Ocular syphilis in Pacific peoples—are we making misdiagnoses secondary to yaws?

Hannah Gill, Helen V Danesh-Meyer, Joanne L Sims, Mitzi Nisbet, Rachael L Niederer

ABSTRACT

AIMS: To determine the demographic and clinical features of patients with ocular disease consistent with syphilis and positive treponemal serology in Auckland, and to compare patients who lived in a Pacific nation before 1960 with all other patients with regard to these features, considering a possible history of yaws infection.

METHODS: Retrospective review of subjects seen in uveitis and neuroophthalmology clinics at Auckland District Health Board between January 2006 and June 2019.

RESULTS: Two thousand four hundred and ninety-three subjects were reviewed in uveitis clinics during the timeframe, of whom 45 were diagnosed with syphilitic uveitis (1.8%). Mean age was 56.2±14.8 years and 34 (75.5%) were male. Ethnicity was Caucasian in 16 (35.5%), Pacific peoples in 16 (35.5%), Māori in two (4.4%), Asian in six (13.3%) and other in five (11.1%). Pacific peoples were older at presentation (p=0.001) and 75.0% were aged <60 compared to 24.1% of non-Pacific peoples (p=0.002). Comparing Pacific people born prior to 1960 (aged >60) to the rest of the cohort, older Pacific subjects had lower RPR titres (median 3 vs 32 p=0.004), less optic nerve swelling (0% vs 28.0% eyes p=0.014) and less posterior uveitis (6.25% vs 32.0% eyes p = 0.033). No difference was observed in anterior and intermediate uveitis between the groups. No difference was observed in the resolution or recurrence of inflammation between the groups.

CONCLUSION: Syphilitic uveitis is common in New Zealand, occurring in 1 in 55 patients seen in consultant uveitis clinics. Clinicians should consider a history of yaws in Pacific peoples presenting with ocular inflammation and positive treponemal serology. In these cases alternative causes of ocular pathology should be included as differentials. In cases of diagnostic uncertainty, the risk of treatment versus the potentially severe sequelae of untreated syphilis need to be considered.

Acquired syphilis is a multi-systemic infectious disease which is known as the ‘great imitator’ because of its wide variety of clinical presentations and ability to mimic many other conditions. The disease is caused by the spirochete Treponema pallidum spp. pallidum and spread via the mucocutaneous route. Sexual transmission is most common, however it may also be transmitted to a fetus or neonate during pregnancy or childbirth. Four stages of the disease are recognised and overlap can exist between the stages. Syphilis is successfully treated with antibiotics; however, untreated can result in chronic complications or death. Ocular syphilis is relatively uncommon; however, syphilis may involve any structure of the eye. The time course and presentation of ocular involvement is equally variable. The most common ocular involvement is uveitis (intraocular inflammation), accounting for 1.3% of all uveitis. Syphilis has also been reported to cause optic neuritis, chorioretinitis, retinal vasculitis, conjunctivitis, dacrophyadentitis, dacrocystitis, episcleritis, scleritis and interstitial keratitis. A high index of suspicion should be enforced in cases of unexplained ocular inflammation to avoid long-term sight-threatening complications.
Once ocular involvement is confirmed, it is regarded as neurosyphilis. The recommended treatment for neurosyphilis, and therefore ocular syphilis, is intravenous penicillin for 10–14 days.\cite{8}

The rate of syphilis infection in New Zealand has been increasing since 2012, with 470 cases reported in 2017 compared to 225 in 2015.\cite{1} The annual incidence continues to increase in parallel with rates observed internationally.\cite{1} The increase in prevalence is partly explained as a result of syphilis being more prevalent in some groups of patients with HIV (human immunodeficiency virus), including men who have sex with me (MSM), with co-infection rates reported to be between 20–70%.\cite{9} As of January 2017, syphilis was made anonymously notifiable in New Zealand, with an aim to identify at-risk groups and provide targeted public health interventions.\cite{3,10} In 2019, the New Zealand Ministry of Health published the National Syphilis Action Plan with an aim to guide a coordinated and systematic response to interrupt ongoing transmission of infectious syphilis and prevent congenital syphilis.\cite{10} While MSM with HIV co-infection have the highest risk of acquiring syphilis, the incidence of cases in heterosexual males and females has also been rising.\cite{1,3} Rates of syphilis presentations have increased across all ethnicities in New Zealand, with New Zealand European reporting the highest rates of infection in the male sub-group, and Māori reporting the highest rates of infection for females. For both men and women, the highest risk age group is 20–39 years.\cite{1}

