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Limited Utility of Keratic Precipitate Morphology as an Indicator of Underlying Diagnosis in Ocular Inflammation

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ABSTRACT

Objectives: We aimed to establish the degree of consensus among clinicians on descriptors of KP morphology.

Methods: A web-based exercise in which respondents associated KP descriptors, as identified through a scoping review of the published literature, to images from different disorders. Inter-observer agreement was assessed using the Krippendorff kappa alpha metric.

Results: Of the 76 descriptive terms identified by the scoping review, the most used included “mutton-fat” ($n = 93$ articles, 36%), “fine/dust” ($n = 76$, 29%), “stellate” ($n = 40$, 15%), “large” ($n = 33$, 12%), and “medium” ($n = 33$, 12%). The survey of specialists ($n = 26$) identified inter-observer agreement for these descriptors to be poor (“stellate,” kappa: 0.15, 95% confidence interval 0.13–0.17), limited (“medium”: 0.27, 95% CI 0.25–0.29; “dust/fine”: 0.36, 95% CI 0.34–0.37), or moderate (“mutton fat”: 0.40, 95% CI 0.36–0.43; “large”: 0.43, 95% CI 0.39–0.46).

Conclusion: The clinical utility of KP morphology as an indicator of disease classification is limited by low inter-observer agreement.

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Uveitis is a significant cause of blindness.¹ A descriptive term rather than a diagnosis, uveitis can be associated with a range of diverse conditions united by the manifestation of inflammatory change.² The heterogeneity and multiplicity of these associated conditions may be an obstacle to the prompt diagnosis of potential underlying disorders in patients presenting with ocular inflammation.

Keratic precipitates (KPs), seen on slit-lamp biomicroscopic ophthalmic examination as aggregated deposits of inflammatory cells on the corneal endothelium, are a marker of the presence of intraocular inflammatory material.^{2,3} Leukocyte populations in aqueous humour can differ by uveitis aetiology, with, for example, HLA-B27 uveitis being characterized by an accumulation of lymphocytes, while neutrophils are uncommon in samples from eyes with viral uveitis.⁴ KP morphology, as an indicator of leukocyte population, has been used as an informative adjunct for decision-making on potential disease classification, and through that a facilitator of diagnosis.^{5,6} This is particularly important in the paediatric population, for whom uveitis may be the first presenting sign of disorders, such as Juvenile Idiopathic Arthritis, Sarcoidosis, and Behçet disease.^{1,2} The


extraocular phenotype may not emerge for years after uveitis onset,^{1,2} preventing the elicitation of suggestive systemic symptoms or signs at presentation with ocular disease.

Multicenter observational studies, which aim to describe disease natural history and the determinants of outcome across and within complex inflammatory conditions, are reliant on harmonized phenotype and disease taxonomy.⁷ Within the recent Standardization of Uveitis Nomenclature (SUN) group work on disease classification, KP morphology formed part of the classification criteria for specific disorders, with stellate KP included in the criteria for Fuchs Uveitis Syndrome.⁸ Conversely, the work of the SUN group, which relied on retrospectively collected clinical data, also highlighted the apparent variability of KP morphology within the different autoimmune, autoinflammatory, and infective uveitides (Table 1).

Given the absence of an agreed international classification system for KP morphology, we sought to define the degree of consensus around, and inter-observer agreement of the most used descriptors, within the context of a national prospective inception cohort study of childhood onset uveitis.

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Table 1. Distribution of different KP morphologies within different uveitis populations. Derived from the standardization of uveitis nomenclature working group⁷

Underlying disorder	Keratic precipitate morphology (% of individuals)					
	None	Fine	Round	Stellate	Mutton Fat	Other
Sarcoidosis, <i>n</i> = 278	52	18	6	0	23	0
Tubercular, <i>n</i> = 277	88	5	3	0	4	0
JIA, <i>n</i> = 202	68	22	7	0	1	0
Behcet, <i>n</i> = 194	84	24	2	0	0	0
Syphilis, <i>n</i> = 187	34	39	14	3	10	0
ARN, <i>n</i> = 186	19	27	18	6	29	1
HLA-B27, <i>n</i> = 184	0	41	54	5	0	0
Fuchs, <i>n</i> = 146	1	25	7	68	0	0
VZV AU, <i>n</i> = 123	30	42	11	3	13	1
Intermediate, <i>n</i> = 114	82	13	3	0	1	1
Sympathetic ophthalmia, <i>n</i> = 110	59	23	8	0	10	0
VKH, <i>n</i> = 103	53	28	3	1	15	0
HSV AU, <i>n</i> = 101	26	24	18	5	26	2
CMV, <i>n</i> = 89	12	27	33	8	14	5

