Original Article

Iridocorneal endothelial syndrome: Evaluation of patient demographics and endothelial morphology by *in vivo* confocal microscopy in an Indian cohort

Chintan Malhotra, Natasha G Seth, Surinder S Pandav, Arun K Jain, Sushmita Kaushik, Amit Gupta, Srishti Raj, Deepika Dhingra

Purpose: To evaluate the patient demographics and morphological characteristics of corneal endothelium by *in vivo* confocal microscopy (IVCM), in patients with Iridocorneal Endothelial (ICE) Syndrome. **Methods:** In this retrospective observational series, IVCM acquired endothelial images of patients with ICE syndrome were evaluated. 'ICE cells' morphology was classified as "−" or "+" if they were larger or smaller than contralateral normal endothelium. It was correlated with patient demographics and clinical manifestations. **Results:** IVCM was performed on 41 eyes of 21 patients, with 13 males (62%) and 8 females (38%). The disease was unilateral in 19 (90.5%) and bilateral but asymmetric in two (9.5%) patients. Total ICE was seen in 91% eyes. Eighty percent patients (12 out of 15) with ICE—cells were males while 83.3% (5 out of 6) patients with ICE + cells were females. Mean age of patients with ICE- cell type and ICE + cell type was 45.8 ± 17.8 years and 40.3 ± 9.2 years respectively ($P = 0.02$). Both ICE − and ICE + eyes had similar incidence (33.3%) of corneal edema. ICE + eyes had more severe (grades 2/3) glaucoma ($n = 5/6$ eyes, 83.3%) compared to ICE − eyes ($n = 8/15$ eyes, 53.3%). **Conclusion:** A male preponderance, predilection of ICE − and + cell variants for male and female gender respectively, lack of association of the endothelial cell morphology with corneal edema, and apparent association of ICE + phenotype with more severe glaucoma occurring at a relatively younger age, are some novel findings of the present study. In the clinical setting correlation of patient demographics with these IVCM findings may help in better long-term prognostication of eyes with ICE syndrome.

Key words: Iridocorneal endothelial syndrome, Confocal microscopy, Endothelium

Iridocorneal endothelial (ICE) syndrome which includes Chandler's syndrome, Progressive Iris Atrophy (PIA), and Cogan-Reese/Iris Nevus Syndrome (INS) manifests clinically with varying combinations of corneal edema, iris atrophy, peripheral anterior synechiae (PAS), and secondary glaucoma.[1-5] Differential diagnosis includes multiple other ocular conditions presenting with one of more of these findings e.g. Fuchs' endothelial dystrophy (FED), Posterior Polymorphous Dystrophy (PPD), Reiger's syndrome and iridoschisis.

Endothelial abnormalities have been reported to be a consistent feature across the varied manifestations of ICE syndrome.[6,7] PAS, iris atrophy/nodules and glaucoma are believed to occur secondary to acquisition of epithelial-like structural and proliferative properties by endothelial cells which then migrate across the anterior surface of the iris into the angle.[2,8,9] Clinically the "hammered silver" or "beaten metal" appearance of the posterior corneal surface on specular reflection, as classically described initially for Chandlers Syndrome,[10] and later on also for PIA and INS, is however not diagnostic and may also be seen with the corneal guttata present in FED.[2,8]

Ultra-structural assessment of the endothelium by *in vivo* techniques like specular microscopy and *in vivo* confocal microscopy (IVCM), can thus play a pivotal in confirming the clinical diagnosis. Vis a vis specular microscopy, IVCM has the advantage of superior resolution and less deterioration of image quality in the presence of corneal edema or mild scarring.[11] Abnormal endothelial cells initially labeled "ICE cells" by Sherrard *et al.*,[12] have subsequently been identified on both specular and confocal microscopy by various groups.[2,5,8,9,11-18]

