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Hot cross bun sign in JC-Virus Granule cell neuronopathy in HIV infected patient – a case report

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Abstract

Background John Cunningham virus related granule cell neuronopathy (JCV-GCN) is a rare manifestation of the reactivation of infection of the cerebellar granule cells by the JCV, mostly in immunocompromised individuals. The "hot cross bun" (HCB) sign is a cruciform hyperintensity seen in the midpons on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences on magnetic resonance imaging (MRI) of the brain. An index sub-Saharan Africa report of a case of JCV-GCN with HCB sign follows.

Case Presentation A 27-year-old HIV positive female with JCV-GCN was re-evaluated for chronic ataxia complicated by subacute progressive horizontal diplopia. Cerebrospinal fluid (CSF) had trace *Mycobacterium tuberculosis* (MTB) detected by GeneXpert Mycobacterium Tuberculosis/Rifampicin resistance (MTB/RIF) assay test. Brain MRI revealed diffuse severe cerebellar atrophy with a hot cross bun sign and patchy enhancement contiguous to the cerebellar dentate nuclei bilaterally. She continued Highly Active Antiretroviral Therapy (HAART) pending CSF HIV viral load counts and started standard brain TB local treatment regimen protocols with progressive improvement in limb ataxia.

Conclusions In conclusion, finding of the HCB sign may be indicative of and aid diagnosis of JCV-GCN in the right clinical context. This could be an important neuroimaging marker in this context, that may radiologically be more evident in later stages of the condition.

Keywords Granule cell neuronopathy, Hot cross bun sign, John Cunningham virus (JCV)

Background

Granule cell neuronopathy (GCN) is a rare manifestation of the reactivation of infection of the cerebellar granule cells by the John Cunningham virus (JCV), that is mostly observed in immunocompromised individuals [1–3]. The "hot cross bun" (HCB) sign, a cruciform hyperintensity in the midpons on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences on magnetic resonance imaging (MRI) of the brain, has been described in the cerebellar form of multiple system atrophy [4] but not exclusively [5]. It has also has been reported in the course of JCV infection of the brainstem and cerebellum with considerable volume loss of these structures (olivopontocerebellar atrophy) [4]. An index sub-Saharan Africa description of a case of JCV related GCN (JCV-GCN) with HCB sign follows in this case report.

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Case presentation

A 27-year-old female was re-evaluated a year after her initial interaction with S.S, at which time she had been referred from a peripheral unit with a diagnosis of suspected ischemic stroke presenting with 3 months of insidious gait ataxia syndrome. At that interaction, a diagnosis of HIV infection was confirmed alongside John Cunningham virus related granule cell neuronopathy (JCV-GCN) with JCV PCR positive mildly lymphocytic cerebrospinal fluid (CSF), in the absence of another detectable cause for her clinic-radiologic presentation. She had along the way developed a persistent cerebellar head tremor that was initially refractory to optimized doses of oral baclofen, gabapentin and clonazepam treatments but showed improved response to a topiramate and clonazepam combination in addition to mirtazapine and her tenofovir, lamivudine and dolutegravir - Highly Active Antiretroviral Therapy (HAART) regimen. She was still taking this medication at the time of her re-evaluation.

Her re-evaluation was prompted by her attendants reporting her showing less tolerance for physiotherapy, compounded by worsening double vision for about two weeks prior to the clinical visit. She was virally suppressed in serum on her HAART regimen. The double vision was reported worse with left ward horizontal gaze and distant vision. She had no headaches, fever, altered level of consciousness, nausea or vomiting and no limb weakness, extrapyramidal symptoms or sphincter dysfunction.

Clinically, she was in fair general condition, not in respiratory distress, had normal vitals and normal cardiorespiratory and abdominal examination. Neurologically, she was noted to have normal sensorium and cognition with no meningism but she had staccato speech. She had mild left eye abduction weakness with no other notable cranial nerve deficits. She had gaze evoked nystagmus that was more evident in horizontal gaze. She had normal limb tone, bulk and power in all limbs. She had an overt head tremor worse when erect and otherwise had no bradykinesia or other extrapyramidal signs. She had symmetrical globally brisk deep tendon reflexes with a normal sensory exam. Her finger-nose testing, heel shin test and tandem walk were bilaterally impaired and she had ataxic gait.