A presumptive diagnosis of syphilis, based on the patient’s epidemiological and clinical features, may be supported by serology consistent with a current treponemal infection.\cite{1,5} Serology testing is most commonly performed on serum samples using rapid plasma reagin (RPR) testing, but occasionally may also be tested on CSF, using venereal disease research laboratory (VDRL) testing. These are non-specific treponemal tests and may normalise during tertiary and latent stages, therefore serological testing should also include specific treponemal antibody tests such as fluorescent treponemal antibody absorption (FTA-ABS) or Treponema pallidum particle agglutination (TP-PA).\cite{5,11}

One complexity of syphilis result interpretation is the lack of diagnostic tests available to distinguish between syphilis and other non-venereal treponemal diseases, such as yaws.\cite{5,11} Yaws is a chronic skin infection caused by spirochete Treponema pallidum spp. pertenue. It presents with tender skin ulcers that persist for three to six months, typically in children younger than 15. Yaws was highly prevalent in the South Pacific in the 1950s and early 1960s, until a mass treatment campaign utilising penicillin resulted in a dramatic decline and eventual eradication of the disease.\cite{12,14} Despite treatment, previously infected subjects will still return a positive treponemal serology.\cite{11} Due to New Zealand’s large Pacific Island population, yaws needs to be considered as a differential on return of a positive syphilis serology in Pacific peoples born before 1960. There is no data currently published connecting yaws and ocular pathology.

The current study aimed to investigate the cohort of patients diagnosed with ocular syphilis in Auckland, New Zealand. It wanted to consider whether older Pacific patients presented differently to other subjects, due to potentially incorrect ascription of positive treponemal serology to syphilis rather than yaws.

**Methods**

This is a retrospective study reviewing the medical records of patients diagnosed with ocular inflammation and positive treponemal serology between January 2006 and June 2019 at a tertiary referral center in New Zealand.

**Subject selection**

A database of subjects seen in the uveitis or neuro-ophthalmology clinics at Auckland District Health Board between 1 January 2006 and 1 June 2019 was reviewed. Electronic coding was used to identify subjects from this database who has returned a positive RPR and or TP-PA in the setting of uveitis or optic neuropathy consistent with syphilis. Subjects were excluded by an experienced consultant ophthalmologist or infectious disease physician if they believed syphilis not to be the primary reason for uveitis or optic neuropathy. This study adheres to the tenets of Declaration of Helsinki. Ethics approval NTX/12/EXP/085.
Data collection
Clinical notes, imaging and laboratory testing was reviewed for all subjects and data recorded on a standardised de-identified pro forma. Ethnicity was defined using self-identified ethnicity recorded within the health record. Country of birth was not routinely available.

Vision was recorded in the clinical notes as Snellen acuity. Best corrected visual acuity results were converted to logarithm of the Minimum Angle of Resolution (logMAR) units for analysis with the following conversion used for vision of counting fingers or worse; counting fingers 2.0 logMAR; hand movements 2.3 logMAR; light perception 2.6 logMAR; no light perception 2.9 logMAR.\(^\text{15}\) The outcome of permanent moderate vision loss (MVL; range 6/15–6/60) and severe vision loss (SVL ≤6/60) was defined according to the Standardization of Uveitis Nomenclature (SUN) Working Group.\(^\text{16}\) Anatomical classification of uveitis was defined according to SUN nomenclature.\(^\text{14}\) All subjects with a diagnosis of uveitis or optic neuropathy who were considered to have syphilis were referred to an infectious disease physician for further investigation and treated with intravenous benzylpenicillin either in hospital or at home for 10–14 days' duration.

Statistical analysis
Data was entered into an Excel spreadsheet and analysed in STATA version 15. Categorical variables are reported as n (%) and continuous variables as mean ± standard deviation (sd) for normal distribution and median (interquartile range [IQR]) for skewed distribution. Groups were compared with chi square, t test or Mann-U-Whitney for subject variables, and a generalised estimating equations approach with eyes nested within subjects was used for eye data. All tests were two-tailed and a p value of <0.05 was considered significant.

