Rapid brain atrophy after COVID-19 encephalitis;Disintegrata Furiosa!

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Case Report

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Abstract

Objectives: We had a patient with COVID-19 encephalitis who demonstrated striking brain atrophy on 3 MRI scans 60 days apart. We aimed to quantify the volume loss and brain atrophy. This is the first report that quantifies brain atrophy with COVID encephalitis.

Methods: A 75 year old partially vaccinated man with COVID encephalitis underwent 3 serial MRI scans. Manual volumetry using PACS software was used to average and quantify brain atrophy between the three scans.

Results: In 60 days, our patient had approximately 11.52 % (117 ml) of forebrain atrophy, which corresponded to 78 years of accelerated aging. Cerebellar atrophy of 6.2% (7.7 cc) was also noted.

Discussion: We have demonstrated striking brain atrophy with COVID encephalitis. Brain involvement and atrophy or connectome disruptions might contribute to post COVID cognitive impairment. Serial MRI scans after COVID-19 and volumetric analysis may detect post COVID brain atrophy as a cause of cognitive dysfunction.

Main Text

A 75-year-old healthy man came back from his farm and fell unconscious onto his bed for a few minutes. He had been partially vaccinated with the ChAdOx1 (Astra-Zeneca) vaccine 2 months earlier. On evaluation, he was febrile (38.5^{o}C) akinetic, mute, and rigid. Serum CPK levels were normal. Nasopharyngeal swab for SARS-CoV2-RT-PCR was positive. Routine workups for other causes of fever were negative.

MRI brain showed a right frontal FLAIR hyperintensity with overlying leptomeningeal contrast enhancement. CSF showed 90 cells (L90 N10) with high protein (164mg/dl). A pan-encephalitic PCR panel was negative. Serum inflammatory markers and troponin were elevated. CT Thorax was normal. COVID encephalitis was diagnosed and he was started on Remdesivir, Dexamethasone, and levodopa 800mg/day. He improved slightly and was extubated on day 7. On day 26 a repeat MRI showed striking brain atrophy.

Over the next 1 month, he improved to a modified Rankin score of 4 (moderate disability, unable to walk without assistance, and needing full-time care) but remained apathetic, mute, and rigid with a requirement of up to 600 mg of Levodopa per day. A third MRI was performed on day 60.

Due to COVID-19 limitations, only partial MRI studies could be obtained in our patients. As FLAIR sequences had been performed consistently in all studies, axial FLAIR images were used for brain volume

analysis instead of T1 weighted images. Corresponding sections (at least axial 3 sequences each of the forebrain and cerebellum, at 5 mm thickness) were used for volume calculation. Using our in-built PACS software (InstaRISPACS version 5.0), manual contouring was performed and auto-calculation of the area was obtained (brain region volume minus ventricular volume). The average of 3 measurements was taken and the absolute and percentage of decrease in brain volumes were calculated between both sequences.

The total number of neurons in the average human brain, estimated by modern techniques is ≈170 billion.[1] Of these, the vast majority, 50% are non-neuronal cells (~ 85 billion), and < 19% are neurons in the human neocortex (~16 billion).[2] The normative volume of the human forebrain (excluding the ventricular spaces) is ~ 1020 cc (cubic centimeter) and that of the cerebellum is 124.8 cc (CV-0.13).[3] Due to normal aging, neurons are lost at different rates in different regions of the brain. In the neocortex, an average of ≈31 million neurons is lost per year.[4,5] [Table] In the cerebellum, the anterior lobe cortical volume reduces by 30%, and Purkinje cells are lost at a rate of 2.5% per decade (especially after the age of 60). To estimate brain elements lost per unit time in our patient, we used a modified Saver's equation [(VF - Vi) ×TB] / time].[3] Here, VF =final area of contoured brain regions (forebrain excluding the ventricles and cerebellum), Vi= initial area of the same region, and TB = the total number of the elements (neurons, synapses, etc) in the brain region.

Recalculating this equation, 1% of forebrain volume is equivalent to 10.2 cc (ml) of the forebrain, the loss of which is proportionate to ~ 6.8 years of aging (approximately 6 years and 10 months of aging). By day 60, our patients had a calculated percentage of forebrain atrophy of approximately 11.5 % (117 ml) which corresponded to 78 years of accelerated aging.[3] Cerebellar atrophy of 6.2% (7.7 cc) was also noted.

Although many neurological complications and MRI changes of COVID-19 have been described, few have looked at COVID-19 induced brain atrophy. One study noted that >70% of critically ill patients developed an increase in ventricular size (a surrogate of brain atrophy), and linked it to hypoxia or a cytokine storm.[6] Olfactory bulb atrophy and optic nerve/ tract hyperintensities (35%) are also described in COVID-19. As there are a high expression of ACE 2 and TMPRSS2 proteases receptors in the olfactory epithelium, rapid invasion of the brain occurs via this route, followed by widespread brain dissemination.

