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Analysis from a year of increased cases of Acanthamoeba Keratitis in a large teaching hospital in the UK

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ABSTRACT

Purpose of the study: To report an observational study of Acanthamoeba Keratitis (AK) in University Hospital Coventry & Warwickshire (UHCW), Coventry, UK and determine risk factors, outcomes as well as incidence rates.

Methods: A retrospective analysis was done of consecutive patients who were treated for AK by the corneal service at UHCW from January 2017 to January 2018. Cases were identified from 2 sources; the department of microbiology and the hospital pharmacy. Patient data was collected by 3 of the authors using both paper and electronic medical records. Information was also gathered over the telephone using a predefined questionnaire. The primary endpoint used for assessing duration of disease was time to resolution after the initial diagnosis.

Results: 9 eyes were identified over the 12-month period, a drastic increase from previous years. All were contact lens (CL) wearers and 3 used daily disposable CL's. 8 out of 9 patients had an improvement in best corrected visual acuity (BCVA) which was consistent with their baseline levels pre-infection. The average length of treatment was 107.25 days for the 8 resolved cases. 1 case is still having ongoing treatment. No case has required surgical treatment. Several patients admitted to exposing their CL to unsterile water either via swimming, showering or tap water. All patients had purchased their lenses from contact lens practitioners.

Conclusion: Overall, our study shows excellent outcomes. Almost all patients had resolution of symptoms with medical treatment and an improvement in visual acuity. Several contributing factors have aided us in achieving this including early diagnosis, a robust treatment protocol and diagnostic modalities such as Polymer Chain Reaction (PCR) and Confocal Microscopy (CFM). However, the increased incidence compared to previous years is a worrying trend and there will be an ongoing analysis looking at patterns of incidence in the future.

1. Introduction

Acanthamoeba Keratitis (AK) is a relatively uncommon but sight-threatening infection of the cornea [1]. Historically, the strongest risk factor for AK has been contact lens (CL) wear though AK can still occur in non-CL wearers.

In recent literature, AK outbreaks have been reported in several countries, including: USA [2–4], Canada [5], Australia [6], Singapore [7] and New Zealand [8]. Conversely, some studies have also shown relatively low numbers of AK [9–11]. This variability in incidence rates is thought to be due to a spectrum of factors concerning CL use including hygiene practices, exposure to water (swimming, showering), amoebicidal efficacy of CL solutions (with solutions withdrawn previously due to insufficient effectiveness), availability of diagnostic techniques and the quality of domestic water supply [1,12]. For example, Kilvington et al [13] reported that in 27 culture proven cases of AK, free-living amoebae were isolated from the water supply in 24 out of 27 of the homes of these patients. However, only six of the 24 isolates in the water supply matched the acanthamoeba grown on the corneal culture. The same paper states that at time of publication in 2004, AK in the UK was 15 times more common than in the USA and seven times more common than in Holland.

In the UK, there have been numerous publications on the subject of AK but limited studies examining prevalence of the condition in different regions of the country. One was published in 2012, where 19 new cases were observed over a five-year period (2007–2012) in Bristol [32]. Another was published in 2014, where 16 cases were identified over a 16-month period (2011–2012) in Manchester [14]. Very recently, a comprehensive paper by Carnt et al [15] from the Moorfields group also suggested a three-fold increased incidence in AK between periods 2004–2009 as compared to 2010 onwards. These are worrying findings and would suggest a continuing epidemic on the background of

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what has been established as a largely preventable disease. Nevertheless whilst the major centres have reported their findings, there is still insufficient data to identify potential disease hotspots that may be skewing national rates of AK incidence.

There is an increased awareness of AK within the community, with optometrists now much more sensitive to possible cases of acanthamoeba and lower thresholds for diagnostic measures. In the last decade there has been an increase in the number of optometrists in our region seeing acute patients in both the hospital and community setting. Many anterior segment presentations are initially seen by trained acute hospital optometrists in our department. This in turn has led to more patients being referred urgently to our eye casualty for findings suspicious of acanthamoeba. Elsewhere the majority of patients with suspected AK initially attend eye casualty or the local emergency department with eye pain, red eye or reduced vision; although vigilance in these settings has also enabled accurate diagnosis. Additionally, access to diagnostic modalities such as PCR has become more widely available and this will potentially aid the recognition of AK cases which would otherwise be missed. This awareness is paramount as the number of contact lens wearers in the UK has increased steadily to 4.2 million in 2016 [16].

