



Case report

Isolated Cranial Nerve VI Palsy and Neurosyphilis: A Case Report and Review of Related Literature

Jao Jarro B. Garcia^{a,1,*}, Jalea L. Coralde^a, Marjorie Anne C. Bagnas^{b,2}, Kathleen Joy O. Khu^{c,3}^a Division of Adult Neurology, Department of Neurosciences, College of Medicine and Philippine General Hospital, University of the Philippines Manila, Philippines^b Division of Neurology, Department of Medicine, University of Toronto, Ontario, Canada^c Division of Neurosurgery, Department of Neurosciences, College of Medicine and Philippine General Hospital, University of the Philippines Manila, Philippines

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ABSTRACT

An isolated cranial nerve VI palsy is a rare initial manifestation of undiagnosed neurosyphilis. A 33-year-old male presented with a one month history of progressive headache and diplopia. Neurologic examination only revealed an isolated abducens palsy on the left. Cranial imaging was unremarkable. Examination of his cerebrospinal fluid revealed lymphocytic predominant leukocytosis and elevated protein. Microbiologic work-up were all negative. Further work-up revealed the patient to be serum Rapid Plasma Reagin and Enzyme Immunoassay reactive. Enzyme-linked immunosorbent assay for Human Immunodeficiency Virus also tested positive. His cerebrospinal fluid was then sent for Rapid Plasma Reagin to confirm the diagnosis of neurosyphilis. He completed 14 days of intravenous penicillin and was eventually discharged with partial resolution of the abducens palsy. We describe the second case of neurosyphilis presenting only with an isolated cranial nerve VI involvement. On further review, ours was the first case documented on an individual who had an undiagnosed Human Immunodeficiency Virus infection. There are various differentials for an isolated cranial neuritis but infectious causes, particularly neurosyphilis, should be considered among young individuals with known risk factors despite their apparently benign medical history.

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Introduction

A resurgence in the cases of neurosyphilis had been observed during the start of the acquired immunodeficiency syndrome (AIDS) epidemic [1]. Although registries exist, there is still a lack of

epidemiologic data regarding the neurologic sequelae of syphilis [2]. Originally, late symptomatic forms such as tabes dorsalis and dementia paralytica heralded the diagnosis. However, early forms such as syphilitic meningitis and meningovascularitis recently became the predominant clinical presentation [3]. Tagged as the “great mimicker” [4–6], this condition may present with a gamut of manifestations. This article aims to present an atypical presenting manifestation of neurosyphilis.

Case Description

A 33-year-old man was admitted because of a one-month history of progressive headache and diplopia. He did not have vomiting, blurring of vision, other focal deficits, or seizures. There was no fever, weight loss, anorexia, or cough. He reported having 10 previous male partners of unknown sexual promiscuity but denied any history of sexually transmitted infections. The rest of his medical, family, and social history were non-contributory.

Vital signs were stable on admission. Systemic examination was unremarkable. There were no lymphadenopathies, palpable masses, or skin lesions. Neurologic examination revealed intact higher

Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; CALAS, Cryptococcal Antigen Latex Agglutination System; CDC, Centers for Disease Control and Prevention; CN, cranial nerve; CNS, central nervous system; CSF, cerebrospinal fluid; EIA, Enzyme immunoassay; FTA-ABS, Fluorescent Treponemal Antibody Absorption; HIV, Human Immunodeficiency Virus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBC, red blood cells; RPR, Rapid Plasma Reagin; USA, United States of America; VDRL, Venereal Disease Research Laboratory; WBC, white blood cells

* Correspondence to: Division of Adult Neurology, Department of Neurosciences College of Medicine and Philippine General Hospital University of the Philippines Manila, Philippines Taft Avenue, Manila 1000, Philippines.

E-mail addresses: jbgarcia14@up.edu.ph, jaojarrogarcia@gmail.com (J.J.B. Garcia), jaleacoralde@gmail.com (J.L. Coralde), mdbagnas@up.edu.ph (M.A.C. Bagnas), kathleen.khu@neurosurgery.ph (K.J.O. Khu).