Results
Forty-five subjects were included for analysis, with 66 affected eyes. Mean age at presentation was 56.2±14.8 years and 34 (75.5%) subjects were male. Ethnicity was Pacific peoples in 16 subjects (35.5%), Caucasian 16 subjects (35.5%), Asian six subjects (13.3%), Māori two subjects (4.4%) and other five subjects (11.1%). Pacific peoples with syphilis were significantly older compared to other ethnicities (65.7 vs 51.0 years p<0.001) with lower proportion of males (56.3% vs 82.6% p=0.021) (Table 1).

The presumed mode of transmission was documented in 29 subjects (64.0%) and included MSM in 10 subjects. The remaining 19 subjects had heterosexual relationships.

At presentation median RPR was 8 (IQR 2–64) with lower values in Pacific peoples although this did not reach statistical significance. Lumbar puncture was performed in 30 subjects and returned positive VDRL tests in 4/30 (13.3%). HIV status was documented in 30 subjects and was positive in six of those tested (20.0%). All subjects with documented MSM transmission had HIV tested. Pacific peoples were more likely to have undocumented HIV status (62.5% vs 17.2%). Of the six Pacific peoples who underwent HIV testing, none were positive. HIV status was recorded in 24 non-Pacific subjects and was positive in six (25%), all of whom were MSM.

Clinical presentation
Median presenting visual acuity was 6/12 (IQR 6/7.5–6/30). MVL was present in 10 eyes (15.1%) and SVL in 12 eyes (18.2%). Isolated anterior uveitis was the most frequent presentation occurring in 22 eyes (33.3%) with anterior and intermediate uveitis in five eyes (7.6%). Two eyes had isolated intermediate uveitis (3.0%), four eyes had intermediate and posterior uveitis (6.1%). Panuveitis was the second most frequent presentation in 16 eyes (24.2%) and 10 eyes had isolated posterior uveitis or disc swelling (15.2%). In eight eyes there was no active inflammation, only optic nerve atrophy (12.1%).

There were notable differences between the clinical presentation of older Pacific peoples and others (Table 2). Older Pacific peoples (born before 1960) were less likely to have posterior uveitis (p=0.033) and less likely to have optic nerve swelling at presentation (p=0.014).

The Islands from which the Pacific Island subjects originated were Samoa (70%), Niue (18%), Tonga (6%) and the Cook Islands (6%).

Treatment
Forty-one subjects (91.1%) received treatment for syphilis. Treatment was intravenous (IV) in 32 subjects, and not
documented (performed at another centre) in five subjects. Four subjects received intramuscular (IM) penicillin prior to presentation with eye symptoms and declined further IV therapy, despite guideline recommendations for IV treatment. Four subjects declined any treatment. The duration of treatment in those receiving IV therapy was 10 days in 21 subjects and 14 days in 11 subjects. Inflammation resolved in 37 subjects (82.2%) following treatment, was chronic (persisting for ≥ three months) in six subjects (13.3%) and was unknown in two subjects who left the country following diagnosis. In those that did resolve, five subjects (13.5%) had recurrence of inflammation. Chronic inflammation and recurrent disease did not significantly differ between the older Pacific peoples group and others. Median visual acuity at the last follow up visit was 6/7.5 (IQR 6/6–6/12). At last follow up, 11 eyes (16.7%) had MVL and four eyes (6.0%) SVL. Complications of inflammation included: glaucoma seven eyes (10.6%), epiretinal membrane five eyes (7.6%), cystoid macular oedema four eyes (6.0%), macular scar two eyes (3.0%), optic neuropathy six eyes (9.1%), and corneal scar in one eye (1.5%).

Clinic letters for eight of the 16 Pacific subjects (50%) made reference to yaws as a possible cause for the positive treponemal serology. Seven (87.5%) of these patients still received treatment for syphilis. The eighth patient declined treatment in New Zealand and returned to Samoa for follow up.

Table 1: Comparison between clinical presentation of Pacific peoples and non-Pacific peoples.

<table>
<thead>
<tr>
<th></th>
<th>Pacific peoples N=16 subjects</th>
<th>Non-Pacific peoples N=29 subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.7±12.9</td>
<td>51.0±13.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>9 (56.3%)</td>
<td>25 (82.6%)</td>
<td>0.021</td>
</tr>
<tr>
<td>RPR</td>
<td>Median 3 (IQR 2-8)</td>
<td>Median 32 (IQR 2-64)</td>
<td>0.004</td>
</tr>
<tr>
<td>HIV status</td>
<td>Negative 6 (37.5%)</td>
<td>Negative 18 (62.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Positive 0 (0%)</td>
<td>Positive 6 (20.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not recorded 10 (62.5%)</td>
<td>Not recorded 5 (17.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Clinical presentation.

