

## Case Report

# Concomitant acute bilateral hearing and vision loss as presenting symptoms of human immunodeficiency virus encephalopathy

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**Abstract:** Objectives: Human immunodeficiency virus (HIV) encephalopathy is a progressive primary encephalopathy caused by HIV infection and is manifested by various cognitive, motor, and behavioral abnormalities. However, concomitant deafness and blindness as presenting symptoms of HIV encephalopathy have not been mentioned in the literature. Methods: We present the case of an 18-year-old male patient with concomitant acute bilateral hearing and vision loss as presenting symptoms of HIV encephalopathy. Results: The patient developed progressive drowsiness, generalized weakness, mental status deterioration, and intermittent fever after admission, despite the administration of highly active antiretroviral therapy. He was in a comatose state (E1M1Vt) at the most recent follow-up (6 months after admission). Conclusion: This is the first case report of concomitant acute bilateral hearing and vision loss as presenting symptoms of HIV encephalopathy. Therefore, clinicians should be aware that concomitant acute bilateral hearing and vision loss in HIV-positive patients imply the subsequent development of HIV encephalopathy, although brain magnetic resonance imaging and routine cerebrospinal fluid examination may be normal in these immunocompromised patients.

**Keywords:** Deafness, blindness, HIV encephalopathy

### Introduction

Human immunodeficiency virus (HIV) can directly affect the central nervous system (CNS), causes distinct neurological symptoms, and indirectly result in opportunistic infections, which include herpes virus simplex (HSV)-1, HSV-2, varicella zoster virus (VZV), and cytomegalovirus (CMV) encephalitis caused by immunodeficiency [1]. In addition to opportunistic CNS infections and cerebral lymphoma, approximately 20% of HIV-positive patients have been reported to develop HIV encephalopathy [2]. HIV encephalopathy is a progressive primary encephalopathy caused by HIV infection and is manifested by various cognitive, motor, and behavioral abnormalities. HIV encephalopathy is a potentially lethal complication [1]. Herein, we present a case of concomitant acute bilateral hearing and vision loss as presenting symptoms of HIV encephalopathy. Based on our research, reports of concomitant deafness

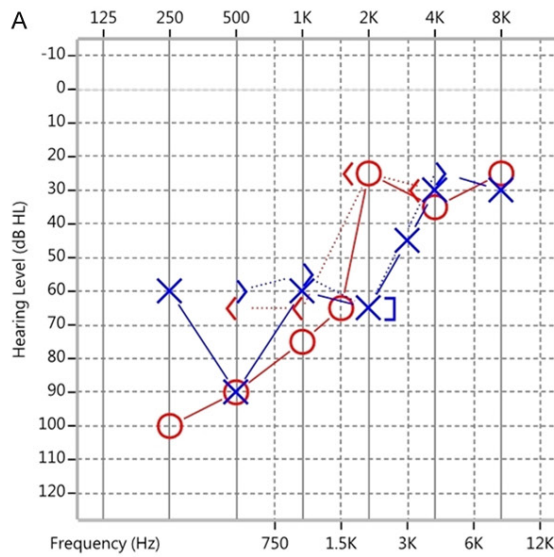
and blindness as presenting symptoms of HIV encephalopathy are rare. Similar presentations in patients with HIV encephalopathy, as in our case, have not been mentioned in the literature.

### Case report

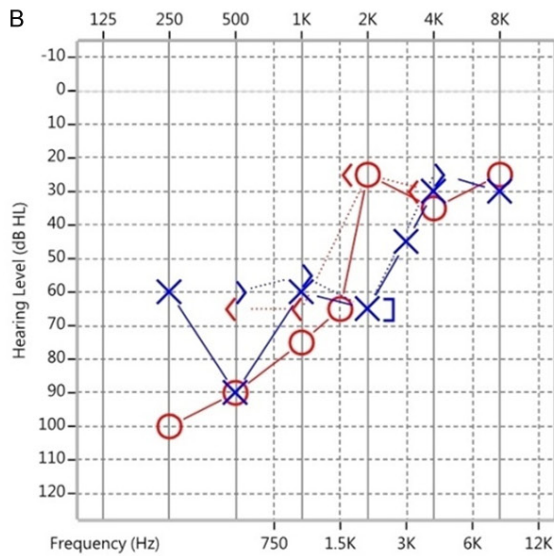
An 18-year-old male patient presented to our hospital with a 1-week history of acute bilateral hearing and vision loss in January 2017. The onset of hearing and vision loss was sudden, symmetrical, and painless. No associated aural discharge, ocular discharge, diplopia, or photophobia was observed. His family claimed that he had intermittent low-grade fever, lethargy, and reduced appetite in the recent 1 week before admission. Nevertheless, recently, he did not have headache, vertigo, or body weight loss.