Shield *et al.*,[1] have reported severity of corneal involvement and presence of secondary glaucoma to be prognostic factors in cases of ICE syndrome. Similarly, Laganowski *et al.*,[19] documented the utility of specular microscopic appearance of the posterior cornea in predicting likelihood of glaucoma development. In contrast, Liu and colleagues,[16] found that specular microscopy did not reliably predict the prognosis with neither ICE grading nor endothelial cell density (ECD) correlating with corneal edema or intraocular pressure (IOP). In the background of conflicting reports in literature, the spectrum

For reprints contact: reprints@medknow.com

Department of Ophthalmology, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to: Dr. Chintan Malhotra, Room No 125, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drchintansingh@yahoo.co.in

of micro structural endothelial alterations as visualized by *in vivo* confocal microscopy (IVCM) and their clinical implications in an Indian cohort are reported in this study.

Methods

This retrospective, observational study was carried out at a tertiary care referral center in North India. It adhered to tenets of the Declaration of Helsinki and institutional ethics committee approval was obtained. Records of patients diagnosed with ICE syndrome between January 2012 and April 2017 on the basis of clinical examination and endothelial imaging by IVCM, were reviewed. Clinical diagnosis of ICE syndrome was based on the presence of at least any 2 of the following 3 main features on slit lamp biomicroscopy and gonioscopy i.e. (a) typical iris changes of holes, corectopia, atrophy or ectropion uvea, (b) PAS, and (c) abnormal corneal endothelium on specular reflection [Fig. 1a-h]. IVCM had been performed bilaterally, using the Rostock Cornea Module of the Heidelberg Retinal Tomograph (HRT) III (Heidelberg Engineering, GmBH, Dossenheim, Germany) which uses a 670 nm helium neon diode laser beam to scan the cornea in a raster pattern and achieves magnification levels up to 800 times, with axial and lateral resolutions as low as 4 μm and 1-2 μm, respectively.[20] As a routine practice, in order to facilitate acquisition of a larger number of scans in a shorter duration, the 'volume scan' option is chosen with the corneal apex being applanated first followed by the superior, nasal, inferior and temporal quadrants. On IVCM, presence of 'epitheloid like endothelial cells similar to those described previously in literature,[2,5,8,9,11-18] for ICE syndrome i.e. presence of prominent hyper reflective nuclei and loss of regularity of cellular shape and size in the clinically involved eye had been considered diagnostic of ICE syndrome in the patient records.

For this study 42 eyes of 21 patients were included, though records of endothelial evaluation on IVCM was available only for 41 eyes i.e. bilaterally in 20 patients and unilaterally in one patient, the other eye having significant corneal edema and hence precluding adequate visualization of the endothelial cells by the confocal microscope. Patient demographics (age and gender), anterior and posterior segment findings on slit lamp biomicroscopy and gonioscopy, presence/absence of corneal edema, intraocular pressure, severity of glaucoma, treatment received (medical or surgical), and follow-up duration were noted for each patient from the medical charts. Corneal edema was graded clinically on slit lamp biomicroscopy as mild (increased corneal thickness as compared to contralateral eye without presence of stromal striae/Descemets membrane folds and clearly visible iris pattern), moderate (increased corneal thickness, presence of stromal striae or Descemet's membrane folds with/without microcystic epithelial edema and visible iris pattern, albeit with some loss of finer details) and severe (increased corneal thickness, presence of bullae/subepithelial fibrosis, complete inability to visualize iris details or anterior segment). Severity of glaucoma was classified as: Grade I (mild)- IOP ≤ 21 mm Hg on topical anti glaucoma medication only; Grade II (moderate)-maintaining IOP ≤ 21 mm Hg required systemic anti glaucoma drugs and/or surgery despite being on maximal tolerable topical medication; and Grade III (severe)- the patient required > 3 topical anti glaucoma and/or systemic medication after initial surgery or needed resurgery for maintaining IOP ≤ 21 mm Hg.

