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A CASE OF EXTENSIVE CEREBRAL TOXOPLASMOSIS IN A PATIENT OF HIV/AIDS

Medicine

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ABSTRACT

CNS is the commonest site for reactivation of toxoplasmosis when the immunity decreases in HIV infected patients who are not taking ART or adequate chemo-prophylaxis. Presentations include headache, fever, progressive focal neurological deficit, localization related seizures or features of increased intracranial tension. Diagnosis relies on IgG antibodies, whose absence makes the diagnosis less likely. CEMRI brain is superior to CECT and typically shows multiple lesions of variable size appearing hyperintense on T2/FLAIR images with associated vasogenic edema. A presumptive diagnosis is based on a clinical backdrop of HIV patient having CD4 count < 100 cells / mm3, not taking ART or adequate prophylaxis and having typical clinical features, positive Toxoplasma gondii IgG antibodies and brain imaging (preferably CEMRI). The major differential diagnosis in such a clinical setting and imaging features is primary CNS lymphoma (PCNSL). A definitive diagnosis requires demonstration of organism on brain biopsy along with clinico-radiological features. Recommended treatment is regimen containing Sufadiazine & Pyrimethmine with Leucovorin. Clinical improvement precedes radiological improvement and is the initial guide to assess response to therapy, which is generally seen in first 1-2 weeks. Alternate diagnosis needs consideration in the event of lack of clinical or radiological improvement in first 1-2 weeks.

KEYWORDS

HIV, CEMRI, Toxoplasma, antibodies

INTRODUCTION

Toxoplasma gondii is an obligate intracellular protozoan parasite that is acquired through ingestion of infectious oocysts present in cat litter, contaminated soil or undercooked meat from infected animals of feline species. Immunocompetent hosts generally remain asymptomatic and latent infection persists throughout life. The seroprevalence among HIV patients is a reflection of seropositivity in the general population. [1] Reactivation of disease commonly occurs in HIV infected individuals with CD_4 count < 100 cells/ mm^3, not taking Anti-Retroviral Therapy (ART) or adequate prophylaxis and the most common site for reactivation is CNS. [2] Other sites of disease are pulmonary, ocular and disseminated, however extracerebral sites are less common.

CASE REPORT

A 33 year old male patient, who was diagnosed to be HIV positive 03 years back (initial CD_4 counts and viral load not known), had defaulted on therapy, initially presented at a local hospital with insidious onset left hemiparesis progressing to quadriparesis over 4 weeks duration with associated intermittent fever and dull global headache. There was progressive motor aphasia, deterioration in higher mental functions and dip in the sensorium over previous 1 week before he was finally brought to this center. Initial examination revealed GCS- E3 V2 M3. He was emaciated and febrile. Right pupil was dilated and did not react to light whereas left pupil was 2mm in size and showed sluggish reaction to light. Tone was increased on left side of body with intermittent decorticate posturing on right side. Reflexes were generalized brisk with bilateral ankle clonus being present. Rest of the general and systemic examination was essentially normal.

Investigations 01 month back at the local hospital revealed CD_4 count 29 cells/mm^3, ESR- 46mm/1^{st} hr and LDH- 261 U/L. NCCT head showed an ill-defined hypodense lesion in the right ganglio-capsular region with perilesional edema involving right thalamus, temporo-parietal lobe white matter & right cerebellar peduncle, causing midline shift of 6 mm towards the left. CECT Brain revealed ill-defined non-enhancing lesion in the right thalamus measuring 3.1 x 2.4 cm in size with a midline shift, which 01 month later transformed into ill-defined hypodensity in the right ganglio-capsular region measuring 6.8 x 5.2 cm extending up to thalamus, temporoparietal lobe in the white matter and right cerebral peduncle along with few small hypodense non-enhancing areas also in left thalamus and ganglio-capsular region. A few other smaller ill-defined hypodense lesions were seen scattered in bilateral cerebral and cerebellar hemispheres. Differentials of primary CNS lymphoma, toxoplasmosis and tuberculomas had been considered. He was managed with oral steroids, osmotic diuretics, ART, Anti-Tubercular Therapy (ATT), prophylactic dose of Cotrimoxazole, oral antifungal and other supportive care. The general condition continued to deteriorate along with steady progression of neurological deficits to the present state.