He denied having any previous disease. His family history was unremarkable. His social

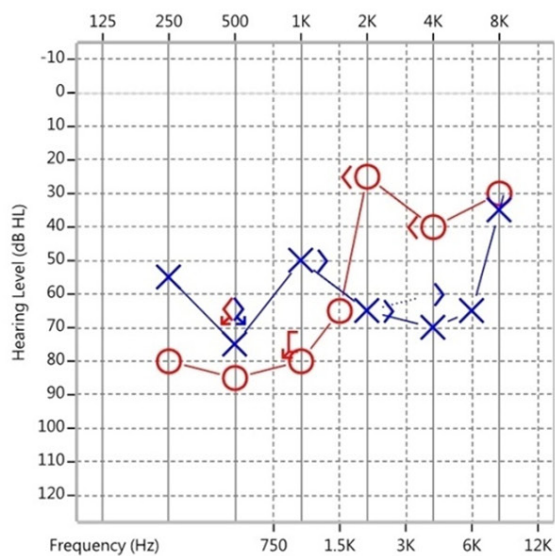
# Concomitant bilateral deafness and blindness of HIV encephalopathy



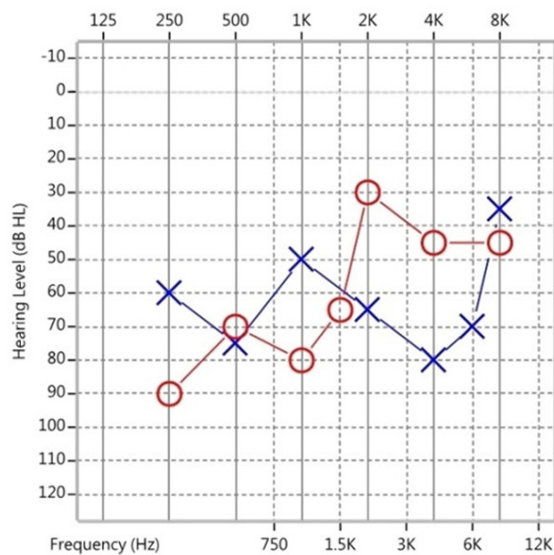
**Figure 1.** A. Pure-tone audiometry on the first hospital day revealed mild to profound (right ear) and mild to severe (left ear) hearing loss. B. Follow-up pure-tone audiometries on the 8<sup>th</sup>, 15<sup>th</sup>, and 22<sup>nd</sup> days did not reveal significant hearing improvement. (○: right ear air conduction without masking; ×: left ear air conduction without masking; <: right ear bone conduction without masking; >: left ear bone conduction without masking; []: right ear bone conduction with masking; ]: left ear bone conduction with masking).



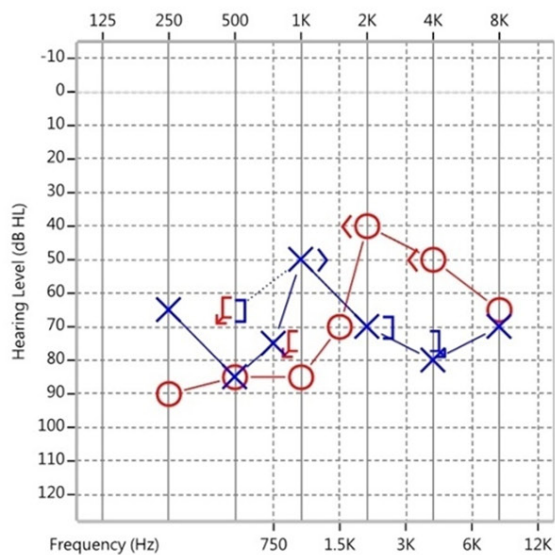
**1<sup>st</sup> hospital day**



**8<sup>th</sup> hospital day**



**15<sup>th</sup> hospital day**



**22<sup>nd</sup> hospital day**

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history was significant for unprotected sex. However, he did not know his HIV status.

On admission, his vital signs were as follows: temperature, 37.5°C; heart rate, 93 beats/min; respiratory rate, 17 beats/min; and blood pressure, 134/85 mmHg. His level of consciousness was normal. He had a Glasgow Coma Score of 15 (E4M6V5).

Physical examination revealed unremarkable findings for his heart, lungs, and abdomen. On neurological examination, his neck was not stiff, and Kerning's sign was negative. Except for the bilateral second and eighth cranial nerves, other cranial nerves were normal. His muscle power was grade 4. Deep tendon reflexes and sensory evaluation were normal. The Babinski reflex was absent, as is typical in adults.

