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Short Communication

Ceftriaxone – A plausible intervention for treating neurosyphilis?

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Neurosyphilis characterized as a tertiary presentation of syphilis [1] is a Central Nervous System (CNS) infection, caused by Treponema Pallidum [2]. The early stage of the infection is marked by asymptomatic meningitis, meningismus, cranial nerve palsies, and blindness or deafness, while late neurosyphilis is typified by general paresis and tabes dorsalis, both of which are the consequences of damage to the adjacent neural tissue. As opposed to syphilis, neurosyphilis is not a reportable disease [3] and studies from previous years have identified features that help determine susceptible groups; male gender, younger age, homosexual men, and those who are infected with HIV [3] Diagnosis is mainly done through CSF, clinical judgment [3], and by serological tests(nontreponemal and treponemal). Nontreponemal tests are based on the measurement of immunoglobulin IgG and IgM antiphospholipid, whereas treponemal tests are based on the use of spirochete bacterium, T palladium as an antigen only in the presence of lesion exudate [5,6].

Treatment of neurosyphilis revolves around a beta-lactam antibiotic regime [1] and currently, Benzylpenicillin, (given as: 1.8–2.4 g IV every 4 h for 14 days) is the gold standard therapy [8]. β-lactam antibiotics arrest the bacterial peptidoglycan cell wall synthesis that disrupts normal bacterial growth and development [1]. However, the drawbacks associated with this treatment include, an increased hospital length of stay, hypersensitivty reactions [9], and a short-term immunologic reaction known as Jarisch-Herxheimer reaction. Fever, chills, headache, myalgia, and exacerbation of existing cutaneous lesions are some clinical manifestations of this reaction, occurring 24 hours after the commencement of the treatment [5,6].

Other interventions for treating neurosyphilis include the following: Doxycycline(, used 100 mg orally, twice a day, for 21–30 days),Tetracycline(used orally at 500 mg four times daily for 30 days),Chloramphenicol (1 g intravenously for 14 days). Ceftriaxone which is a well known β-lactam antibiotic having a long serum half life and good CNS penetration can also be a plausible candidate used in the treatment of neurosyphilis [10]. Previous studies have demonstrated that 2g/d IV ceftriaxone is a suitable substitute for penicillin for those individuals allergic to penicillin [3].

In the Lancet Infectious Diseases May 2021 issue, Thomas et al. [6] concluded that Ceftriaxone is a potential alternative for treating neurosyphilis alongside the well-known β-lactam antibiotic regime mentioned earlier [6]. In this retrospective multicentre study [6] the authors compare ceftriaxone with benzylpenicillin, the current gold standard therapy, by dividing the patient population into two groups receiving intravenous ceftriaxone (2 g once daily) or intravenous benzylpenicillin (3–4 million units every 4 h) respectively [6]. While the results report no significant difference in serological responses, between the two study groups at 6 and 12 months, and a subgroup analyses according to HIV status, neurosyphilis subtype, and CSF leucocytosis delineate no differences in complete response rates between the groups [6]. Thomas et al. evaluated that the cohort in the ceftriaxone group had a shorter length of stay in hospital compared to benzylpenicillin group, a parameter that had not been shed light in previous studies. Ceftriaxone can also be used in the completion of OPAT(outpatient parental antimicrobial therapy) shortening hospital stay, lessening treatment costs, and ameliorating a patients quality of life [6].

Clinicians have been advised to monitor CSF and serum measures after treating HIV-infected neurosyphilis patients [11] and throughout most trials in yesteryears, ceftriaxone has been mostly considered as a stand-in for benzylpenicillin. In a pilot study from 1989, it was deduced that in contrast to clemizole penicillin G 1 million IU given intramuscularly daily for 15 days (control group), a dosage regime of 4(multiply) 1 g ceftriaxone IM given every 2 days was well tolerated and efficacious in treating primary or secondary syphilis with no difference in serological response and clinical healing from the control group [12]. Another pilot study by Marra et al., in 2000 prospectively comparing the effect of iv ceftriaxone versus iv penicillin in HIV-1–infected patients with neurosyphilis comprising 36 enrolled subjects found that IV ceftriaxone can be a plausible alternative to penicillin for treatment of HIV-1–infected patients with neurosyphilis and concomitant early syphilis but there was no decisive statement in regards to either abandoning iv penicillin or adopting iv ceftriaxone [6,11]. However, limitations in these studies, such as small sample sizes, made them inadequate in ascertaining the efficacy of ceftriaxone. Conversely, results from Thomas et al.'s study deduced from 365 patients can be more

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pivotal in influencing treatment decisions due to the large sample size.

Still, the authors warrant the results to be interpreted carefully. Ceftriaxone use resulting in a shorter hospital stay [6] might be due to the benzylpenicillin group undergoing a more severe disease course than the ceftriaxone one. Moreover, Ceftriaxone has a wide antimicrobial spectrum compared to BPG and stands second to clindamycin in offering antibiotic resistance so its extensive use could lead to disturbance of natural microbial flora and increased susceptibility to Clostridiodes Difficile infection [13,14].

While these speculations might pose some questions, the merit of lesser expense and better quality of life can still be derived from ceftriaxone use as it is inoculated via fewer injections for the same hospital stay as benzylpenicillin. Some researchers also assess the cross-reactivity [6] between penicillin's and cephalosporins to be overstated with the risk with third- and fourth-generation cephalosporin being minimal [10], and this might rule out the caveat suspected by Thomas et al. However, a major challenge that remains is to reliably confirm if ceftriaxone can be used in OPAT (Outpatient Antimicrobial Therapy) for neurosyphilis specifically. This would be the only way for the drug to be employed largely and reduce hospital stay, the most important outcome in establishing ceftriaxone's effectiveness. Records from a Glasgow OPAT service from 2001 to 2010 revealed most instances of OPAT treated with ceftriaxone were infections with gram-positive bacteria [15], while neurosyphilis is caused by *Treponema pallidum* [4] which is a gram-negative bacterium and indication for OPAT with ceftriaxone for first patient episodes for syphilis was found to be negligible [15,16].

The success of neurosyphilis treatment is governed by normalizing or steadying clinical abnormalities and by controlling CSF abnormalities [3]. A 2019 study by Tuddenham and Ghanem concluded that [16] results from small observational studies endorse IV ceftriaxone as an alternative to 3 doses of 2.4 MU of BPG as BPG has been unable to achieve consistent treponemicidal levels in the CSF. The Lancet study has added new perspectives in the treatment discourse for neurosyphilis, ones which clinicians can take into consideration while weighing the potential downsides of the drug in the discussion. However, the results are still a long way to go due to the paucity of clinical data on the optimal dose, duration of treatment, and long-term efficacy of ceftriaxone and other antimicrobials [6]. Multiple large-scale trials are needed to understand the safety and efficacy of Ceftriaxone use in patients suffering from neurosyphilis, and to gauge if it can be recommended as first-line treatment over benzylpenicillin.

Ethical approval

The paper did not involve any patients, hence no ethical approval was required.

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Author contribution

SYED HASAN SHUJA:Conception of the study and literature search. UNAIZA NAEEM: Literature search and drafting the manuscript. FAREA EQBAL: Drafting the manuscript and writing the manuscript. MUHAMMAD HAMZA SHUJA: Literature search and final approval.

Registration of research studies

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Guarantor

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Farea Eqbal.
Muhammad hamza shuja.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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