ARN: acute retinal necrosis; AU: anterior uveitis; CMV: cytomegalovirus; HLA-B27: human leukocyte antigen B27; HSV: herpes simplex virus; JIA: juvenile idiopathic arthritis; VKH: Vogt–Koyanagi–Harada disease; VZV: varicella zoster virus.

Materials and methods

We undertook a cross-sectional consensus survey study informed by a review of the evidence base.

Scoping review

To identify the terms used to describe keratic precipitate morphology, we conducted a review of available literature following PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines for scoping reviews.⁹ We searched for relevant articles published between database inception and 19 November 2020 (inclusive) in the electronic databases MEDLINE and PubMed. In the absence of a MESH term for keratic precipitate,¹⁰ we used free search terms to develop the search strategy. The following search term was used: “keratic precipitates.” These search terms were limited to “Human.” Eligible studies were those which used descriptive terms for keratic precipitate morphology directly observed through slit-lamp examination by the investigators in human eyes with intraocular inflammation. All study types were eligible. We excluded articles not available in English. Two independent reviewers (ALS and OC) screened the title and abstract of all publications identified by the literature search. Any discrepancies were resolved by consensus after re-reviewing the article. Microsoft Excel was used to manage the search output. Reviewers (OC, ALS) extracted from each eligible article the following: the date of publications, the KP descriptor used by the investigators, and the associated uveitis diagnosis.

Survey

We developed an image-based survey consisting of 29 slit-lamp images of KPs from different disorders self-administered individually and independently by survey participants. Survey content development was aimed at representation of a range of disorders ensuring inclusion of child and adult cases, and infectious and non-infectious diseases (details of image sources available in

supplementary table S1). Survey participants were presented with each image and asked to indicate the types of precipitates present in the image by selecting one, or more, descriptive term. Terms which were used as KP descriptors in at least 10% of articles within the scoping review were offered as potential descriptors within the survey. Participants comprised members of the UK’s Paediatric Ocular Inflammation Group (POIG), which was established in 2019 in order to develop an evidence base to support clinical practice and health policy for children, young people, and adults with childhood onset ocular inflammatory diseases.^{11,12} Eligible POIG members who were those consultant (“attending”) ophthalmologists who had been identified as relatively high volume practitioners through their role as collaborators on the Uveitis in childhood prospective national cohort study (UNICORN) study.¹³ Members received an email invitation to take part in the survey, followed by a reminder email 4 weeks later.

This work, as part of the UNICORN study, was approved by the London-Bloomsbury Research Ethics Committee (REC reference 20/LO/0661). Formal written consent was not taken, as there was no research enrolment, and activities were limited to a research survey deployed via an online survey platform.

Analyses

Descriptive analysis of scoping review results was undertaken to report the most used descriptive terms, with subgroup analysis to report frequency of use by diagnosis and year of publication. Analyses of survey findings sought to describe the degree of agreement through two methods: to assess the degree of consensus for each keratic precipitate image and morphological term, an arbitrary threshold of 80% agreement was set. In addition to quantifying consensus, we also examined inter-observer agreement (i.e., reliability) using Krippendorff’s alpha coefficient, chosen for its flexibility regarding missing values, and since the

response variables, i.e., the morphological terms, were not mutually exclusive. Values were computed using the SPSS software and the KALPHA macro developed by Hayes et al.¹⁴ The interpretation of the Krippendorff's Alpha values was adapted from Landis and Koch's definitions of Fleiss' Kappa, with values less than zero reflecting poor, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect agreement.¹⁵

Results

Of the 469 articles identified from the literature search, 259 eligible articles were included for review of the descriptive morphological terms for KPs (Figure 1). Across these articles, 41 descriptive terms were identified across different disorders (Table 2). Frequency of use ranged from 93 to 1 incidence, with a total of 15 terms being used only once in the literature. The most used terms were “mutton-fat” ($n = 93$ articles, 36%), “fine” ($n = 76$, 29%), “stellate” ($n = 40$, 15%), “large” ($n = 33$, 12%), and “medium” ($n = 33$, 12%). Tracking of term use over time revealed increased use of different descriptive terms, with nine different descriptors used between 1951 and 1999, versus 41 terms used from 2000 to 2021 (Table 2). Almost half of the

identified terms (19/41, 46%) had only been in use over the preceding decade.