Initial laboratory studies revealed the following findings: white blood cell count, 3300/mm<sup>3</sup>; platelet count, 110000/mm<sup>3</sup>; and serum sodium, 132 meq/L. In addition, all other hematological and biochemical parameters were within normal limits. Moreover, C-reactive protein and the erythrocyte sedimentation rate were within normal limits, and blood cultures were negative.

Serum tests for rheumatoid factor, antinuclear factor, antiextractable nuclear antigen, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin IgG and IgM, and lupus anticoagulant were negative.

On otologic examination, otoscopy was unremarkable. Pure-tone audiometry on the first hospital day revealed mild to profound hearing loss in the right ear and mild to severe hearing loss in the left ear (**Figure 1A**). An acoustic reflex test revealed that the ipsilateral and contralateral acoustic reflexes were absent in both ears. Auditory brainstem response examination revealed no wave was present at 90 dB nHL in both ears (**Figure 2A**). However, transient evoked otoacoustic emissions examination revealed otoacoustic emissions in both ears (**Figure 2B**). The results of these audiologic examinations indicated that the patient's hearing loss was caused by retrocochlear lesions.

On ophthalmic examination, he was profoundly blind in both eyes. His pupil size/light reflex was 2.5/+, 2.5/+ (OD, OS). His extraocular movements were full and free. Fundoscopy revealed

that the optic discs and retinal vessels were normal, and no retinal hemorrhage or exudates were observed. Visual electrophysiology examination revealed a poor response in both eyes with slow pupil reaction. Visual field examination revealed an advanced visual field defect in both eyes (**Figure 3**).

Brain magnetic resonance imaging (MRI) with gadolinium contrast revealed no significant abnormality in the brain as well as in the bilateral orbits, optic nerves, or inner ear (**Figure 4A**). Electroencephalography revealed diffuse cortical dysfunction.

A lumbar puncture was performed and showed normal opening pressure. Cerebrospinal fluid (CSF) was clear in appearance. Routine CSF examination revealed acellular CSF. Moreover, glucose, protein, and lactic dehydrogenase levels in the CSF were within normal limits. Gram staining, acid-fast bacillus staining, potassium hydroxide (KOH) mount, and Indian ink staining of the CSF were negative. CSF cultures - including mycobacterial cultures - were negative. CSF Venereal Disease Research Laboratory (VDRL) test, cryptococcal antigen, Japanese encephalitis virus (JEV) IgM and IgG, HSV polymerase chain reaction (PCR), VZV PCR, CMV PCR, enterovirus PCR, and Epstein-Barr virus PCR were negative.

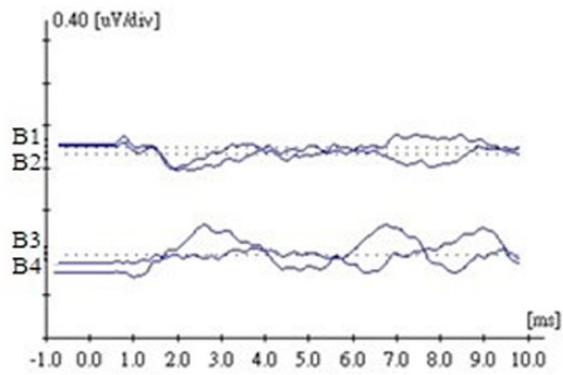
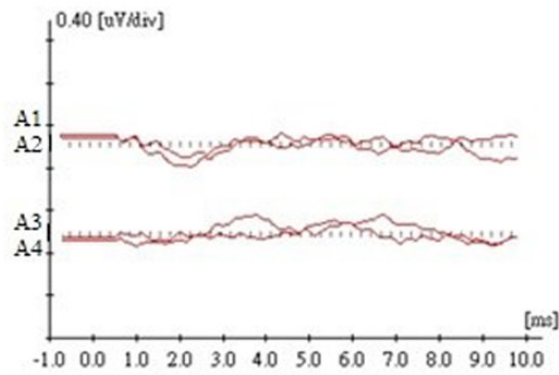
However, according to an enzyme-linked immunosorbant assay and Western blot analysis, his serum tests for HIV antibodies were positive. Moreover, his CD4+ T lymphocyte count was 6 cells/mm<sup>3</sup>. His serum tests for HSV-1, HSV-2, VZV, CMV, JEV, syphilis, mumps, measles, rubella, toxoplasma, and chlamydia (*Chlamydia pneumoniae*, *C. trachomatis*, and *C. psittaci*) were negative. Nasopharyngeal swab tests for influenza virus A and B were negative.

Clinically, the patient developed progressive drowsiness, generalized weakness, deterioration of mental status, and intermittent fever after admission. Therefore, HIV encephalopathy was diagnosed on the basis of clinical features and previous laboratory tests.