Our study took place in University Hospitals Coventry& Warwickshire which is a large NHS hospital within the Coventry and Warwickshire region serving a substantial population. The Ophthalmology department has a busy eye casualty unit serving the region and is a tertiary referral centre for neighbouring ophthalmic units and beyond.

This study evaluates incidence, risk factors and final visual outcomes of AK patients over a 12-month period and demonstrates an unusual, sudden increase in incidence against previous yearly audits of AK in our department. It also adds to the published literature of AK within the UK, which is currently limited to the more recognised major ophthalmic units within the country. For balance, reporting these unusual findings would also help determine whether this is the start of a pattern of increased incidence of AK within our unit and elsewhere.

2. Methods

A retrospective analysis was done of consecutive patients who were treated for AK by the corneal service at UHCW during a 12-month period from January 2017 to January 2018. AK patients were identified from two sources; the department of microbiology and the hospital pharmacy. The hospital pharmacy database identified patients who had been prescribed polyhexamethylene (PHMB) 0.02%, chlorhexidine 0.02% or propamidine (Brolene) 0.1% during the study period. The department of microbiology database provided documentation on patients who had a positive culture for acanthamoeba from corneal scrapes as well as patients with positive PCR results. This data was correlated with AK patients seen in corneal clinic for urgent opinion.

Cultures were performed by applying the specimen centrally onto a 90 mm 1.5% non-nutrient agar plate which was covered with a lawn (100 μL) of a 24-hour old culture of non-mucous bacteria (Escherichia Coli). The plates were then sealed with a parafilm, incubated at 30 degrees Celsius and screened daily for amoebae. PCR, collected on a dry swab abraded over the area of suspicion on the cornea, was performed by standard laboratory techniques.

Patient data was collected by three of the authors using both paper and electronic medical records. Information was also gathered over the telephone using a predefined questionnaire. This included information on: age, gender, duration of symptoms before presentation, time delay between presentation and diagnosis, identifiable risk factors, BCVA at both presentation and follow-up, medical treatment, surgical interventions and complications (Table 1). Contact lens wear details were also taken at this stage. Visual acuity (VA) was recorded using a Snellen chart and converted logarithm of minimal angle resolution (logMAR) units. For consistency, the logMAR units have been converted to Snellen using a conversion table [18]. The primary endpoint used for assessing duration of disease was time to resolution after the initial diagnosis. For the purposes of the study, resolution was defined as the point where cessation of treatment occurred. However, remission from AK was achieved when there was no recurrence of AK 2 months post-cessation of treatment.

Table 1
Patient demographics and risk factors.

Feature	No. of patients (%)
Demographics	
Gender	
Men	1 (11)
Women	8 (89)
Age (years)	
< 25	3 (33)
26-60	5 (56)
> 60	1 (11)
Diagnosis	
Duration of symptoms before presentation	
< 3 days	2 (22)
< 10 days	7 (78)
> 10 days	0
Number of visits needed	
To the department before diagnosis	
1	3 (33)
2	1 (11)
3	3 (33)
4	2 (22)
> 4	0
Risk factors	
CL type	
Daily disposable	3 (33)
Monthly disposable	6 (67)
Non-CL wearer	0
Additional risk factors	
Swimming in lenses	1
Showering in lenses	3
Recent foreign travel (within 4 weeks)	2
Non-sterile rinsing (tap)	2
Prolonged CL use	1
Prolonged CL wear	1
Source of CL	
Internet	0
CL practitioner	8 (100)
CL solutions	
Easyvision Multipurpose	3 (60%)
Easyvision Easypurpose	1 (20%)
Synergi	1 (20%)

Our study, including the questionnaire, was approved by the UHCW Research & Development department. Informed consent was sought for each patient prior to commencement of survey. Each patient was informed of the purpose of the study and the questions to be asked. No patient identifiable information was used for data collection.