Survey

The terms chosen for the online survey of clinicians were “mutton fat,” “stellate,” “fine,” “medium,” and “large.” Despite the relatively high frequency of their use, terms relating to colour of KPs, specifically “pigmented” and “white,” were not selected in recognition of the variable impact across viewing platforms (different PCs, tablets, smartphones) on the colour spectrum of the presented image. Of the 32 clinicians invited to take part in the survey, we received completed responses from 26 (response rate 81%).

Three terms surpassed the arbitrary threshold of 80% mean agreement across images (Table 3): “large” (consensus threshold reached in 25/29 images), “mutton-fat” (23/29), and “stellate” (25/29). The terms “fine/dust” (12/29) and “medium” (11/29) did not reach the threshold. With regard to inter-observer agreement, the overall Krippendorff's alpha for all descriptive terms was 0.229 (95% confidence interval, CI 0.207 to 0.262), and for each term, the results showed either poor, slight, fair, or moderate inter-observer agreement (Table 3).

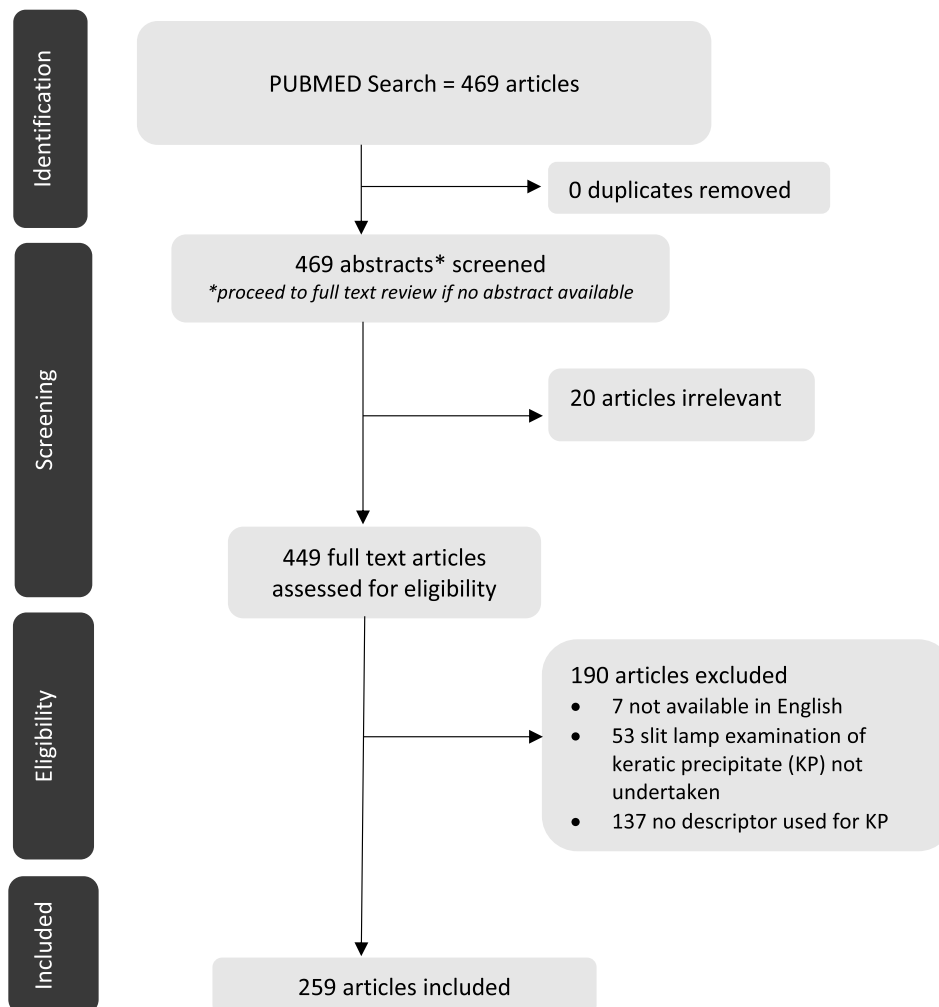


Figure 1. PRISMA flowchart of screened and included studies in scoping review.