<table>
<thead>
<tr>
<th></th>
<th>Total N=66 eyes</th>
<th>Pacific peoples born prior to 1960 N=16 eyes</th>
<th>Other N=50 eyes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.557</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>43 (65.2%)</td>
<td>11 (68.8%)</td>
<td>32 (64.0%)</td>
<td>0.722</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>29 (44.0%)</td>
<td>5 (31.3%)</td>
<td>24 (48.0%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>20 (33.3%)</td>
<td>1 (6.25%)</td>
<td>19 (32.0%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Optic nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal 45 (68.1%)</td>
<td>Normal 14 (87.5%)</td>
<td>Normal 31 (62.0%)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Atrophic 8 (12.1%)</td>
<td>Atrophic 3 (18.8%)</td>
<td>Atrophic 5 (10.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swollen 14 (21.2%)</td>
<td>Swollen 0 (0%)</td>
<td>Swollen 14 (28.0%)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion
Ocular syphilis is a rare but sight-threatening manifestation of systemic syphilis infection.\textsuperscript{4,7} There are no current data available regarding national ocular syphilis rates, however internationally the reported risk of a patient with syphilis developing ocular pathology is low, at 0.6–2.7% of total syphilis infections.\textsuperscript{6,17} Uveitis is the most common manifestation of ocular syphilis,\textsuperscript{4} accounting for 1.3% of all uveitis presentations;\textsuperscript{6} this is consistent with the results of the current study. It can be expected that rates of ocular syphilis will continue to rise in parallel with the increasing incidence of systemic infection in New Zealand and worldwide.\textsuperscript{17,18} The data demonstrated a sharp increase in incidence of presentations over the study time frame.

The 2016 National Sexually Transmitted Infection (STI) surveillance report produced by the New Zealand Ministry of Health (MoH) found that 64% of all reported syphilis cases in New Zealand occurred in Auckland City.\textsuperscript{19} In context of the nationwide syphilis epidemic, the current study is therefore likely to represent a majority of ocular syphilis cases in New Zealand over a 13-year period.

Early recognition, treatment and recovery have been reported as the strongest predictors for ophthalmological recovery (cure with no recurrence of symptoms) following a diagnosis of ocular syphilis.\textsuperscript{7,20} Treatment (91.1%) and recovery rates (82.2%) in the study population group were high. Vision impairment occurred in 22.7% of subjects.

A large focus of the current study was to examine the epidemiology of subjects presenting to the Auckland Regional Eye Clinic at Greenlane Clinical Centre with ocular syphilis and to look for differences in the clinical presentation in older Pacific peoples for whom interpretation of syphilis serology is more difficult due to possible yaws exposure. Yaws is a chronic skin infection caused by Treponema pallidum spp. pertenue. Yaws was a common infection in Pacific Island Nations until 1960, after which it was eradicated in a World Health Organization treatment campaign. The Islands from which the Pacific Island subjects in the current study originated (Samoa, Niue, Tonga and the Cook Islands), now remain free of the disease with no cases documented in recent years.\textsuperscript{14} Pacific peoples born prior to the WHO campaign who suffered from yaws may still have antibodies to the infection.\textsuperscript{12,13} These antibodies are the same as those tested for in serological testing when investigating for syphilis, therefore a positive treponemal serology could indicate present or past infection with syphilis or yaws.\textsuperscript{12} Due to the inability to distinguish between these two infections on serological testing, yaws should be considered in older Pacific peoples presenting with positive treponemal serology alongside clinical signs and symptoms. The study wanted to consider whether prior yaws infection may have resulted in older Pacific peoples returning positive treponemal serology on screening tests, and therefore receiving a misdiagnosis of syphilis as a cause of their ocular pathology. It is the first study of its kind to describe the nature of presumed ocular syphilis presentations, treatment and outcomes in the Auckland Pacific Island population group.