3. Results

Figs. 1 and 2 show a comparison between previously observed AK incidence in UHCW and the time-period that is being evaluated. Overall, there is an average incidence of 2.29 cases from 2010 − 2016. In comparison, 2017 has had an incidence of 9 cases with a particular emphasis on the 5-month period between September 2017 to January 2018 where 8 new cases were confirmed. One patient was excluded due to a false positive PCR result. Table 1 shows demographic data for all patients identified. 9 patients were diagnosed with AK over the course of the study period. Average age observed was 33.6 years (range: 22–61 years). The male:female ratio was 1:8. All patients presented within 10 days after the onset of symptoms with no delay in diagnosis in roughly one third of the patients (33%, n = 3).

Nine eyes were identified with predominantly left laterality (89%, n = 8). All cases were CL wearers. Several patients admitted to exposing their CL to unsterile water either via swimming (11%, n = 1),

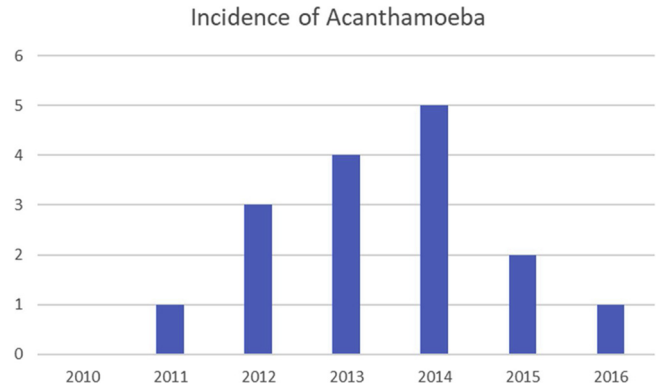

Fig. 1. Incidence of acanthamoeba from 2010 – 2016.

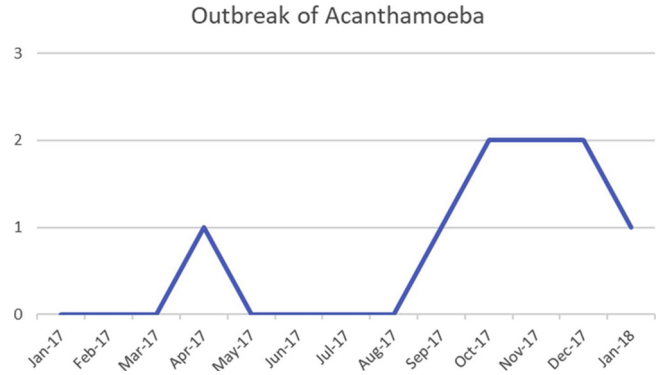

Fig. 2. Incidence of acanthamoeba during the study period; including the major increase in incidence from September 2017 – January 2018.

showering (33%, n = 3) or tap water (22%, n = 2). All patients had purchased their lenses from CL practitioners and no patients had purchased lenses from the internet. Three out of nine patients used daily disposable lenses. The average length of wear for CL users was calculated to 9.38 ± 5.07 h per day. Only 1 patient admitted to wearing lenses for longer than 16 h at a time. Data on CL solutions was available for 5 out of 6 of the monthly CL users. 60% (n = 3) of these patients used Easyvision Multipurpose solution. Easyvision multipurpose solution contains Polyaminipropyl Biguanide 0.00013%, hyaluran, sulfobetaine, poloxamine, boric acid, sodium borate, edetate disodium, sodium chloride, and polyquaternium 0.0001%. Data on source of CL's, CL solutions, CL practitioners and average length of wear was not available for one patient as they were not contactable.

4. Diagnosis

Five out of nine patients (56%) were diagnosed by epithelial culture of acanthamoeba on non-nutrient agar plates. Four out of nine patients (44%) had PCR positive acanthamoeba; one patient was positive for both PCR as well as epithelial culture. One patient did not have a positive plate/PCR result but had a clinical diagnosis of AK and responded to treatment. Confocal microscopy was used in eight out of nine patients (89%) overall and in three out of nine patients to aid diagnosis on initial presentation.