Endothelial images were evaluated in accordance with the specular microscopic classification proposed by Sherrard *et al.*,[12] and labeled as "disseminated ICE," i.e. ICE cells scattered individually or in small clusters amongst an otherwise normal endothelial mosaic, "subtotal ICE" when 25–75% of the
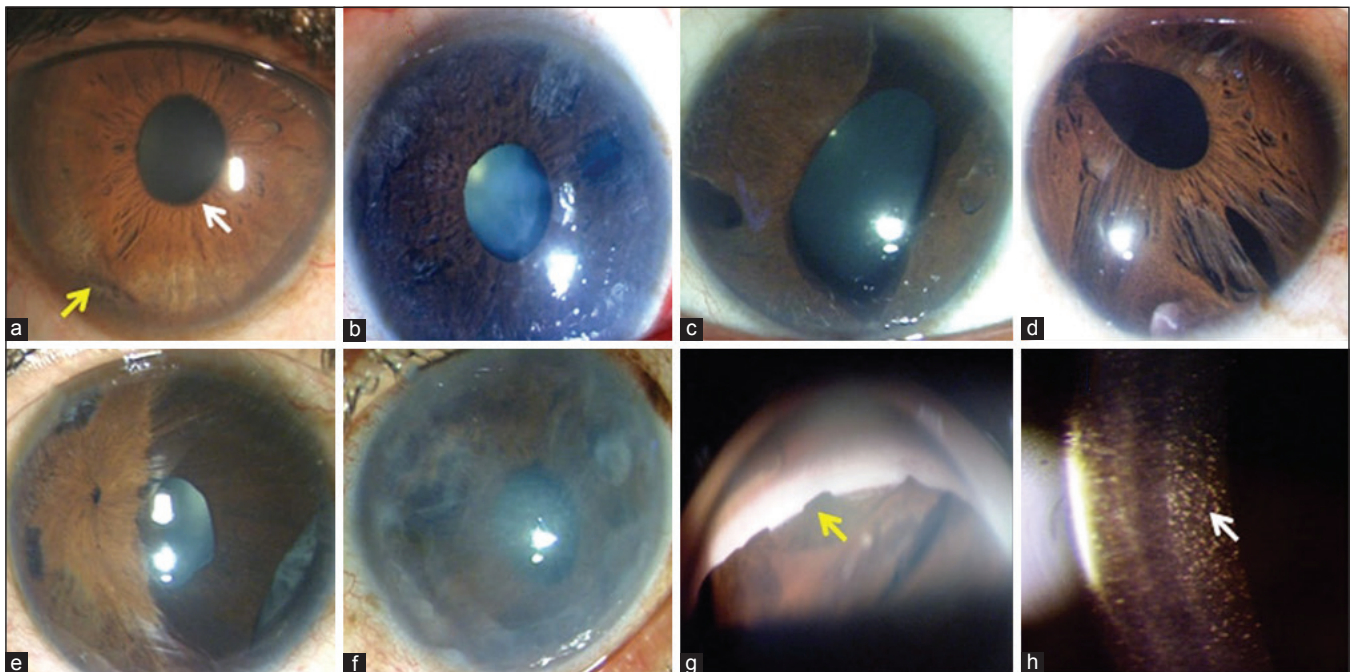
Figure 1: Representative pictures of anterior segment findings seen in patients clinically suspected to have ICE syndrome (a) small patch of iris atrophy (yellow arrow) with slight corectopia (white arrow) (b) multiple patches of iris atrophy with corectopia (c) ectropion uvea with a distorted pupil (d and e) iris atrophy, iris holes and severe corectopia (f) diffuse corneal edema with iris details visible faintly (g) broad PAS seen on gonioscopy (yellow arrow) (h) "hammered silver" appearance of endothelium seen on slit lamp biomicroscopy (white arrow)