The typical large vessel, supratentorial ischemic stroke volume is approximately 54 mL (19-100 mL).[3] This type of stroke loses 22 billion neurons or over 1.9 million neurons per minute, (31,000 neurons per second). However, it is completed and reaches its final volume in around 10 hours. Hence the average large vessel occlusion with a supratentorial cerebral infarction destroys approximately~ 5.29% of the human fore-brain (~54 ml), which corresponds to accelerated aging of 36 years. In our patient with

COVID-19 encephalitis, there was progressive brain atrophy over 60 days. Although the rate of neuronal loss was less (30 million neurons per day) or 350 neurons per second (more than 350 times the neuronal loss due to normal aging), the prolonged evolution resulted in around 78 years of accelerated aging due to COVID-19 encephalitis within 60 days. (Table)

Many patients develop cognitive difficulties or ‘brain fog’ after COVID-19 or with a post-COVID-19 Syndrome (Long Haul Syndrome). Sub MRI threshold brain atrophy or functional connectivity disruption could be a factor in post-COVID-19 cognitive impairment. Early completion of the full COVID vaccination schedule may be more protective than partial vaccination against COVID-19 complications. CNS complications of COVID-19 itself can greatly diminish the Quality of life.

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Declarations

Conflict of interest- None

All necessary patient consent has been obtained

An ethics committee waiver has been obtained as it is a single case report

Figures

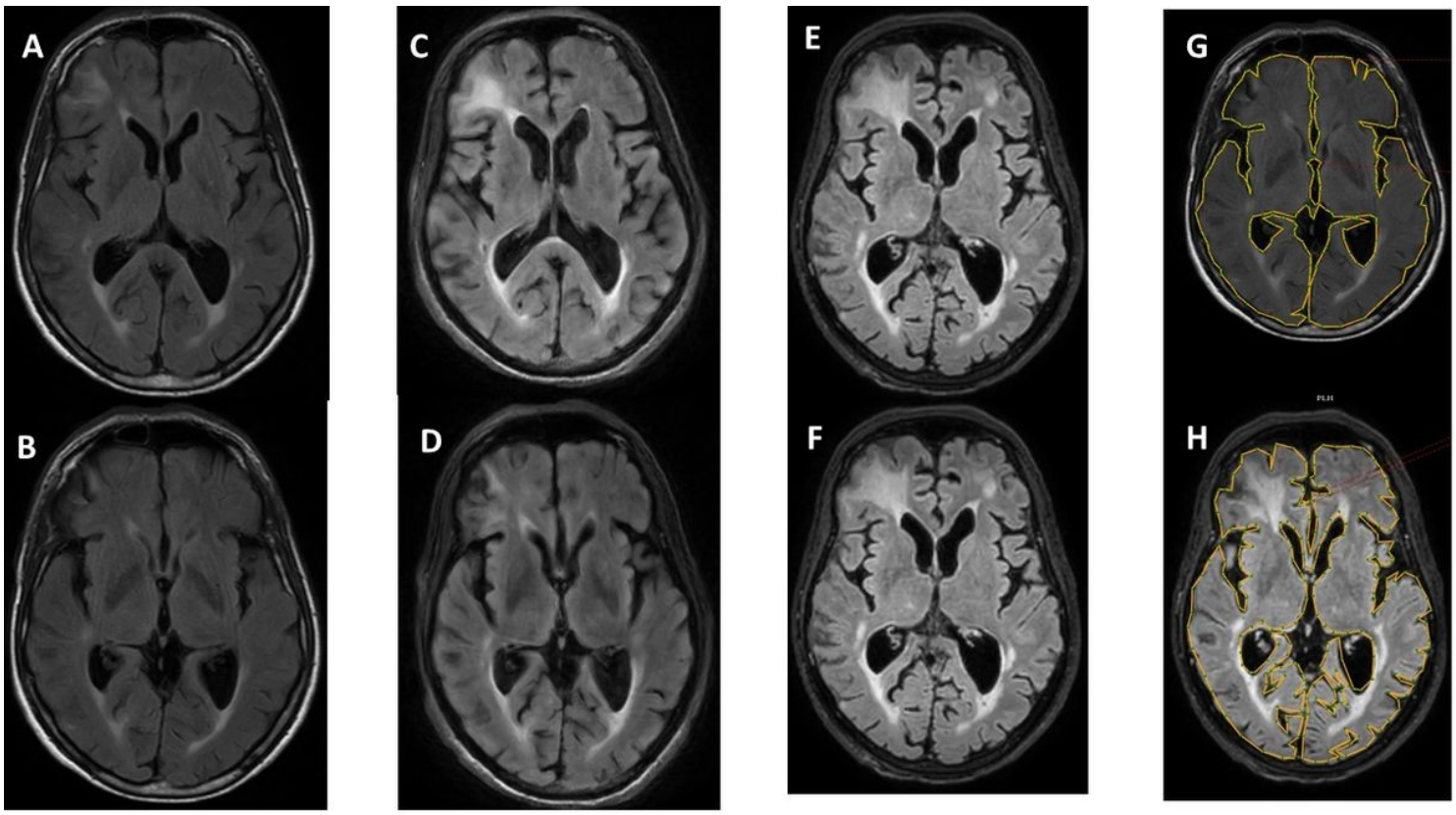

Figure 1

Panel A, C and E. FLAIR axial MRI images at day 1, day 16 and day 60. Panel B, D and E. FLAIR axial MRI images at day 1, 16 and day 60 (lower cuts). Panel G and H - Descriptive figures showing contouring analysis of the brain area and ventricular area (for exclusion).