Specific therapy for HIV infection, namely highly active antiretroviral therapy (HAART) [abacavir (600 mg/d), dolutegravir (50 mg/d), and lamivudine (300 mg/d)], was administered after HIV encephalopathy was diagnosed. Because of

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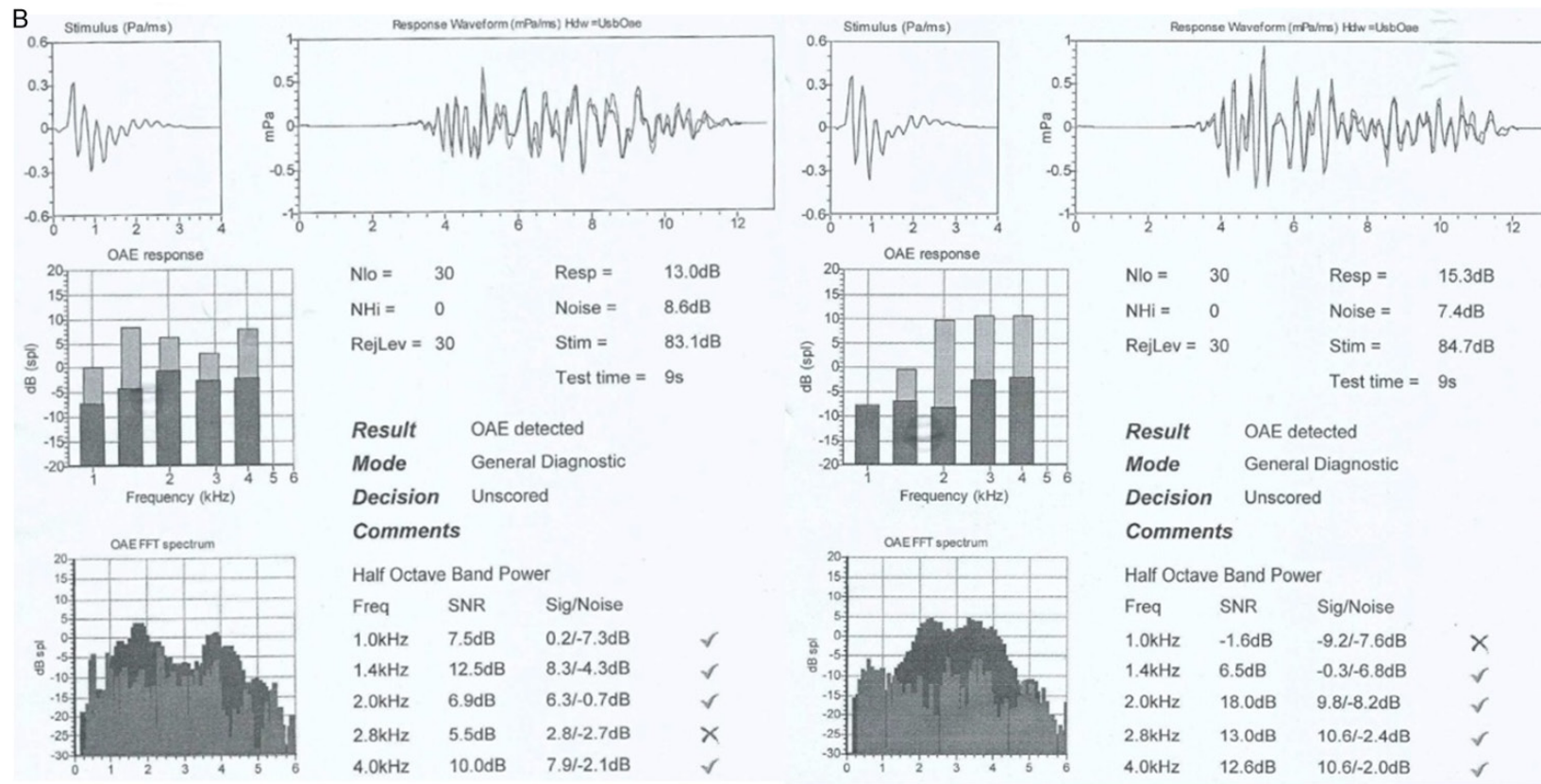
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| <i>Collection Parameters</i> |                   |            |                  |             |                  | <i>Latencies (ms)</i> |           |            |           |          | <i>Interlatencies (ms)</i> |              |            |
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| A1                           | Insert Earphones  | Right      | 90dB nHL         | Click       | N/A              |                       |           |            |           |          |                            |              |            |
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| B4                           | Insert Earphones  | Left       | 90dB nHL         | Click       | N/A              |                       |           |            |           |          |                            |              |            |



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**Figure 2.** A. Auditory brainstem response examination (ABR) revealed no wave was present at 90 dB nHL in both ears. (vertical axis: amplitude (microvolt); horizontal axis: latency (millisecond); red response: right ear; blue response: left ear). B. Transient evoked otoacoustic emissions examination (TEOAE) revealed otoacoustic emissions in both ears (✓: pass; ✗: fail). The results of ABR and TEOAE indicated that his hearing loss was caused by retrocochlear lesions.