Figure 2: Representative *in vivo* confocal microscopy images showing (a) ICE – variant of endothelial cells (large cells with widely sp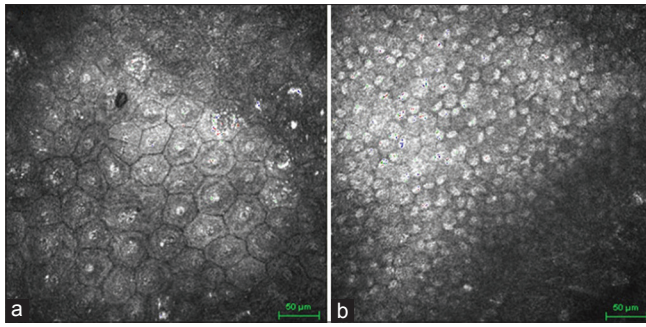aced yet centrally placed hyperreflective nuclei) (b) ICE + variant of endothelial cells (smaller cells with more tightly packed, eccentrically placed hyper reflective nuclei)

endothelial surface was occupied by the abnormal ICE cells and "total ICE" where the entire endothelium was replaced by abnormal cells. Though Sherrard *et al.*,[12] categorized only cases of subtotal ICE into the "plus"(+) or "minus" (−) variants depending on whether the ICE cells were smaller or larger respectively than the apparently normal endothelium in the same eyes, due to the majority of patients having total ICE in our cohort, we compared ICE cell size/area of the affected eye with the contralateral normal eye. Due to unavailability of a more sophisticated software which could numerically quantify cellular dimensions, this contralateral comparison was primarily made on the basis of visual inspection, aided by a caliper tool (equivalent to 50 µm) available as an overlay on the IVCM images. Thus abnormal ICE cells were labeled as "minus (−) variant" if on visual inspection they appeared larger than the endothelial cells of the contra lateral unaffected eye with widely spaced nuclei present predominantly in the center of the cells [Fig. 2a] and as "plus (+) variant" if they appeared smaller with more eccentrically located yet closely packed nuclei, in the endothelial mosaic [Fig. 2b]. ECD was evaluated for both eyes using a semi-automated software provided with the confocal microscope, wherein a rectangular area identifying the region of interest was plotted, followed by manually marking all endothelial cells completely within rectangle as well as those not completely within the rectangle but touching the left and lower borders of the rectangle. The software then computed the endothelial cell count along with the standard deviation. Only frames where at least 50 cells could be marked were selected for calculating ECD to ensure a reliable cell count. Association of the cell variant i.e. ICE + or ICE – cells with the patient demographics (age and gender), presence of corneal edema and glaucoma severity was also noted.

Statistical analysis

Analysis was conducted using IBM SPSS statistics (version 22.0, Chicago, IL, USA). The normality of quantitative data was checked by measures of Kolmogorov-Smirnov test of normality. Continuous data was expressed in the form of its mean, standard deviation (SD) and range. Gender was compared using the chi square test. The Mann-Whitney test was applied for comparison of 2 groups. All the statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$. A *P* value of < 0.05 was considered significant.
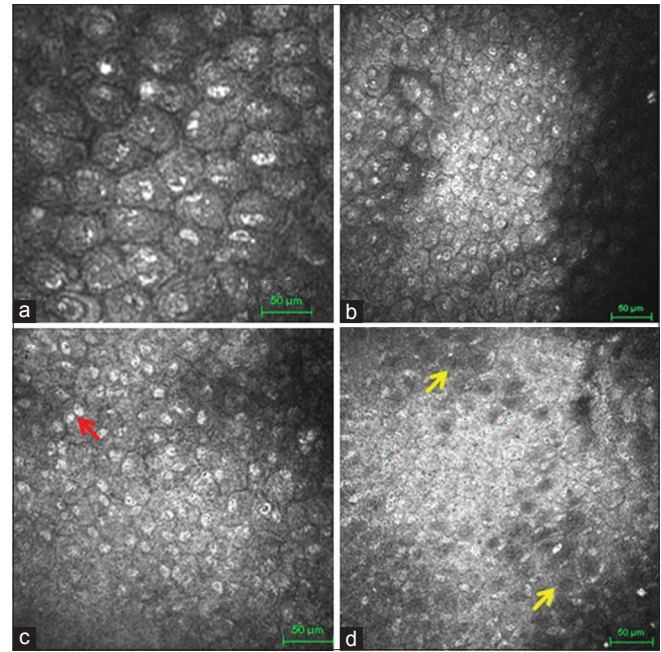