Table 2. Frequency of use of keratic precipitate descriptors in identified articles.

Keratic precipitate descriptors	2010–2021	2000–2009	1990–1999	1980–1989	Pre-1980	Total
Mutton fat	59	17	11	2	4	93
Fine	50	3	2	4	1	60
Small	30	11	2	4	0	47
Pigmented	34	5	1	1	0	41
Stellate	27	11	1	1	0	40
Medium	26	7	0	0	0	33
Large	19	8	1	4	0	32
White	20	8	2	2	0	32
Linear	16	4	4	1	0	25
Granulomatous	23	2	0	0	0	25
Coin-shaped	20	3	0	0	0	23
Round	10	3	1	1	0	15
Dendritiform	12	2	0	0	0	14
Globular	10	2	0	0	0	12
Smooth-rounded/dome-shaped	10	2	0	0	0	12
Stippled	8	2	0	0	0	10
Non-pigmented	7	1	0	0	0	8
Cruciform	6	1	0	0	0	7
Infiltrating	5	1	0	0	0	6
Grey	4	1	0	0	0	5
Non-granulomatous	4	1	0	0	0	5
Brown	3	0	0	0	0	3
Granular	3	0	0	0	0	3
Circinate	2	0	0	0	0	2
Ink-blot	2	0	0	0	0	2
Nodular	2	0	0	0	0	2
Oval-shaped	2	0	0	0	0	2
Ring-shaped	2	0	0	0	0	2
Nummular	2	0	0	0	0	2
Spiculated	1	0	0	0	1	2
Corral	1	0	0	0	0	1
Crenated	1	0	0	0	0	1
Greasy	1	0	0	0	0	1
Reticular	1	0	0	0	0	1
Saw-tooth	1	0	0	0	0	1
Sentinel	1	0	0	0	0	1
Subclinical	1	0	0	0	0	1
Supraspinous	1	0	0	0	0	1
Thin	1	0	0	0	0	1
Tiny	1	0	0	0	0	1

Table 3. Agreement metrics for each KP morphological term.

Term	Mean agreement across images (% of respondents, range)	Krippendorff's alpha (KA)	KA 95% CI
Mutton fat	91%, 54–100%	0.39	0.36–0.43
Stellate	90%, 57–100%	0.15	0.13–0.17
Dust/fine	74%, 50–96%	0.36	0.34–0.37
Medium	72%, 50–96%	0.27	0.25–0.29
Large	91%, 52–100%	0.43	0.39–0.46
<i>Kappa result interpretation:</i>			
<i>Kappa scale</i>		<i>Kappa scale</i>	
–1 to –0.01	Poor agreement	0.41 to 0.60	Moderate
0 to 0.20	Slight	0.61 to 0.08	Substantial
0.21 to 0.40	Fair	0.81 to 1	Almost perfect

Discussion

From our scoping review, we report multiple descriptors of keratic precipitate morphology in use in the literature, particularly over the last decade. A review-informed survey of clinicians managing uveitis in children and adults identified variation in use for the most common descriptors of KP morphology. Terms such as “mutton-fat” and “large” had moderate inter-observer agreement, while the remaining terms, including descriptors such as “fine” or “stellate” had only poor or limited agreement.

This work has some limitations. By design, the review aimed to identify the articles in which clinical examination was

reported. This resulted in the inclusion of many case reports. As novelty and rarity are key determining factors for successful publication of case reports, there may be an over-representation of the rarer disorders within the scoping review, resulting in a literature database in which atypical keratic precipitate morphology dominates. The most used terms identified by the review were, however, those which are commonly used within the Standardisation of Nomenclature (SUN) literature,^{5,7} suggesting an appropriate representation and good external validity. We did not control for the viewing parameters for survey respondents, and it is possible that the magnification of the photograph differed among respondents with resultant impact on decisions on descriptors. However, keratic precipitates, when