¹ ORCID: 0000-0002-8926-4023² ORCID: 0000-0003-2822-3196³ ORCID: 0000-0003-4526-6235

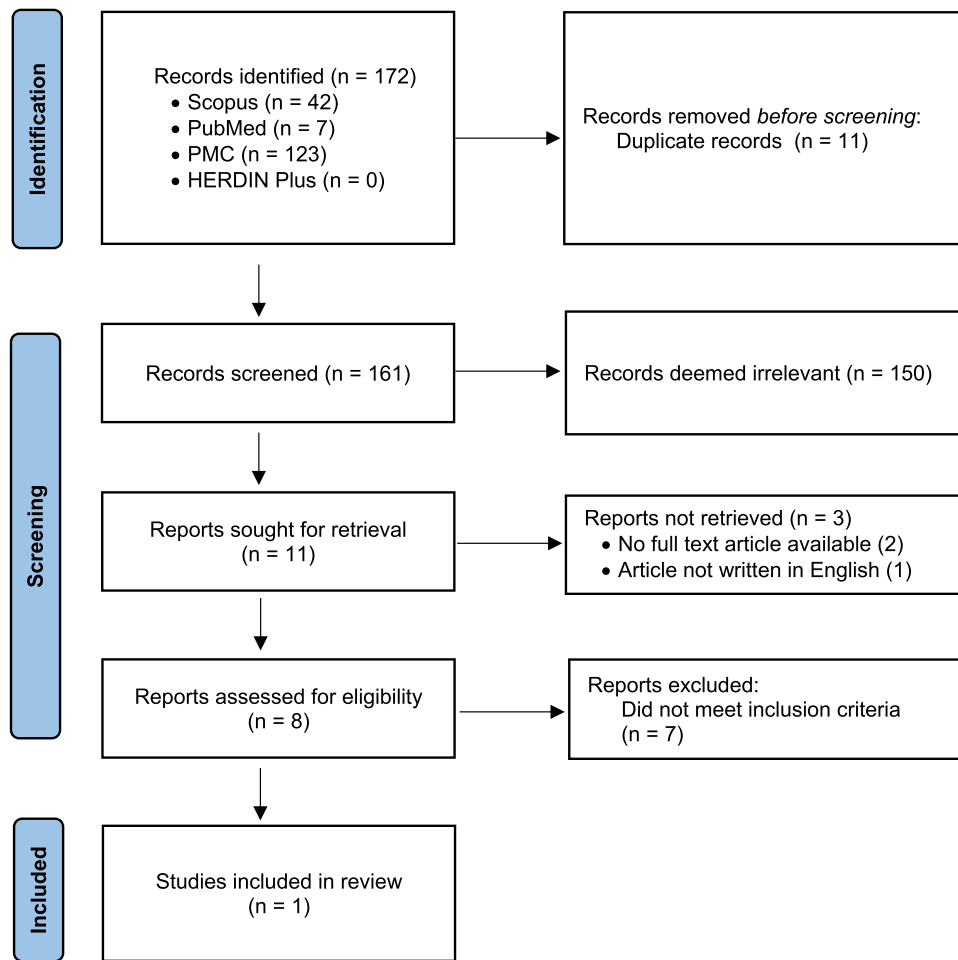


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the systematic review.

cortical functions. Cranial nerve (CN) examination was normal save for limited abduction of the left eye on version and duction. Extremities were normotonic, normoreflexic, and had good muscle strength. There were no cerebellar or meningeal signs. He also denied sensory deficits.

Full blood count showed a white blood cell (WBC) count of 5.5×10^9 cells/L with 48% neutrophils, platelet count of 242×10^9 cells/L, hemoglobin of 139 g/L, and hematocrit of 0.41. His HBA1c and lipid profile were also normal. His cranial CT Angiogram did not reveal any infarcts, hemorrhages, or aneurysms. His contrast enhanced cranial MRI also showed unremarkable results. He was referred to Neurology service and a lumbar tap was done which showed normal opening and closing pressures. CSF was clear and straw-colored, with 20 cells/mm³ of red blood cells (RBC) and 87 cells/mm³ of WBC, with the following differential cell count: 92% lymphocytes, 5% neutrophils, and 3% monocytes. Protein was elevated at 0.80 g/L (Reference 0.12–0.60 g/L) but glucose was normal at 3.4 mmol/L (Reference 2.2–3.9 mmol/L). There were no polymorphonuclear cells on Gram Stain and no encapsulated organisms on India Ink. Cryptococcal Antigen Latex Agglutination System (CALAS) and Bactigen yielded negative results. No acid-fast bacilli were seen in the CSF, and TB-PCR was negative. CSF aerobic, fungal, and TB cultures were negative. There were no malignant cells on cytology.