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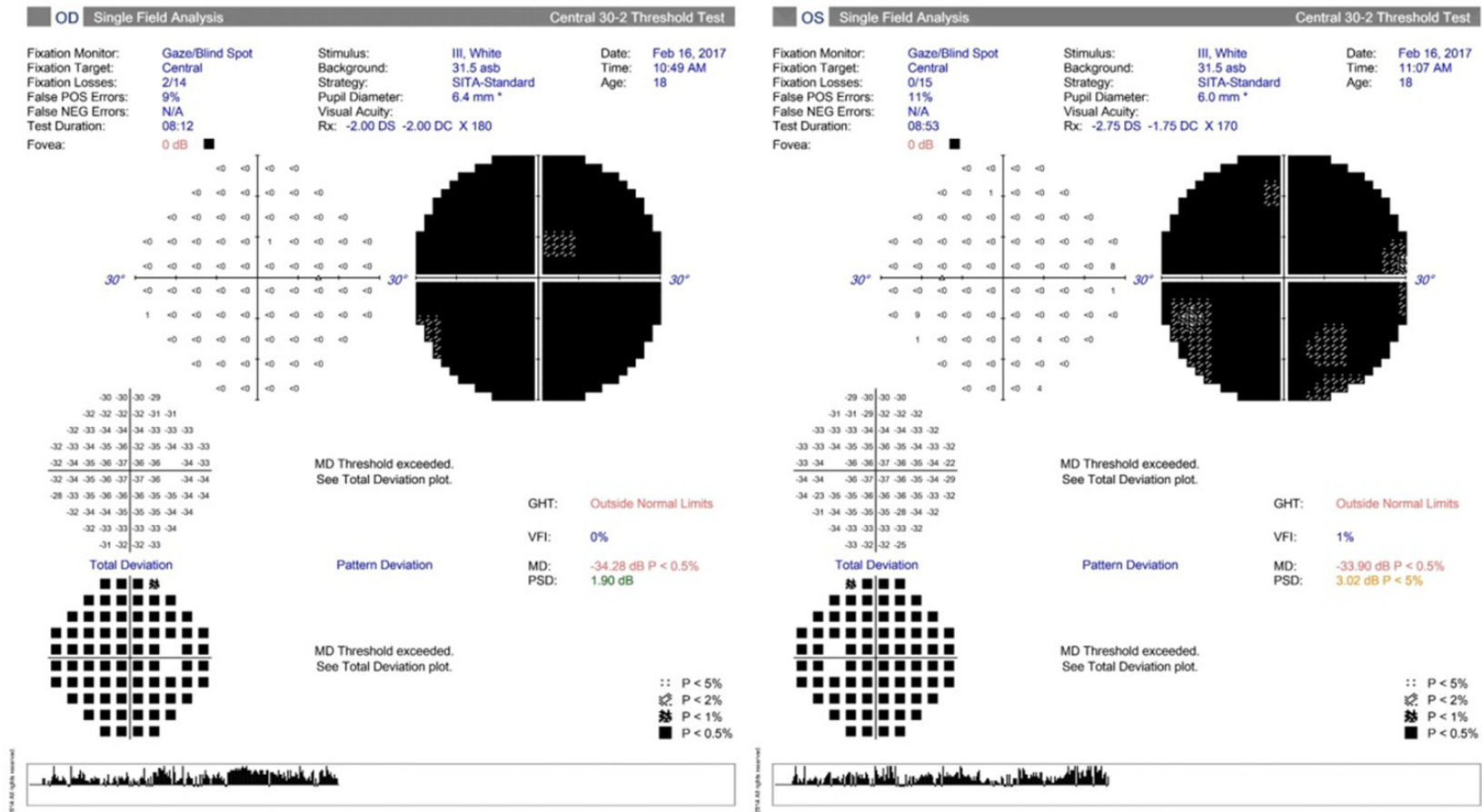
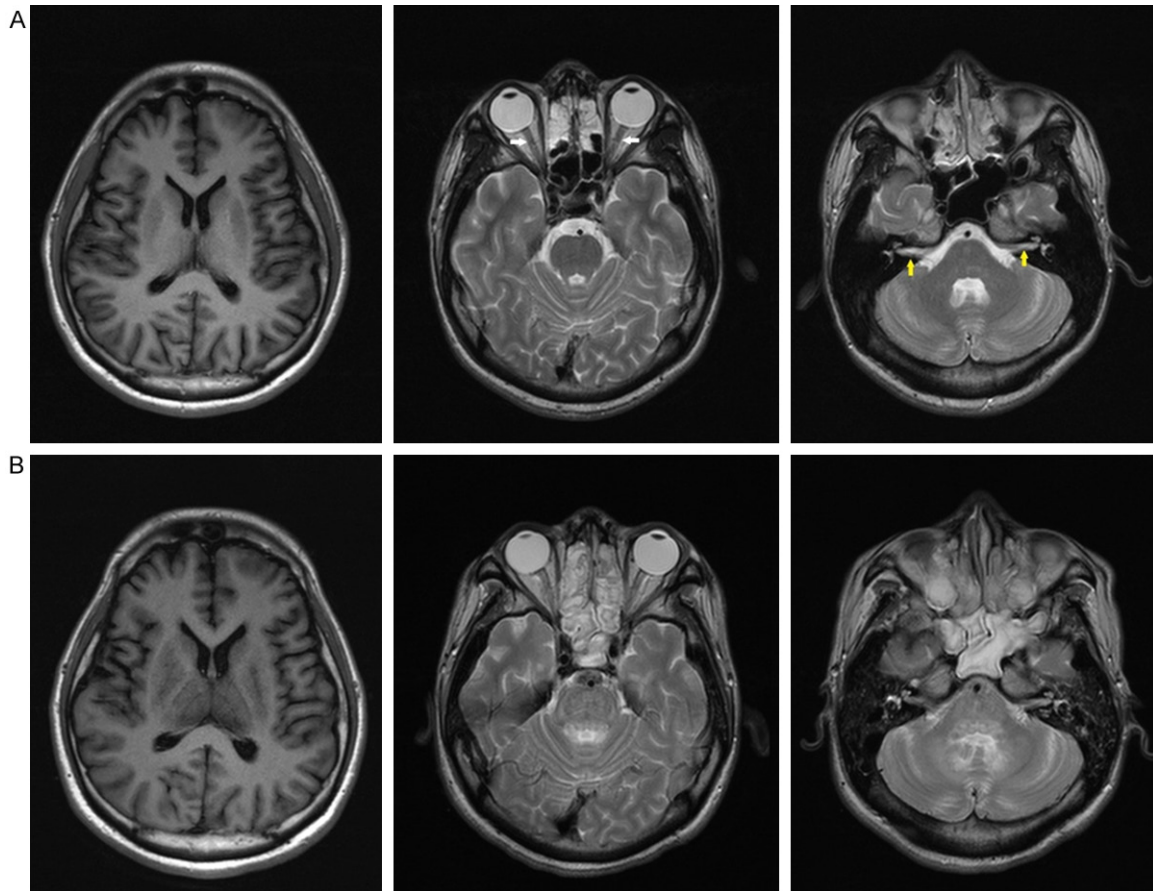