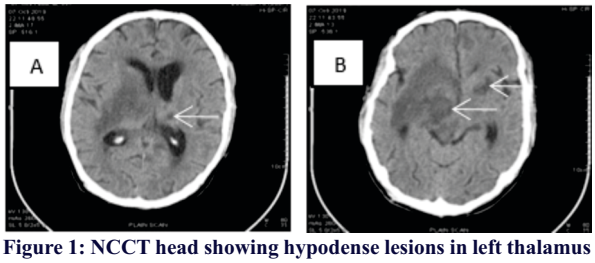

Figure 1: NCCT head showing hypodense lesions in left thalamus (A) and bilateral ganglio-capsular region (B).

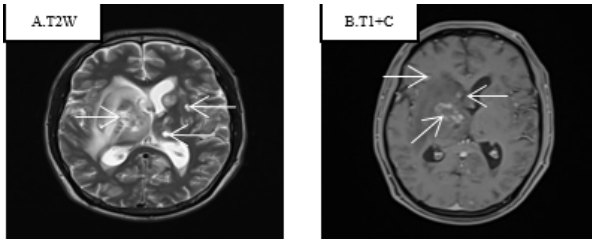

Figure 2: CEMRI T2W image (A) showing heterogeneously hyperintense lesion in bilateral cerebral hemispheres with surrounding edema (white arrows) & T1+C images (B) showing heterogeneously lesions in right basal ganglia and right frontal region (white arrows)

CEMRI Brain on admission at this center revealed multiple variable sized round to ovoid lesions appearing heterogeneously hyperintense on T2W/FLAIR and iso to hypointense on T1W images scattered randomly in the grey and white matter of bilateral cerebral & cerebellar hemispheres and brainstem and had perilesional edema around them. The largest of these lesions was seen in the right ganglio-capsular region diffusely involving right thalamus and the right half of mid brain showed heterogenous post contrast enhancement with perilesional edema which caused mass effect and left sided midline shift of approximately 10 mm, overlying sulcal effacement and subfalcine herniation towards left side. Few smaller lesions in the right frontal lobe also showed faint nodular enhancement. However, majority of other smaller lesions did not show post contrast enhancement.

Differential diagnoses of etiologies causing cerebral lesions with mass

lesions in HIV patients were considered, namely Cerebral Toxoplasmosis, Primary CNS Lymphoma, Tuberculoma and Cryptococcoma. Investigations showed markedly increased IgG Toxoplasma titres (>400 IU/ml; normal <7.2 IU/ml) and normal IgM Toxoplasma (4.4 IU/ml). Serum CrAg was negative. A guarded lumbar puncture was performed which was acellular, CSF CrAg Negative, CSF ADA – Negative, CSF Biochemistry was normal and no organism was isolated. Serum β-D Glucan and Mantoux were negative. ESR -40 mm/1st hr. C - reactive protein was positive. He had pancytopenia and all biochemical parameters were within acceptable limits.

Diagnosed as Extensive Cerebral Toxoplasmosis with mass effect and midline shift in in background of HIV/AIDS with extreme immune deficiency he was managed with tapering dose of dexamethasone, therapeutic dose of cotrimoxazole, continued on ART drugs with optimum modified CNS Penetration Effectiveness Rank Score, prophylaxis for MAC, anti-epileptics and other supportive measures. Later, due to progressively deteriorating sensorium and respiratory distress, he also required mechanical ventilation.

Over the next 4 weeks there was a steady improvement in the general condition. GCS improved to E4 VT M4. He intermittently localized pain. Left pupil started reacting to light; tone improved in limbs. Intermittent spontaneous movement of limbs on right side was seen. Fever resolved. However, he continued to require ventilator support and later developed Ventilator Associated Pneumonia after having been 5 weeks on mechanical ventilation. Tracheal aspirate culture revealed MDR *Pseudomonas aeruginosa*, which was also cultured from blood. Despite best of care, because of extreme immune deficiency, his condition continued to deteriorate. He developed MODS and succumbed to his illness.

DISCUSSION

CNS is the commonest site of toxoplasmosis reactivation in HIV infected patients; probability of which is about 30% when CD_4 count is < 100 cells/ mm^3. [3] The reactivation is commonly seen in patients not taking ART or adequate prophylaxis. [2] Patients generally presents with headache, fever, progressive focal neurological deficit, localization related seizures or features of increased intracranial tension. Although no routine laboratory investigations are specific for toxoplasmosis, toxoplasma antibodies suggest past exposure. IgG antibodies have clinical significance, whose absence makes the diagnosis less likely. [5] IgM antibodies are generally absent and value of quantitative assessment of IgG antibodies is questionable. Also, LDH is significantly increased and CSF may show mild pleocytosis and increased protein in cases with disseminated toxoplasmosis.