viewed on a slit lamp, are not viewed in isolation, but instead their dimensions are judged relative to their surroundings, for example corneal diameter and curvature, and pupil size. Thus, the impact of magnification is likely to have been minimized for this clinical sign. The survey design, with the use of a representative but not exhaustive collection of images of keratic precipitates, may have resulted in insufficiently characteristic images of keratic precipitates presented to respondents. However, more recent work, again undertaken by the SUN group,^{5,7} has identified that a range of KP types may be present within individual inflammatory disorders, suggesting that a “platonic ideal” KP morphology type is uncommon, and strengthening the broader representativeness of the images used in our work. It is possible that a wider sample of clinicians may have resulted in stronger inter-observer variability, but inclusion of practitioners from different subspecialties may also have resulted in lower agreement. Our measures of agreement (Krippendorff’s alpha) were robust, as opposed to a single arbitrary threshold for percent-agreement (e.g., 80% level consensus, as used in previous studies).¹¹ Percent-agreement metrics are intuitive, simple to calculate, easy to explain, but can overinflate agreement, particularly where there is a low incidence of a specific response in a consensus exercise. This may have been the case with the “stellate” descriptor within the survey responses. Measures such as Krippendorff’s alpha correct for the element of chance agreement among raters. Uveitis is a heterogeneous disease area, and our study respondents (a mix of adult and paediatric practitioners, from high volume centres across England, Northern Ireland, Ireland, Scotland, and Wales) are a good reflection of the range of clinicians who are typically involved in multicenter inflammatory eye disease studies, undertaking collaborative work with a need for harmonized, reliable, and repeatable phenotypic classification. Our findings may benefit from comparison to those from larger populations of clinicians internationally.

Morphological analyses of KPs have been reported as helpful in determining the underlying cause of intraocular inflammation. In terms of pathophysiology, KPs can consist of polymorphonuclear cells, lymphocytes, and epithelioid cells in varying proportions, this diversity being thought to give rise to a wide range of their physical presentation.¹⁶ While KPs in the non-granulomatous uveitides tend to be described as round, and pale in colour,^{16,17} the KPs seen in granulomatous disease tend to be larger, with less defined shapes, and a “mutton fat” appearance.¹⁸ Although the correct usage of the term “granulomatous” is for the description of histopathological features seen in uveal biopsies from the eyes of patients with, for example, ocular sarcoidosis, tuberculous uveitis, or Vogt–Koyanagi–Harada,^{19–21} the description remains to facilitate clinical terminology, characterising the phenotype of the anterior segment manifestations of such disorders. The differentiation of anterior uveitis into non-granulomatous and granulomatous clinical phenotypes, as suggested by SUN,⁷ is supported by our evidence of strong inter-observer agreement around “large” and “mutton fat” as KP descriptors. This differentiation also appears to remain helpful to aid the direction of investigation.^{3,7,19–21} As the SUN group themselves suggested, however, a KP descriptor reference resource, based on a series of standardized images, is needed.⁷

Inter-observer variability is an arguably unavoidable aspect of clinical examination, appearing across clinical fields and across different examination modalities. The negative impact of this variability is diminished at patient level, where clinical signs are considered in the context of the associated history, signs and symptoms, and outcomes of investigations. At population level, however, the precision, reliability, and reproducibility of disease phenotype underpins the ability to undertake meaningful research.²² Our study demonstrates the low agreement between expert clinicians regarding the terms used to describe the morphology of KPs, other than for “large” or “mutton-fat.” Future work should aim to develop consensus-based definitions of the other morphological descriptors, with their use demonstrating strong inter-observer (consistency of use between different observers) and intra-observer (consistency of use by a single observer) reliability. An imaging-assisted classification system, using confocal microscopy or optical coherence tomography to limit subjectivity and bring a greater degree of standardisation and repeatability, may be most appropriate, particularly as this may elicit additional features which are not appreciated on slit-lamp examination.³ Our work should support future attempts at classifying the morphological terms used to describe KPs and build towards more reliable diagnosis and management of uveitis. Until there is an international consensus on definitions for these heterogeneous clinical features, the clinical utility of KP morphology as an indicator of uveitis type, and underlying systemic or ocular diagnosis, is limited. These terms should be approached with caution by clinicians and researchers seeking to apply the existing evidence base to guide their clinical practice or to map clinical phenotypes.

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