Figure 3. Visual field examination revealed an advanced visual field defect in both eyes.



**Figure 4.** A. MRI of the brain on the first hospital day revealed no significant abnormality in the brain as well as in the bilateral orbits, optic nerves (white arrows), or auditory nerves (yellow arrows). B. Repeat brain MRI was performed on the 60<sup>th</sup> hospital day and revealed no significant abnormality in brain, orbits, optic nerves, or auditory nerves.

the failure of 2-month antiretroviral therapy (CD4+ T lymphocyte count was 38.5 cells/mm<sup>3</sup>, serum HIV viral load was 234 copies/mL, and exacerbation of symptoms) and hepatic and renal failure, the antiretroviral therapy was shifted to tenofovir (300 mg/d), emtricitabine (200 mg/d), and efavirenz (600 mg/d).

The patient underwent repeat lumbar punctures on the 20<sup>th</sup> and 30<sup>th</sup> hospital days. The results of CSF examinations were similar to those of the first examination. Repeat brain MRI was performed on the 60<sup>th</sup> hospital day and revealed no significant abnormality in the brain, orbits, optic nerves, or inner ear (**Figure 4B**). Moreover, his hearing (**Figure 1B**) and vision did not significantly improve at follow-up on the 22<sup>nd</sup> hospital day.

The patient was in a comatose state (E1M1Vt) since the 70<sup>th</sup> hospital day. And he was still in a comatose state at the most recent follow-up (6 months after admission).

## Discussion

### *Causes of deafness in HIV-positive patients*

Deafness in HIV-positive patients might be caused by CMV infection, syphilis, cryptococcal meningitis (CM), and antiretroviral therapy [3]. In the present case, we excluded CMV infection and syphilis because of negative serology. In addition, CM was ruled out because of negative CSF examination results. Furthermore, the patient developed acute hearing loss before the administration of HAART. Therefore, antiretroviral drug reactions were not the cause of deafness.