Figure 3: Representative *in vivo* confocal microscopy images showing the variable appearance of the affected endothelium amongst the study patients a and b) "Epitheloid transformation" with prominent hyper reflective nuclei (c) Doubling of nuclei within a cell (red arrow) (d) "light dark reversal" of the endothelial cells with cell bodies appearing dark and cell boundaries appearing brighter (yellow arrows)

Results

Mean age of the study cohort was 44.24 ± 15.8 years (range 8-79 years). A significant male preponderance was noted with 13 males (62%) and 8 females (38%). On endothelial evaluation with IVCM, the most prominent feature was the presence of rounded or kidney bean shaped prominent hyper reflective nuclei [Fig. 3a and b]. This was associated in varying combinations with other changes suggestive of an epitheloid/epithelial-like transformation of the endothelial cells e.g. doubling of nuclei [Fig. 3c], presence of light dark reversal [Fig. 3d] and diversity in cellular size and shape. IVCM features of "ICE" like cells were visualized in 22 of the 41 eyes examined with IVCM i.e. unilaterally in 20 patients and bilaterally in one patient. The demographic profile, relevant clinical features and IVCM findings, management and follow-up details of all patients included in the study have been outlined in Table 1.

Nineteen patients (90.5%) had unilateral involvement both clinically and on IVCM. Two patients had clinical features suggestive of bilateral and asymmetric ICE. One patient reported previously[15] had bilateral but asymmetric involvement with presence of PAS, iris atrophy, corneal edema, and glaucoma with total ICE—pattern on IVCM in one eye, while the contralateral eye had a normal anterior segment and angle, a "hammered silver" appearance of the endothelium on slit lamp biomicroscopy and disseminated ICE cells on IVCM with an otherwise well preserved endothelial mosaic. In one patient clinical and IVCM features were consistent with the diagnosis of ICE (patches of iris atropy and peripheral iridocorneal adhesions on slit lamp biomicroscopy and

Table 1: The demographic profile, clinical features and in vivo confocal microscopy findings of the study cohort