With a lack of previous national or regional ocular syphilis data, the current study epidemiology data has been compared to that described in the National STI surveillance report. Syphilis ethnicity data from the surveillance report differed from that of the current study population, with New Zealand Europeans contributing the highest percentage of syphilis cases (56.3%), and Pacific peoples contributing only 7.4%, compared to 36% in the current study ocular syphilis population group. This may be confounded by the higher percentage of Pacific peoples living in Auckland (15.2%) compared to the National average (7.75%),\textsuperscript{21} however this group was still over-represented in our data. The overrepresentation could reflect potential misdiagnoses of ocular syphilis in patients who had been infected with yaws earlier in life. This was considered in clinic letters for 50% of Pacific subjects, with comments made regarding the possibility of yaws being responsible for positive treponemal serology. As chronic inflammation and disease recurrence did not significantly differ between the older Pacific peoples group and others, it is difficult to comment as to whether possible misdiagnoses resulted in worse outcomes for this group. The mean age of the current study population (56.2 years) was higher
than that reported in the surveillance report (36.5 years). Gender profiles also differed, with the MoH reporting majority male patients (90.2%) compared to 75.5% in the current study.

The current study identified that older Pacific peoples (born before 1960) had lower RPR titres and presented significantly less frequently with posterior uveitis (6.25% vs 32%, p<0.033) and optic nerve swelling (0% vs 28.0% eyes p=0.014). They most commonly presented with an isolated anterior uveitis (75.0%). It is observed that RPR titers correlate with disease activity and therefore worth considering whether the lower RPR titres represent a prior yaws infection or latent syphilis. If so, both the titre and the presentation differences support the idea that positive syphilis serology in older Pacific peoples with ocular inflammation should be considered a potential red herring. This is supported further by research from Auckland colleagues, who demonstrated that idiopathic anterior uveitis is a much more likely cause of uveitis in an Auckland Pacific Island population when compared to syphilis (30.4% idiopathic vs 3.0% syphilis). Additionally, the mean age and gender profile of the non-Pacific peoples group were closer to those of the syphilis population group published in the national surveillance report.

Despite the above findings, as there is no way to clinically distinguish uveitis caused by syphilis compared to non-syphilitic causes, our current policy remains to treat all cases as if they were definite syphilitic infections. This is due to the potential sight-threatening complications that can arise from untreated syphilitic uveitis as well as potential burden of systemic disease. While yaws has been eradicated in Samoa, Niuea, Tonga and the Cook Islands, it remains endemic in other parts of the pacific, including Papua New Guinea, Solomon Islands and Vanuatu, in addition to parts of Indonesia and East Timor. The above findings may therefore be relevant to patients born after 1960 who have resided in these parts of the world.

An interesting and unexpected result of the current study was the poor documentation of HIV status in Pacific peoples compared to others (undocumented in 62.5% vs 17.2%). It is unclear whether this is related to poor documentation or unconscious bias of the medical professionals ordering the tests, or due to higher suspicion of yaws in these patients and therefore incomplete syphilis work up. We endorse that all patients with suspected syphilis receive a complete set of work-up investigations, including HIV status, even in cases of suspected yaws.

Limitations of the current study include the small study size and low statistical power, however with a rare pathology in a relatively small population group it provides a starting point for research in an area that has yet to be investigated. Further analysis of the rates of ocular syphilis as a percentage of uveitis presentations and syphilis presentations in Auckland City would provide interesting data to follow as the syphilis epidemic develops.

Conclusion

With the current resurgence of syphilis in New Zealand and abroad, physicians need to be aware of the possible ocular manifestations in patients presenting with undifferentiated ocular pathology, particularly in patients presenting with new uveitis. While syphilis and yaws are unable to be differentiated with serological testing, it is important to consider a history of yaws in Pacific peoples living in New Zealand who were born before 1960 to avoid misdiagnosis of their ocular pathology. While the results of this study have shown interesting differences in the presentation of Pacific peoples older than 60 and others with ocular inflammation, our policy remains to treat all cases as if they were definite syphilitic infections. This is due to the potential sight-threatening complications that can arise from untreated syphilitic uveitis, the potential burden of systemic disease caused by syphilis and the low morbidity of the recommended antibiotic therapy. Consultation with an infectious diseases physician is recommended in all cases where ocular syphilis is suspected for guidance of treatment and follow up. Longitudinal follow-up of both the study population group in addition to new ocular syphilis presentations in Auckland City may be warranted to analyse for further trends in the behavior and nature of ocular syphilis within the study population, which may help to guide recognition and management of this easily treatable disease.
Competing interests:
Nil.

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