### *Causes of blindness in HIV-positive patients*

Blindness in HIV-positive patients may be attributed to infectious and noninfectious causes including CMV retinitis, acute retinal necrosis, HIV-related ischemic microvasculopathy, ocular syphilis, tuberculosis, CM, and ocular toxic drug

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reactions [4, 5]. CM may also be considered one of the causes of acute vision loss in pregnant or postpartum women with a positive HIV status [4]. In the present case, funduscopy revealed no pathological abnormality. Thus, retinitis, acute retinal necrosis, and HIV-related ischemic microvasculopathy were ruled out. We excluded syphilis because of negative serology and the absence of symptoms. Furthermore, we excluded tuberculosis and CM because of negative CSF examination results. Our patient developed acute vision loss before the administration of any ocular toxic drug. Therefore, ocular toxic drug reaction was also ruled out.

### *Causes of concomitant deafness and blindness in HIV-positive patients*

Reports of concomitant deafness and blindness following HIV infection are rare in the literature. Watkins et al. and Afsrikordehmahin et al. have described cases of concomitant deafness and blindness after VZV encephalitis in HIV-positive patients. VZV encephalitis is considered an opportunistic infection and the cause of deafness and blindness [6, 7]. Moreover, Prada et al. and Douglas-Vail et al. have described cases of deafness and blindness secondary to CM in HIV-positive patients [8, 9]. Elevated intracranial pressure is one of the hallmarks of CM, which can lead to headache, vomiting, cranial nerve palsies, and ultimately death [9]. Concomitant deafness and blindness can be explained by direct infection or compression of the nerves, secondary to high intracranial pressure or inflammatory adhesions characteristic of arachnoiditis. Moreover, the rapid onset of blindness reflects the direct involvement of the optic nerve, and such blindness is probably caused by infarction or cryptococcal infection. By contrast, the observed slow gradual deterioration of vision indicates that intracranial hypertension is a likely cause [8].

Although VZV encephalitis and CM have been mentioned as opportunistic infections and the causes of concomitant deafness and blindness in HIV-positive patients, detailed examinations revealed negative results for these conditions in our patient.

Furthermore, Rodriguez-Una et al. and Elliot et al. have described simultaneous optic and vestibulocochlear syphilitic neuropathy in HIV-

positive patients [3, 10]. However, the serum test was negative for syphilis in the present patient.

To the best of our knowledge, this is a rare (if not the first) case of acute bilateral deafness and blindness as presenting symptoms of HIV encephalopathy.

### *HIV encephalopathy*

The brain remains a major target for HIV infection and is a site of potential complications in HIV-infected individuals [11]. Research has begun to decipher the pathogenesis of HIV encephalopathy. In brief, the virus reaches the brain through CD4+ T lymphocytes and perivascular monocytes. Microglia seizes free viral particles through receptor-mediated endocytosis or phagocytosis of the infected senescent lymphocytes. The only cells harboring HIV in the brain are perivascular monocytes and microglia. Therefore, brain damage is not caused by the direct effect of HIV on neurons or oligodendroglia, and neuronal dysfunction is not correlated with the viral load. Brain injuries are caused by cytokines such as tumor necrosis factor and by neurotoxins such as glutamate and nitric oxide, which are produced by activated monocytes and microglia. The gp120 protein from the HIV envelope activates N-methyl-D-aspartate receptors, thus inducing a cascade of neurotoxic reactions [12]. Moreover, the CNS is as a potential reservoir of HIV, including initiation and persistence of HIV infection in the CNS. In some individuals, HIV is detectable in cells and tissues of the CNS despite the administration of suppressive antiretroviral treatment. Virally infected cells can traffic out of the CNS and may have the potential to reseed the systemic compartment. Compartmentalized HIV replication in the CNS before the administration of antiretroviral treatment may result in more severe inflammatory and neural injuries that are irreversible or slower to reverse with therapy [11].

Two major histopathological manifestations of HIV encephalopathy have been observed. HIV leukoencephalopathy (progressive diffuse leukoencephalopathy) is characterized by a diffuse loss of myelin in the deep white matter of the cerebral and cerebellar hemispheres, with scattered multinucleated giant cells and microglia but scarce or absent inflammatory reac-



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tion. HIV encephalitis (multinucleated giant cell encephalitis) is associated with the accumulation of multinucleated giant cells, inflammatory reaction, and frequently focal necrosis. In some patients, both patterns may overlap [2].

The overt loss of neural tissue in HIV is thought to be accompanied by Wallerian degeneration of axons. Loss of anatomical connections may contribute to brain dysfunction by impairing information transfer and integration in the brain's neural networks [13].