5. Treatment and outcomes

Eight out of nine patients had an improvement in BCVA which was consistent with their baseline VA pre-infection. Pre-infection VA was determined by the visual acuity recorded in the patient's last local optician appointment. The average length of treatment was 107.25 days for the eight resolved cases. Case number 1 is still having on-going

Table 2
Treatment regimes, treatment length and visual outcomes.

Case #	Affected Eye	VA pre-treatment	VA at 1 week	VA at last follow-up	Treatment	Treatment start	Treatment End	Side effects of treatment	Need for steroids	Need for fluconazole	Need for surgery	Days
1	Left	R 6/9.5, L 6/15	R 6/9.5 L 6/7.5	R 6/15, L 6/24	1 + 3	16.10.17	Ongoing	Severe lid erythema with oedema	Yes	Yes	No	Ongoing
2	Left	R 6/9, L 6/9	R 6/7.5, L6/24	R 6/6, L 6/6	2 + 3	2.5.17	1.8.17	N	No	No	No	91
3	Left	R 6/5, L PL only	R 6/4, L 6/15	R 6/7.5, L 6/7.5	1 + 2 + 3	4.10.17	4.1.18	N	Yes	No	No	93
4	Left	R 6/7.5, L HM	R 6/7.5, L 6/30	R 6/6, L 6/7.5	1 + 3 + 4	1.11.17	13.12.17	N	No	No	No	33
5	Left	R 6/4, L 6/15	R 6/5, L 6/19	R 6/5, L 6/5	1 + 3	28.11.17	29.3.18	N	No	No	No	149
6	Left	R 6/9, L 6/9	R 6/5, L 6/15	R 6/5, L 6/5	1 + 3	7.12.12	25.3.18	N	No	No	No	104
7	Left	R 6/7.5, L 6/19	R 6/7.5, L 6/24	R 6/7.5, L 6/7.5	1 + 2	4.1.18	12.7.18	Lid erythema with oedema	No	No	No	189
8	Left	R 6/5, L 6/7.5	R 6/5, L 6/12	R 6/5, L 6/5	1 + 3	21.9.17	15.11.17	N	No	No	No	56
9	Right	R 6/19, L 6/6	R 6/12, L 6/7.5	R 6/6, L 6/6	1 + 3	8.12.17	29.4.18	N	No	No	No	143

1 = PHMB 0.02%.
2 = Chlorhexidine 0.02%.
3 = Brolene 0.1%.
4 = Hexamidine 0.1%.
L = Left.
R = Right.
PL = Perception of light.
HM = Hand movements.

treatment and has had several fluctuations in their VA as highlighted in Table 2. This was despite prompt diagnosis and treatment by a corneal consultant on their first visit to eye casualty. The patient suffered a loss of VA despite optimal treatment which highlights the potentially devastating effects of AK. Two patients also reported medication-related erythema/swelling of the eyelids. Both were likely due to a chlorhexidine allergy as the symptoms presented soon after commencing treatment and resolved when chlorhexidine was switched to an alternative medication. No other adverse effects were reported. One patient required steroid minim eye drops as adjunct therapy and one patient required oral fluconazole. None of the patients so far have required surgical intervention.

6. Discussion

There has been an increase in the incidence of acanthamoeba in UHCW in 2017 as compared to previous years. All cases were associated with CL wear. Medical management has led to favourable outcomes in all resolved cases with no surgical intervention required thus far. As one patient is still having on-going therapy, the average treatment length overall is increasing with the longest case receiving treatment for 12 months so far. Treatment needs to be carefully tailored for each patient due to the prolonged and variable nature of the disease process. Preferred initial treatment is dual therapy with chlorhexidine 0.02% and PHMB 0.02% hourly in the affected eye (day and night) for the first 72 h at our institution. This is reduced to hourly during the day and then extended to two-hourly based on clinical improvement. The choice of dual therapy with chlorhexidine is due to its known efficacy against both trophozoites and cysts [12], whilst PHMB and Brolene have variable efficacy against cysts. There is some flexibility in treatment, however all patients received the same initial drops upon confirmation of the diagnosis or when there was strong clinical suspicion of AK. The only reason to alter this regime would be intolerance to drops or poor response. The avoidance of steroids also minimised the risk of trophozoites entering their cystic phase, however, steroids would be considered if there was evidence of limbal infiltrates or a strong anterior segment reaction.