Subject	Age/Sex	Eye	Clinical Diagnosis	Clinical features	Endothelial findings on IVCM Sherrard et al.[17]	ECD in affected eye [cells/mm²]	ECD in uninvolved eye [cells/mm²]	Corneal edema	Raised IOP	Glaucoma severity	Surgery	Antiglaucoma Medicine at final follow-up	Follow-up (months)
AKJ	62/F	OU [OD > OS]	Ch	OD- Corneal edema OS-' hammered silver appearance' of endothelium on specular reflection by slit lamp biomicroscopy	OD Total ICE- OS Disseminated ICE cells	OD 1013±24 OS 2514±57	-	OD Yes OS No	OD - Yes OS - No	2	GFS	T-3	120
SG	79/M	OD	PIA	PAS, IA, IH	Total ICE -	680±26	2500±51	Yes	Yes	1	-	T-2	72
SK	43/M	OD	PIA	IA, IH, Ectropion uvea, Corectopia	Total ICE +	2352±44	2800±30	No	Yes	3	GFS	-	72
GK	35/F	OD	PIA	PAS, IA, IH, ectropion uvea	Total ICE +	1827±57	2597±59	Yes	Yes	3	GDD	T-4 S-1	24
Ba K	40/F	OD	CR	PAS, corectopia, iris nodules	Total ICE+	2133±60	2500±50	No	Yes	3	GFS	T-4 S-1	24
Ba S	63/M	OS	PIA	IA, corectopia	Total ICE -	731±50	2807±60	Yes	Yes	1	-	T-3	48
BK	47/M	OS	Ch	Corneal edema	Total ICE -	931±58	2903±63	Yes	Yes	1	-	T-2	36
Ma S	58/M	OS	PIA	PAS, IA	Total ICE -	1026±56	2400±50	No	Yes	3	GFS	-	84
TG	27/F	OS	PIA	IA, PAS	Total ICE -	1053±43	2472±66	No	Yes	3	GDD	-	24
Tu B	8/M	OD	PIA	PAS, IH	Total ICE -	1069±39	2672±48	No	No	-	-	-	3
Arc S	26/F	OD	PIA	PAS, IH	Total ICE +	2017±70	2578±119	No	No	-	-	-	3
Pr B	53/F	OS	PIA	PAS, IA, IH	Total ICE +	2252±30	3030±68	Yes	Yes	2	GFS	T-4	12
Me S	58/M	OS	PIA	IA, corectopia	Total ICE -	523±14	2253±55	No	Yes	3	GFS, GDD	T-4 S-1	24
Bh S	37/M	OS	PIA	IA, IH	Total ICE -	1506±33	2841±81	No	Yes	3	GFS	T-3 S-1	6
Ni	33/F	OD	PIA	PAS, corectopia	Total ICE -	1138±25	2510±59	No	Yes	2	GFS	T-4	12
NKB	51/M	OD	Ch	Corneal edema	Subtotal ICE -	2150±47	2750±45	Yes (sectoral)	Yes	1	-	-	2
Aru S	25/M	OD	PIA	PAS, IA, IH, corectopia	Total ICE -	1260±26	2610±44	No	Yes	1	-	T-1	3
Po B	45/F	OD	PIA	PAS, corectopia	Total ICE+	1766±32	2201±43	No	Yes	2	GFS	T-1	12
SP S	47/M	OU	OD-Ch OS-Ch	OD- Corneal edema OS- diffuse subepithelial fibrosos. AC details not visualized clearly	OD Total ICE - OS endothelium not visualized due to fibrosis	OD 519±18 OS Could not be visualized	-	OD Yes OS No	Yes	2	GFS OU	OD: T-1 OS: T-1	132
RS	46/M	OS	CR	PAS, corectopia, iris nodules	Total ICE-	2114±56	3062±96	No	Yes	1	-	T-2	6
RK	46/M	OS	CR	PAS, IA, Iris nodules	Total ICE -	1061±18	2444±61	No	Yes	2	GDD	T-1	12

ECD: Endothelial cell density; F: Female; IA: Iris atrophy; IH: Iris hole; IOP: Intraocular pressure; KP: Keratic precipitates; M: Male; OD: Oculus dexter (right eye); OS: Oculus sinister (left eye); OU: Oculus uterque (both eyes); PIA: Progressive Iris Atrophy; Ch: Chandeller Syndrome, CR: Cogan Reese Syndrome; PAS: Peripheral anterior synechiae; GFS: Glaucoma Filteration Surgery; GDD: Glaucoma Drainage Device; T: Topical antiglaucoma medicine, S: Systemic antiglaucoma medicine

large cells with widely spaced centrally placed nuclei, hence labelled ICE–cell variant on IVCM) while the contralateral eye had significant corneal edema with subepithelial fibrosis not allowing endothelial images to be captured by IVCM.