At her initial evaluation when she was referred with an insidious gait ataxia syndrome, she had been reported to have a right middle cerebellar peduncle FLAIR hyperintense lesion (images not provided). On re-evaluation, her Brain MRI revealed severe diffuse cerebellar atrophy with abnormal linear T2 hyperintense signal in the central pons giving rise to a hot cross bun sign (Fig. 1A, B). There was patchy enhancement in regions contiguous to the dentate nuclei bilaterally (Fig. 1 C1, C2). CSF analysis showed 1 neutrophil per microliter, 13 lymphocytes, 2 erythrocytes, protein 55.8 mg/dL and normoglycorrhachia. CSF had trace *Mycobacterium tuberculosis* (MTB) with indeterminate Rifampicin (RIF) resistance detected on GeneXpert MTB/RIF assay test and was negative for cryptococcal antigen. She had a negative CSF viral panel including HSV 1/2 and VZV PCRs. Her JCV remains positive in CSF (no quantitative titre provided). Her CD4 was 121. Full blood counts, C-reactive protein (CRP) levels, liver and renal function tests were unremarkable. Chest X-ray was normal.

She was continued on HAART pending CSF HIV viral load counts and started on standard central nervous system (CNS) TB treatment regimen to be continued through intensive and maintenance phases for a planned total duration of 12 months with addition of oral steroids tapered over the first 6 weeks of treatment initiation. Her oral medication on which she was stable prior

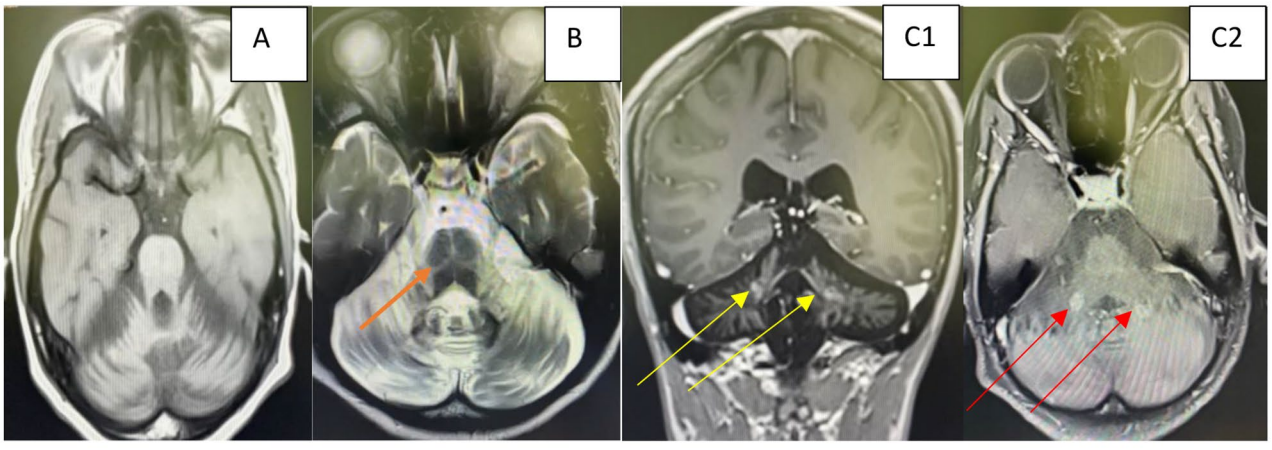

Fig. 1 (**A**) Axial T1-weighted brain MRI demonstrating diffuse cerebellar atrophy. (**B**) Axial T2-weighted brain MRI demonstrating the "hot cross bun" sign (orange arrow) with diffuse cerebellar atrophy. (**C1**), (**C2**) Coronal and axial T1-gadolinium enhanced brain MRIs demonstrating contrast enhancement contiguous to cerebellar dentate nuclei bilaterally (yellow and red arrows)

to re-evaluation was maintained. She continued to show progressive improvement in visual complaints and limb ataxia on the treatments above and maintains normal cognitive function. She continues her scheduled outpatient follow ups.