On further work-up, his serum was Rapid Plasma Reagin (RPR) reactive with a titer of 1:128. Enzyme immunoassay (EIA) confirmed the diagnosis of syphilis. The diagnosis of neurosyphilis was made after the CSF sample sent for RPR turned out reactive. Additional work-up revealed he also had Human Immunodeficiency Virus (HIV)

with a CD4 count of 604 cells/uL. He was treated with Penicillin G 4 million units IV every 4 hours for 14 days with no note of any adverse reactions. There was eventual resolution of his headache and partial improvement in his left abducens palsy. He was discharged after antibiotic completion and was endorsed to a neurologist and infectious disease specialist in his locality for continuity of care.

Discussion

Following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a systematic search of Scopus, PubMed, PMC, and HERDIN Plus databases was done on July 26, 2021 using the keywords “neurosyphilis”, “abducens nerve”, and “cranial nerve VI.” All search hits beginning from the databases’ creation until the time of search were collected. Full text, English articles whose title, abstract, and discussion tackled neurosyphilis and the involvement of cranial nerve VI were included. Fig. 1 shows the PRISMA flow diagram.

A total of 172 hits were acquired during the database search. After removal of the duplicate hits, 161 were screened using the inclusion criteria. Among these, 150 were excluded after being deemed irrelevant. Eleven articles were retrieved; however, 2 did not have available full text and 1 was not written in the English language. The full text of 8 articles were evaluated from which only 1 met the inclusion criteria.

As of the time of review, only 1 other case report had been published documenting an isolated and unilateral cranial nerve VI palsy as the presenting manifestation of neurosyphilis. When

compared to the case presented above, both were males in their 4th decade of life presenting with headache, diplopia, and isolated cranial nerve VI involvement. Serum and CSF studies confirmed the diagnosis of neurosyphilis and both were managed with intravenous Penicillin G for 14 days. In contrast to the case above, the patient reported by Singh and colleagues in 2020 had already been diagnosed with HIV-AIDS prior to the onset of symptoms pertaining to neurosyphilis. Table 1 summarizes pertinent information regarding the two cases.

The start of the AIDS epidemic was also accompanied by an increase in the cases of neurosyphilis. From a rate of 2.1 cases per 100,000 population in 2000–2001, the USA saw an increase in the rates of syphilis in 2016 with 15.6 cases per 100,000 males and 1.9 cases per 100,000 females. Records showed that 58.1% of cases were among men who have sex with men and that 47% of this subgroup had HIV co-infection [7].

Neurosyphilis results from the central nervous system (CNS) invasion of the *Treponema pallidum* spirochete. It is estimated that neural invasion occurs in at least 40% of the population with syphilis. Seventy per cent of this subgroup will be able to clear the spirochetes whereas the remaining 30% will develop a persistent infection called asymptomatic neurosyphilis. Ultimately, 20% of the individuals in this subgroup will develop a symptomatic form [1,3].

Syphilis and HIV have significant interactions. The presence of asymptomatic syphilitic gummas cause mucosal disruptions facilitating the transmission of HIV [8]. Syphilis also causes a transient increase in HIV viral load and a transient decrease in CD4 count which further increase HIV transmission [9]. Rates of early neurosyphilis among HIV-infected individuals also increased because of their bodies' inability to control spirochetal CNS invasion and to facilitate organism clearance [9].

Manifestations during the first two years of infection are tagged as Early Neurosyphilis and affect the meninges and blood vessels leading to asymptomatic meningitis, syphilitic meningitis, or meningovascularitis [10]. Symptomatic syphilitic meningitis presents with elevated intracranial pressure, headache, and focal CN deficits most commonly involving the optic, facial, and vestibulocochlear nerves [1].

In general, among the ocular cranial nerves, abducens nerve palsy has consistently been reported as the most common to occur in isolation [5,11,12]. Epidemiologic studies had frequently identified neoplastic, traumatic, and microvascular causes for isolated abducens palsy especially in the elderly. However, a significant percentage (up to 30%) still had undetermined etiologies and involve inflammatory, demyelinating, or infectious processes [11].