Total ICE pattern was seen in 20 eyes (91%) while 1 eye each (4.5% each) had subtotal ICE (–variant) and disseminated ICE tissue. The ICE – variant was seen in 14 of 20 eyes (70%) having total ICE, while the ICE + variant was seen in the remaining 6 (30% eyes). Twelve out of 15 patients (80%) with ICE minus cells (14 eyes with total ICE - and 1 eye with subtotal ICE -), were males while five of the 6 (83.3%) patients with ICE + endothelial cells were female. Mean age of patients with ICE – and ICE + endothelial cell morphology was 45.8 ± 17.8 years (range, 8–79 years) and 40.3 ± 9.2 years (range, 26–53 years) respectively ($P = 0.02$). Of the 15 eyes having the ICE- type of the endothelial cells, 4 eyes each (26.7% each) were associated with grade 2 and 3 glaucoma, 6 eyes (40%) had grade 1 glaucoma while 1 eye (6.7%) had no glaucoma. Amongst the 6 eyes classified as having ICE + plus cells, Grade 3 and Grade 2 glaucoma was seen in 50% ($n = 3$ eyes) and 33.3% ($n = 2$ eyes) eyes respectively while 1 eye had no evidence of raised IOP/glaucoma. Trabeculectomy with MMC was the primary procedure in eleven eyes while 3 eyes underwent glaucoma drainage device implantation in primary sitting. Due to presence of significant peripheral anterior synechiae and iris being plastered to cornea, the GDD tube was inserted into sulcus behind the iris.

The average ECD of the 22 affected eyes in whom the endothelium could be imaged with IVCM was 1446 ± 653 cells/mm^2 (range, 519–2532 cells/mm^2) while in unaffected eyes ($n = 19$), it was 2628 ± 239 cells/mm^2 (range, 2201–3062 cells/mm^2) ($P < 0.001$). Corneal edema was present in 8 eyes of which 7 could be imaged. Mean ECD of these 7 eyes with corneal edema was 1369 ± 683 cells/mm^2 (range, 680–2252 cells/mm^2) which was similar to the 15 affected eyes without corneal edema where the mean ECD was 1470 ± 595 cells/mm^2 (range, 519 cells/mm^2–2514 cells/mm^2) ($P = 0.42$). Though the difference in mean ECD of the ICE – (1118 ± 489 cells/mm^2; $n = 15$) and ICE+ (2088 ± 284 cells/mm^2; $n = 6$) eyes was statistically significant ($P = 0.003$) the incidence of corneal edema was similar, being seen in 2 of 6 eyes (33.3%) eye with ICE + morphology and 5 of 15 eyes (33.3%) with ICE – morphology.

Discussion

The view expressed by Shields,[1] for ICE syndrome that "the typical patient is a woman" was supported by results of series published by Hirst et al.,[2] (all 17 patients in their series being female), Liu and colleagues.[16] (12 females, 3 males) and Le et al.,[17] (10 females, 2 males). Sherrard et al.,[18] in their series of 57 eyes with ICE syndrome however, noted a lack of sex discrimination by the disease with a male: female ratio 47%:53%. Similarly, Laganowski et al.,[19] in their series of 66 ICE patients had 31 males (47%) and 35 (53%) females. In the present series we noted an apparent male preponderance (61.9%, $n = 13$ patients), which may represent either a true variation from the western populations due to racial and genetic differences or could perhaps be attributable to differences in health seeking behavior of males versus females in India, with the former accessing health care services more frequently.

A sampling bias may also be responsible for the apparent male preponderance seen in this small retrospective study.

The predominantly unilateral occurrence of clinically detectable signs, is usually considered as another well-established feature of ICE syndrome,[1] and often used to differentiate it from PPD which is frequently bilateral.[21] A few cases of clinically manifest bilateral ICE syndrome have also been reported with either the same variant occurring in both eyes,[16,22,23] or two different forms presenting simultaneously.[24] Published literature thus seems to suggest that ICE may occasionally be a bilateral disease with asymmetric presentation rather than a purely unilateral pathology. This is also reflected in the occurrence of bilateral involvement in 2 of our patients who had a varying spectrum of disease severity in the contralateral fellow eye.

