revealed lymphocytopenia-32%. PT/INR, APTT, Platelet count were within normal limits. FDP was normal but D-dimer was raised at 1.4 mg/L. IL-6 level was 1000 pg/l and TNF- α level was 10 pg/ml, both were slightly raised but did not warrant specific intervention. Other tests for unusual strokes as anti-nuclear antibodies, anti-cardiolipin antibodies, protein C, protein S were normal. Liver function tests and renal function tests did not show any abnormality. Cardiac source of emboli was ruled out, and carotid ultrasound, and Magnetic Resonance imaging angiogram of neck vessels was normal. Plain MRI head was advised that showed scattered small lesions in diffusion weighted images (Fig. 1a) with corresponding changes in apparent diffusion coefficient images, in all probability thrombo-embolic, in both hemispheres. Intracranial MR Angiogram (Fig. 1b) was also normal. There were no lifestyle risk factors as smoking, alcohol intake, prior history of thrombosis in the lower limbs,

diabetes, or hypertension or renal disease. The swab Covid-19 RT PCR report came positive. He had salient neurological deficits at discharge two weeks after hospitalization, in a COVID negative state. Chiefly, he complained of blurring of vision, reported he had slowed down in his “mental processing”, (being a school teacher of mathematics), dysnomia, and occasional transient “blank outs” and felt a certain heaviness in his head. Mini mental state examination score was 20. He was oriented to time, place and person, intact memory but had delayed recall, less attentive, would speak less and was unable to follow complex commands. Frontal assessment battery was done which revealed normal conceptualization and mental flexibility but impaired motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. The chief physical finding was a significant pigmentation of his face (Fig. 3b). He is presently on tab HCQ 200 mg, and a clopidrogel-aspirin (75 mg, each) combination, Lamotrigine 100 mg, Clobazam 5 mg, prednisolone 20 mg/day with folic acid supplements. Anticoagulants were not considered appropriate in the absence of a thrombus besides they carried a small risk of hemorrhagic changes.

Three weeks after discharge, his complaints of blurring of vision, “slowing in his thinking process, and frequent “blank outs” showed significant amelioration. “Blank outs” remained were possibly epileptogenic as came out in the Electroencephalogram (Fig. 2).

2. Discussion

The novel SARS-Cov-2, perhaps the most appropriate terminology in

* Corresponding author at: A-761, SaritaVihar, New Delhi, India.

E-mail addresses: anoopkohli009@gmail.com (A. Kohli), guptacharchit21@gmail.com (C. Gupta), shvetdutta2017@gmail.com (S. Dutta), madaan.chirag1@gmail.com (C. Madaan).

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Fig. 1a. Diffusion-Weight MRI Brain image shows scattered thromboembolic lesions on either side.



Fig. 1b. MR Angiogram Intracranial was normal.

terms of being the closest in series of Covid viruses [2], and acute respiratory distress as the major presenting symptom. It is rather tragic that it has become pandemic beyond historical archives, and further spread its activity to other body systems. The mechanism at the core of this, is the propensity of the ‘S’ protein in its tentacles, to merge with the cell wall Angiotensin converting enzyme II receptors. These allow ease of entry into cells, where an RNA virus has the necessary environment to replicate a million times. So much for the acute inflammatory reactions in the lungs, resembling acute respiratory distress syndrome [3]. The prothrombotic activity, is the next formidable weapon, where it can spread to cause acute venous thrombosis, to the extent of spreading as thrombo-embolic phenomenon to add to what was understood as purely inflammation of respiratory tissue. This has led to cautious use of

anticoagulants, in critical cases [4]. Amongst the neurological complications strokes is perhaps on the forefront, due to requirement of deft handling, basic and even secondary care. This has led to various comprehensive editorials [5], American stroke association initiatives [6], counselling bodies, webinars, support groups. The thrust presently, and rather appropriately is on collecting data, and basic, even secondary management in neo-COVID strokes. Certainly, to jump at the theme even at the basic science level of research, of pathophysiology, beyond what may be speculative in the stroke event, may be premature and non-commensurate. Amongst the noted studies [5] are, describing four cases, that had strokes, but actual images, that may give a speculative clue to the cause, are not fully represented, probably due to lack of publication space. A noted study by Avula et al. [2], mentions four cases with occlusion of an ICA, others with moderate tapering of MCA, where infarcts occurred. This was a collection of cases from various centers. All were above seventy years, and had at least two major risk factors for strokes. The article is well illustrated, and at this stage of collecting all possible COVID related stroke data, it records valuable information. Neo-Covid’s ability to spread to different body tissues, including changes in antigenic behavior, one may expect, that stroke manifestations may differ too.

Stroke pathology is not a single entity, and it is usual even in routine therapy, to get clues as to the possible mechanism by neuroimaging. Strokes can be embolic, thrombotic [7], immune related as anti-phospholipid antibodies [1], major immunological vasculitis [8], artery to artery embolism [8], not to miss Miller Fisher’s lacunar infarcts [9].