The diagnosis of neurosyphilis remains a challenge because of its manifestations. The organism's fastidious nature also limits direct microbiologic techniques; hence, indirect tools such as non-treponemal and treponemal serologic tests are used instead [13]. CSF studies typically reveal pleocytosis (> 5 WBC) with lymphocytic predominance, hypoglycorrhachia, and elevated protein (> 0.45 g/L). CSF VDRL is the gold standard for diagnosis because it has a higher specificity as compared to treponemal tests owing to the passive transfer of antibodies across the blood–brain barrier [10,13,14]. According to Ropper [15], CSF VDRL has 100% specificity if the sample is not contaminated by blood whereas its sensitivity is at 75% for early neurosyphilis. CSF RPR may also be used since the former is not readily available in most centers [1]. Should CSF VDRL be negative in a patient with clinical symptoms consistent with neurosyphilis, CSF treponemal tests are advised. CSF FTA-ABS has 50–70% specificity and 100% sensitivity for early neurosyphilis.

To achieve diagnostic uniformity, a proposed set of criteria for the diagnosis of symptomatic neurosyphilis includes (1) reactive serum treponemal test, (2) clinical manifestations consistent with neurosyphilis, and (3) either (a) a reactive CSF VDRL or (b) a CSF WBC > 5/uL or CSF protein > 0.45 g/L [1].

Table 1
Cases of Neurosyphilis Presenting with Isolated Cranial Nerve VI Palsy.

STUDY	SYN-DROME	AGE, SEX, & HIV STATUS	MANIFESTATIONS	SERUM PROFILE	CSF PROFILE	IMAGING	TREATMENT	RESPONSE
Garcia et al., 2021, Philippines	Meningeal Syphilis	33/M HIV: Positive (Newly diagnosed - CD4 604 cells/uL)	<ul style="list-style-type: none"> • Symptoms: headache, diplopia • PE: isolated left CN VI paresis 	<ul style="list-style-type: none"> • RPR (+) 1:128 titer • EIA (+) 	<ul style="list-style-type: none"> • WBC 87 cells/mm³ (92% lymphocytes) • Protein 0.80 g/L 	Cranial MRI: unremarkable	IV Penicillin G, 24 million units daily for 14 days	Resolution of headache and partial improvement in left CN VI palsy
Singh et al., 2020, Barbados	Meningeal Syphilis	34/M HIV: Positive (Known AIDS - CD4 80 cells/uL; viral load 110,000 copies/mL)	<ul style="list-style-type: none"> • Symptoms: diplopia and headache • PE: isolated left CN VI palsy 	<ul style="list-style-type: none"> • RPR (+) 1:32 titer • FTA-ABS (+) 	<ul style="list-style-type: none"> • WBC 21 cells/mm³ (98% lymphocytes) • Protein 0.49 g/L 	Cranial CT and MRI: unremarkable	IV Penicillin G, 18 million units daily for 14 days	Partial improvement of CN VI palsy at discharge

Ultimately, clinical and serologic cure is the goal and management recommendations are the same regardless of HIV status [9]. Because of its capability to enter the CSF, the CDC recommends aqueous crystalline Penicillin G administered at a total of 18–24 millions units per day in 6 divided doses or as a continuous infusion for 10–14 days [1,3].

Success is monitored by checking symptom resolution and CSF normalization following a pattern of CSF WBC decrease at 6 months and resolution of all CSF abnormalities at 2 years posttreatment [1]. For individuals co-infected with HIV, close follow-up is required because of the protracted course of CSF changes and the risk of treatment failures [10,13].

In summary, there are a multitude of differential diagnoses for an isolated cranial neuritis but infectious causes should be considered depending on the patient profile and his clinical presentation. Some other infectious agents reported to cause isolated cranioopathies are *Mycobacterium tuberculosis* [16], Varicella-Zoster virus [17], Dengue virus [18], Epstein-Barr virus [19], and *Cryptococcus neoformans* [20] to name a few. Despite the advances in the work-up and management of neurosyphilis, there is still a need to further streamline these developments to unify the diagnostic criteria and cornerstones of management.

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Authors' Contributions

JLC conceived the idea for the case report and wrote the initial draft. JJBG performed the literature and systematic review and completed the manuscript. MACB reviewed and edited the intellectual content of the manuscript. KJOK reviewed and edited the intellectual content of the manuscript. The authors have verified the accuracy of the details of the case presented. They have also read and approved the submission of this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRedit authorship contribution statement

Jao Jarro B. Garcia: Conceptualization, Investigation, Writing – original draft, Visualization. **Jalea L. Coralde:** Conceptualization, Investigation, Writing – original draft. **Marjorie Anne C. Bagnas:**

Conceptualization, Writing – review & editing, Supervision. **Kathleen Joy O. Khu:** Conceptualization, Writing – review & editing, Supervision.

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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