HIV-associated neurocognitive disorder (HAND) is characterized by cognitive, motor, and behavioral alterations secondary to the preferential impairment of subcortical structures caused by the virus [14]. HAND is common in HIV-positive patients. The frequency of HAND is 25%-33% [15]. Cognitive impairment in HAND is divided into three stages and ranges from asymptomatic neurocognitive impairment to minor neurocognitive disorder to HIV-associated dementia (also called AIDS dementia complex or HIV encephalopathy) [16]. In HIV patients, multiple factors are associated with HAND, with the most important factors being age, duration of HIV infection, low CD4+ T lymphocyte count, previous high plasmatic viral loads, and psychiatric illness [14]. A low CD4+ T lymphocyte count (6 cells/mm<sup>3</sup>) was observed in the present case.

### *Antiretroviral therapy for HIV encephalopathy*

Treatment of an HIV-positive patient is considered to be successful if the CD4 count is elevated to >500 cells/mm<sup>3</sup> (immunological success), the serum viral load is undetectable (viremic success), and the patient does not present any complications clinically (clinical success). Despite successful treatment, viremic blips (intermittent low-level viremic levels) and some opportunistic diseases may occur [17]. The brain is one of the anatomical reservoirs of HIV, and the brain tissue levels of combined antiretrovirals are considerably low in comparison with plasmatic levels. Quasi-continuous minimum levels of HIV replication can be detectable in the brain, even when serum viral loads are undetectable [18]. Considering the variability between the serum viral load and the CSF viral load, as well as the clinical tendency to overlook CSF viremic loads in serum viremic-undetectable patients, HIV activity in the brain is

frequently under diagnosed or misdiagnosed [12].

### *CSF examination for HIV encephalopathy*

In severely immunosuppressed individuals, routine CSF examinations may be normal despite the presence of CNS infection. In patients with severe pancytopenia, routine CSF examinations may not show pleocytosis despite ongoing meningoencephalitis because the patients may not be able to mount an adequate inflammatory response to the infection. Thus, a high index of suspicion is necessary, particularly in immunocompromised patients, and normal routine CSF examination in such patients should not deter physicians from performing CSF cultures [19]. In this case report, CSF cultures were negative in our patient.

Other studies using CSF markers of inflammation such as neopterin and markers of active axonal injury have also suggested ongoing CNS injury in HAND (HIV encephalopathy) [14].

### *Neuroimaging for HIV encephalopathy*

Neuroimaging may be a noninvasive method for evaluating progressive changes in the brain caused by HIV infection. Changes may initially occur within the subcortical regions of the brain and may spread to cortical areas with more advanced disease [11]. Despite these changes, the initial computed tomography scan can be normal in patients with CNS infection, including fungal infection, particularly in immunocompromised patients [19]. Thus, a combination of methods (neuroimaging, CSF examination, and neuropsychologic performance testing) may provide a more complete understanding of changes in the brain caused by HIV infection [11].

MRI is a noninvasive method for detecting and assessing pathological changes caused by various neurodegenerative diseases. For example, structural MRI has revealed volume reduction in various brain regions, which can be linked to cognitive impairment. However, brain atrophy usually occurs at rather late disease stages, with significant and usually irreversible brain damage [20].

The present patient developed progressive drowsiness, weakness, and deterioration of mental status after admission. Thus, for further

investigation, we performed repeat brain MRI and CSF examination. However, repeat brain MRI and CSF examination did not reveal significant abnormality, and their results were similar to those of the initial examinations.

Because of its ability to directly image brain function, functional MRI (fMRI) has the potential to be a critical tool for detecting early signs of HAND (HIV encephalopathy), particularly in clinically asymptomatic patients. By contrast, a more advanced fMRI technique, fMRI-Rapid Adaptation, has been proven to be able to measure neural specificity more directly than conventional fMRI techniques, with a direct link to behavioral performance. Liu et al. suggested that prior to the onset of detectable behavioral deficits, significant neuronal dysfunctions are already present in HIV-positive individuals, and these early neuronal dysfunctions can be detected and assessed by measuring neural specificity; neural specificity measurement in combination with the novel  $H_{corr}$  technique has a strong potential to serve as a biomarker of asymptomatic HAND and other neurodegenerative diseases [20].

### Conclusion

Our case report demonstrates two pertinent points. First, this is the first case report of concomitant acute bilateral hearing and vision loss as presenting symptoms of HIV encephalopathy. Second, clinicians should be aware that concomitant acute bilateral hearing and vision loss in HIV-positive patients imply the subsequent development of HIV encephalopathy, although brain MRI and routine CSF examination may be normal in these immunocompromised patients.

### Disclosure of conflict of interest

None.

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