The case under discussion, had fever with rigors, and started HCQ once daily on his own, On the fifth day consulted his family physician for frequency of stools. Inj. Cefuroxime was given intravenously at home, during which he developed generalized tonic-clonic seizures. He was ventilated for a day, on account of the seizures. His respiratory system showed no abnormality. The COVID test came positive. Magnetic Resonance Imaging brain showed multiple bilateral hyper-intense lesions on diffusion weighted images (Fig. 1a) with corresponding apparent diffusion coefficient changes, confirming infarcts. Intracranial MR angiogram was normal (Fig. 1b), showing no thrombosis or stenosis, thereby making thrombo-embolic phenomenon, a strong possibility. Visual evoked potentials, cervical MRI were done to rule out a faint chance of demyelinating overlap. They were normal. Such acute thrombotic events generally come under the umbrella term “cytokine storms” Simply put, these are events, when a local thrombotic event, has a sudden unexpected widespread effect, affecting various tissues. The term was first used in 1993, in a donor-host tissue reaction [10]. It has been widely used, but of relevance the article, is its use in various bird-flu reactions [11]. A noteworthy analysis is published in inflammation and influenza [12].

Another notable feature was the pigmentation of his face, the one at the time of discharge (Fig. 3b), compared to a photograph of Sept ‘19 (Fig. 3a) and the last taken in follow-up this week (Fig. 3c). Hyperpigmentation is a known response to skin repair. Binding to Angiotensin converting enzyme II, is essential in to this reaction. Extending the speculation of widespread intracranial thrombotic emboli, embolization of extra-cranial vasculature cannot be ruled out. Initial hypoxia could have set in motion the Angiotensin converting enzyme II reparative reaction, leading to facial hyperpigmentation, including reparative fibrosis, leading to dysmorphic facial feature changes [13,14]. Steroids given as a part of brain edema therapy, by suppressing inflammation, somewhat substantiates the mentioned hypothesis in leading to depigmentation. Besides the pigmentation, which is showing signs of reversal, there are morphological changes in his facial features, probably due to reparative fibrosis, is a skin complication not noted so far.

He was discharged on HCQ 200 mg twice a week, aspirin, anti-epileptics, and prednisolone 20 mg for ten days, now reduced to 10 mg. The blurring is better, “blank-outs” have stopped, and he does not feel dull as before.

Pertaining to strokes in COVID, though the final theme is



10-20 Bipolar montage, anterior-posterior leads, 30mm/sec, gain 7.5 μ v

Fig. 2. EEG showing epileptogenic activity posterior right temporal lobe (blue arrows), to a lesser extent in the left temporal lobe. (Bipolar montage, anterior-posterior leads, 30 mm/sec, gain 7.5 μ v). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

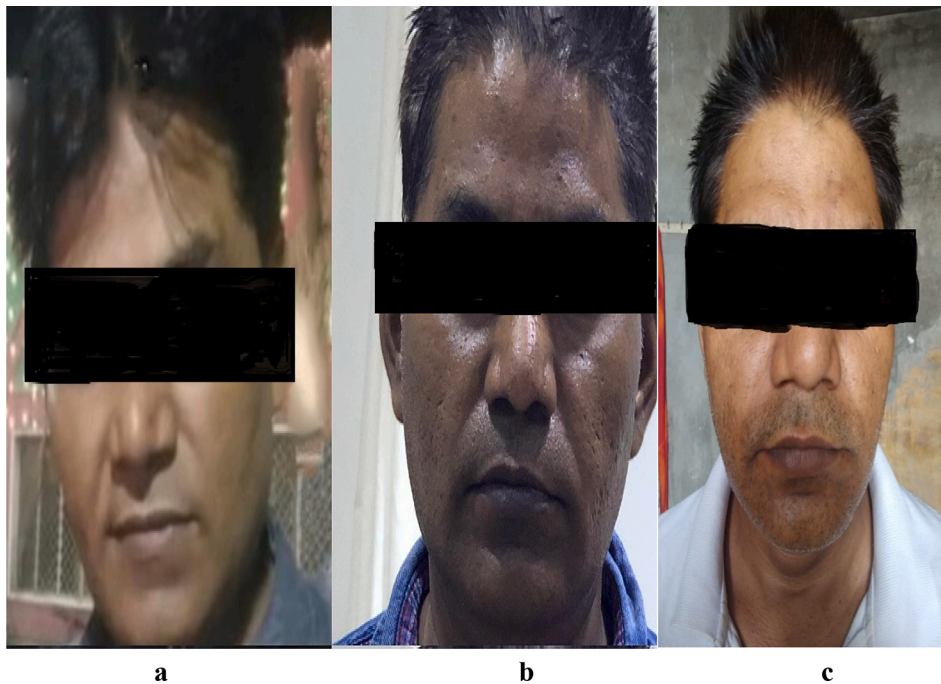


Fig. 3. Face pigmentation and morphological features changes September '19 (left), middle one at the time of discharge, present, (right).

appropriately set for future analysis, appropriate data, including convincing neuro-imaging may not be ignored, as it may be crucial in the final analysis.

3. Summary

A case of multiple embolic strokes, involving bilateral cerebral hemispheres is presented. This case is perhaps the first one that shows clear multiple thromboembolic stroke phenomenon, facial

pigmentation, adding a new variant to neo COVID strokes. At the level of speculation, perhaps the “cytokine storm” flared up into a multiple thromboembolic phenomenon localized only to the brain [10]. Any association of a second order cephalosporin given intravenously in patient moderately symptomatic, is yet another aspect to note particularly in critical cases [15].

Ethical statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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