Cerebral toxoplasmosis is the most common opportunistic infection and most important cause of mass lesions in patients with HIV/AIDS. A presumptive diagnosis is based on a clinical backdrop of HIV patient having CD_4 count < 100 cells / mm^3, not taking ART or adequate prophylaxis and having typical clinical features, positive *Toxoplasma gondii* IgG antibodies and brain imaging (preferably CEMRI) with typical radiological appearance. [6] The major differential diagnosis to be considered in such clinical setting and imaging features is primary CNS lymphoma (PCNSL). The features which favour CNS toxoplasmosis over PCNSL are multifocal lesions scattered in the basal ganglia, thalami, corticomedullary junction and cerebellum, indicating a hematogenously disseminated process unlike PCNSL. Only 15-20% of toxoplasmosis lesions present as solitary masses. The lesions in toxoplasmosis are usually smaller and average between 2-3 cm in diameter. Toxoplasmosis usually does not abut an ependymal surface vis-à-vis PCNSL. Sub-ependymal spread is characteristic feature of lymphoma which is usually not seen in toxoplasmosis.

Thallium SPECT scanning has been found to be excellent means to differentiate between PCNSL and toxoplasmosis. The lesions in toxoplasmosis do not show activity with thallium SPECT scanning; however PCNSL lesions are thallium avid. On FDG-PET the toxoplasmosis lesions are not avid, whereas PCNSL lesions show avidity. On NCCT, most common finding is multiple ill-defined lesions in the basal ganglia or thalamus with moderate to marked peripheral edema. The enhancement on CECT is closely correlated with the CD_4 count of the patients. With CD_4 count less than 50cells/mm^3, the enhancement is either absent or very faint as was seen in this case. The enhancement gets more pronounced as the CD_4 count increases with treatment indicating response to the treatment. On MRI, in toxoplasmosis the common finding is alternating concentric zones of hyperintensity and hypointensity with marked perilesional edema on T2W/FLAIR images. The perilesional hyperintensity on T2WI/FLAIR also represents edema and demyelination. Post contrast T1W images show one or more nodular and ring enhancing masses if the CD_4 count is > 100cells/mm^3. "Eccentric target sign" has also been described on T1+C which represents ring shaped zone of peripheral edema with eccentric mural nodule. On MRS, there is decreased choline level in toxoplasmosis. MR perfusion imaging shows decreased regional cerebral blood volume (rCBV).

If all of these features are present, the probability of presumptive diagnosis being true is 90%. [4] A definitive diagnosis requires demonstration of organism on brain biopsy along with clinico-radiological features. [8] Treatment is to be started presumptively without delay. Therapeutic options include regimen containing Sufadiazine & Pyrimethmine with Leucovorin. [9] Effective alternatives include cotrimoxazole and combination of Clindamycin, Pyrimethamine & Leucovorin, Atorvaquone based regimen either alone or in combination with Pyrimethamine & Leucovorin or with Sulfadiazine.

Clinical improvement is the initial guide to assess the response to therapy, generally seen within first 1-2 weeks and precedes radiological improvement. Repeat neuroimaging in generally required 2-3 weeks following the clinical improvement or within the first week when the patient has not improved or has rather deteriorated. Alternate diagnosis needs consideration in the event of lack of clinical or radiological improvement in first 1-2 weeks. 75-80% of patients with the right diagnosis and treatment show clinical and radiological improvement. Initial therapy is generally given for 6 weeks after which maintenance therapy is started to prevent re-infection. Secondary prophylaxis is generally stopped in the event of CD_4 count >200 cells/ mm^3 and the patient on ART, both for at least 6 months.

CONCLUSION

Cerebral Toxoplasmosis is one of the most common CNS infections in HIV patients causing mass effect. Approach to presumptive diagnosis requires typical clinical features, serological evidence and radiological features. CEMRI brain is a better modality of neuroimaging to diagnose cerebral toxoplasmosis than CECT. [7] Generally multiple ring enhancing CNS lesions are seen with predilection for ganglio-capsular region and corticomedullary junction. However, in case of severe immune deficiency (e.g. very low CD_4 count < 50 cells/mm^3) typical ring enhancement may be absent causing diagnostic dilemma. MR perfusion and MRS can aid in diagnosis to certain extent. Thallium SPECT and FDG-PET imaging can be used with certainty as problem solving tool in equivocal cases. Treatment should be started based on presumptive diagnosis. Clinical improvement precedes radiological improvement and is an earlier reliable sign to guide and monitor response to therapy, and is seen within 1-2 weeks of initiation of therapy. Nodular and ring enhancement in the follow-up MRI scan in the pre-existing non enhancing lesions following treatment can be used as a reliable marker as response to therapy.

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