Chlorhexidine did cause an allergic reaction (delayed and acute) in two patients requiring cessation and treatment with alternative medications. Brolene 0.1% was used as an alternative in such instances. Where there was poor response, oral fluconazole was considered. Furthermore, two patients developed raised intraocular pressure presumably from the inflammatory reaction. Timolol 0.25% preservative free was the preferred drop in such cases (unless there was a history of allergy/asthma) due to documented anti-acanthamoeba properties [17]. When the treatment course for AK was ending, eye drops were initially tapered down to BD then finally stopped with a view to review the patients in clinic two weeks after cessation of treatment. Patients remained under review for at least eight weeks after the treatment course ended to ensure no recurrence developed. Steroids were avoided if possible. Case number 1 was the only exception to this and required topical steroids due to significant limbal infiltrates developing during treatment. The acanthamoeba treatment was continued during this period. This patient was also started on oral fluconazole.

Surprisingly, eight out of nine of our patients (89%, n = 8) developed AK in the left eye. We postulate that this may be associated with the laterality of which eye the patient puts the lens into first, or perhaps whether the patient is right or left handed. However, this phenomenon was not analysed in our study and further investigations are required.

We have reviewed the literature concerning outbreaks of AK in the UK [14] and other countries such as the USA [2,4], Canada [5] and Singapore [7], which have observed similar numbers of AK cases as our study. Historically, these outbreaks have been associated with AMOCMP solution. This phenomenon was first observed by the University of Illinois in Chicago [2] and reported to the Centres for Disease Control and Prevention (CDC). The CDC's conclusion was that AMOCMP solution had insufficient anti-amoebicidal activity and this led to a voluntary recall of the product in 2007 [19,20]. More recently, both studies done in the UK [32,14] report an association with one of the main high street optometrist's All in One Multipurpose Solution and attribute the risk to low levels of PHMB in the product. Our study found three out of five monthly CL wearers (60%) to be using Easyvision Multipurpose Solution; a similar percentage to the other two studies from the UK [32,14]. Though this may indicate an association between this CL solution and AK, the sample size is too low to draw any definitive conclusions. This association may simply be due to the increased use of the solution amongst the CL user population as it is sold through a main high street supplier.

One concern from the Manchester trial [14] was that the anti-amoebicidal efficacy of CL solutions needed further scrutiny and a basic standard needed to be enforced. The CDC also stated "premarket standardized testing of contact lens solutions for activity against acanthamoeba spp. is warranted" after their study and subsequent recall of AMOCMP solution [20]. Thankfully, a protocol is now being introduced by the FDA that can effectively evaluate the efficacy of CL solutions against acanthamoeba trophozoites as of 2018 [21]. This method involves generating acanthamoeba cysts which are then soaked in CL solutions for the suggested manufacturer time. The amount of surviving acanthamoeba trophozoites are then counted. The FDA state that this is a well-controlled and reproducible procedure which will hopefully alleviate concerns about future CL solutions as they become introduced [21].

Our results reflect those from previous studies which show that a higher percentage of AK cases are associated with CL wear with numbers ranging from 94.7%–100% [12,32]. This association with CL wear is primarily observed in developed countries. In developing countries, the majority of AK cases occur in non-CL wearers. A large-scale trial conducted by Lalitha et al in South India showed that only three out of their 372 A K cases were CL wearers. Other risk factors which predispose to corneal trauma were more prevalent in these areas. These include exposure to contaminated water sources, extended agricultural harvests and severe windy seasons [22].

Daily disposable contact lens (DDCL) use is thought to reduce the risk of AK developing due to the nature of its short-term use [20]. No DDCL users were reported in the Brisbane study [6] or Chew et al's series of 59 patients [24] so it was surprising to find that three of nine (33%) CL wearers from our study reported using daily disposable contact lenses. This is similar to Lee et al [10] and Yamazoe et al's [25] studies which included five out of 34 DDCL users (14.7%) and seven out of 34 DDCL users (20.5%) respectively. From these findings, it is important to note that although using DDCL's may reduce the risk of contracting AK, it does not absolve the individual from the disease completely; particularly if the individual is misusing the lens.