Discussion

The case described demonstrates the presence of the HCB sign in JCV-GCN. Although JCV infection of the cerebellum and brainstem as in this case has been documented from as far back as four decades ago and with subsequent radiological descriptions of pontocerebellar findings in JCV infection of the brain [4], this index sub-Saharan case report of the hot cross burn sign in JCV-GCN resonates with the scarcity of this finding in global literature. Only two previous case reports, both from Asian literature had a similar finding [6].

The human JCV causes lytic infection of glial cells in the CNS and can be reactivated in immunocompromised patients with impaired T-lymphocyte immune responses [4] like the patient in this case. JCV-GCN is associated with mutations in the C terminus of the JCV VP1 gene [2] and may present variably with nonspecific chronic cerebellar symptoms as in the described case. Unlike in this case, serum and CSF may be normal and it is not unusual for patients to have normal or nonspecific brain MRI findings [3]. Brain biopsy is the gold standard for diagnosis of JCV-GCN [3].

The HCB sign, which is rarely reported in patients with JCV-GCN, is reported more commonly in degenerative diseases like the cerebellar subtype of multiple system atrophy [6] but like in our case, it is evident that it can also be seen in other conditions. It has also been documented in spinocerebellar ataxia (SCA) 1, 2, 3, 7, and 8 and paraneoplastic cerebellar degeneration secondary to testicular tumor amongst others [5]. It is reported to follow selective loss of myelinated transverse pontocerebellar fibre tracts and neurons in the pontine raphe and sparing corticospinal fibres that traverse the pons as well its tegmentum [6]. In patients like the above with cerebellar JCV infection, it is further postulated to follow gliotic changes in affected pontocerebellar and intra-cerebellar fibres [6]. Its sensitivity and specificity, frequency, prognostic significance or implications on treatment in these cases are unknown.

Notwithstanding, other cerebellar findings like the shrimp sign have been detailed in earlier descriptions of JCV infection of the cerebellum [4]. The shrimp sign is "a well-defined T2- or FLAIR- hyperintense and T1-hypointense lesion in the cerebellar white matter that abuts but spares the dentate nucleus and has the shape of a shrimp" [4]. These previous descriptions are of interest because it is possible that the patient in this report also earlier had a shrimp sign that prior to referral for her initial evaluation, had been misdiagnosed as ischemic infarct in the right middle cerebellar peduncle and that at the time of her later re-evaluation, was radiologically obscured by marked cerebellar atrophy. This radiological chronology of findings would raise the question: Is the shrimp sign an earlier radiological marker of JCV-GCN in comparison to the hot cross bun sign? The answer to this question from further focused neuroscientific research in this area may guide prediction models of the pathological evolution of JCV-GCN that could inform therapeutic approaches to this condition.

Conclusion

In conclusion, finding of the HCB sign may be indicative of and aid diagnosis of JCV-GCN in the right clinical context. This could be an important neuroimaging marker in this context, that may radiologically be more evident in later stages of the condition.

Abbreviations

GCN	Giant Cell Neuronopathy
JCV	John Cunningham Virus
HCB	Hot Cross Bun
FLAIR	Fluid Attenuated Inversion Recovery
MRI	Magnetic Resonance Imaging
HIV	Human Immunodeficiency Virus
CSF	Cerebrospinal Fluid
MTB	Mycobacterium tuberculosis
CNS	Central Nervous System
TB	Tuberculosis
HAART	Highly Active Antiretroviral Therapy
PCR	Polymerase Chain Reaction
HSV	Herpes Simplex Virus
VZV	Varicella Zoster Virus
IgG	Immunoglobulin G
CD4	Cluster of Differentiation 4
CRP	C–reactive protein
FXTAS	Fragile X Tremor Ataxia Syndrome
VP1	Viral Protein 1
SCA	Spinocerebellar Ataxia

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Author contributions

S.S. wrote and reviewed the main manuscript text and prepared Fig. A – C2.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent for publication was obtained in writing from the anonymized case in this case report via a surrogate.

Competing interests
The authors declare no competing interests.

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