One reason for our high incidence rates may be due to the availability of PCR at our institute. We noticed that studies that have reported lower rates of AK [9–11,25] did not have PCR available and therefore may be underestimating the disease burden. Several studies have suggested PCR is far more sensitive in detecting acanthamoeba than microscopic examination or culture alone [26,27]. It is also particularly sensitive in situations where large volume samples are involved as these usually have a demonstratable dilutional effect; such specimens may be subject to poor smear and culture results [28].

We also have confocal microscopy (CFM) imaging available at our institute. This diagnostic modality was not available within our department but within another regional ophthalmic unit, so referrals had to be made accordingly. For this reason, not all patients had confocal microscopy. In patients with uncertain diagnoses, or those who had prolonged treatment and/or poor initial response, a confocal was urgently requested. Similarly to PCR, we noticed that studies with a lower incidence of AK [11,10,25] did not use CFM as an imaging modality whilst studies with higher incidence [4] did use CFM. Using both CFM and PCR as diagnostic modalities may have increased the number of

cases identified in our study. Using CFM as an aid is invaluable as reported by Tu et al [29]. CFM was compared to superficial corneal smears/cultures and the imaging was analysed against a microbiological standard. The authors showed that CFM had a sensitivity of 90.6% and specificity of 100% for 53 patients who had clinical characteristics of AK. This high sensitivity and specificity is attributed to the fact that CFM is a user-dependent diagnostic tool, in the hands of very experienced users who have appropriate and relevant clinical information. On the other hand, smear techniques were only positive in 30 out of 41 cases (73% sensitivity) and cultures were positive in 23 out of 42 cases (52% sensitivity) [29]. Other studies have shown similar results with the sensitivity and specificity of CFM ranging from 94%–100% and 84%–100% respectively [30,31].

Another reason for the high incidence rates reported in our study may be the cleanliness of the water supply in the UK. This hypothesis stems from a paper by Kilvington [13] which states that the incidence of AK is 15 times higher in the UK than in the USA due to higher levels of amoebae in municipal water supplies. Kilvington sampled fresh water tap outlets from the homes of 27 patients with AK and free-living amoebae were found in 89% of the samples [13]. Radford et al [33] also suggested that there is an increased risk of acanthamoeba associated with 'hard' water in the UK. Nevertheless, unless the quality of the water supply has changed acutely, it would not explain the sudden increase in incidence we observed. It does, however, reinforce the need to educate our patients about the risks associated with water coming into contact with their lenses.

Overall, our observational study shows excellent outcomes for AK in a department which has a busy regional eye casualty unit. Almost all patients had resolution of symptoms with medical treatment and an improvement in visual acuity. Several contributing factors have aided us in achieving this. Firstly, several of our AK patients were diagnosed early with 33% (n = 3) being diagnosed upon the first visit to eye casualty. Secondly, the ophthalmology department at UHCW receives regular corneal training which highlights AK as a potential diagnosis; diagnosing acanthamoeba can be a difficult process so it is important to keep a high index of suspicion. AK is also included as part of the diagnostic protocol for CL related keratitis which aids clinicians in their decision making. In addition, we have lead optometrists as well as a corneal consultant in our eye casualty department which leads to such patients receiving senior review fairly early in the treatment process. Of course, the availability of diagnostic modalities such as PCR and CFM also aid with early diagnosis and monitoring. Treatment is also prolonged and intensive; in several cases, treatment was continued if the patient had signs of AK on CFM despite resolution of symptoms.

Since this study, we have noticed only two further confirmed cases of AK in the following 8 months. Both have responded very well to treatment and have not required further surgical intervention. This would highlight the fundamental variability one sees in the presentation of this potentially devastating disease. However, this is on a background of an increasing numbers of CL wearers. The increased incidence compared to previous years is a worrying trend and there will be an ongoing analysis looking at patterns of incidence in the future.

7. Limitations

This was a single centre, non-comparative study with a relatively small sample size. Patients were also asked to report retrospectively which, of course, can lead to recall bias. Observer bias may have also been present as 3 of the authors participated in data collection.

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Declarations of interest

None.

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