Based on the morphological appearance of the endothelial cells seen on IVCM, several important differences were noted in our series as compared to that reported from western literature.[18,19] While 91% of our patients (20 of 22 eyes) had total ICE, with only one eye each (4.5% each) having disseminated ICE and subtotal ICE, previous studies,[18,19] have documented significantly higher occurrence of the subtotal variant (50–58% cases) as compared to total ICE (30–36%). The ICE – cells were predominant in our cohort, occurring in 70% ($n = 14$) of the 20 eyes with total ICE. Liu et al.,[16] in another Asian population, documented ICE- endothelial morphology in 5 eyes and the ICE + variant in 3 eyes with subtotal ICE. Conversely, both Sherrard et al. and Laganowski et al. had a reverse ICE- (30%, $n = 10$ eyes) to ICE + (70%, $n = 23$ eyes) ratio albeit in eyes with subtotal ICE.[18,19] Though the number of eyes in both the present series from the Indian subcontinent and that of Liu et al.,[16] from Taiwan is relatively small, the differences in the extent (total versus subtotal) and morphology of abnormal cells (ICE– versus ICE + variant) amongst Asian and Caucasian populations,[18,19] may have clinical implications and merits further evaluation. The ICE– variant was commoner in males (80%) and the ICE + variant commoner in females (83.3%) in the present series. To the best of the authors' knowledge, this gender specific predilection for the morphological variants of ICE cells has not been reported previously in published literature.

Overall 86.4% ($n = 19$) of the 22 eyes with endothelial abnormalities included in the study, had evidence of raised IOP/glaucoma which was comparable to the 76.7% incidence reported from an Asian (Thai) population,[25] but much higher than the 40%–50% incidence reported from Caucasian populations.[18,19] While Teekhasaenee et al.,[25] did not evaluate endothelial morphology in their series of ICE eyes, a subgroup analysis of the series by Sherrard et al. and Laganowski et al. revealed that the incidence of glaucoma was much higher in patients with total ICE, ranging from 71% to 75%, as compared to eyes with subtotal ICE where glaucoma was noted in only 17–20% eyes.[18,19] The overall higher incidence of glaucoma in the present cohort may thus be a reflection of the predominance of total ICE pattern which was seen in our patients.

Grupcheva et al. using IVCM found less uniform cellular organization and greater multilayering of the endothelium in patients with ICE – type of endothelial cells as compared to patients with the ICE + variant.[5] They suggested that the latter may represent early disease which usually did not require surgery, as also evidenced by the lack of histopathological

Table 2: Comparison of Demographic and clinical parameters with the studies published in Literature

	Liu *et al.*[16] 2001	Le *et al.*[17] 2009	Sherrard *et al.*[18] 1991	Laganowski *et al.*[19] 1992	Our study
Demographic profile					
Number of patients	15	12	57	66	21
Age (years) Mean±SD (Range)	32-72 (54)	27-64 (44.6)	19-74 (44)	19-65 (45)	8-79 (44.2)
Sex (M:F)(%age)	20:80	17:83	47:53	47:53	62:38
Unilateral: bilateral (%age)	93.33:6.66	100:0	-	100:0	91.5:9.5
Clinical type (%)					
Chandler syndrome	73.33%	33.33%	32%	36.36%	19.05%
Essential iris atrophy	6.66%	33.33%	65%	59.09%	66.67%
Cogan Reese syndrome	20%	33.33%	3%	4.54%	14.29%
ICE type (%age)					
Total	30.7%	-	30%	36.36%	91%
Subtotal	61.5%		58%	50%	4.5%
Disseminated	7.69%		12%	13.63%	4.5%
Morphology of cells (%age)					
ICE -ve	62.5%		30%	30%	70%
ICE+ve	37.5%		70%	70%	30%
Mean endothelial cell density (cells per mm²)	-	869.7±85.8 (affected eyes) 2523.6±78.8 (unaffected eyes)	689-1501	-	1446±653 (affected eyes) 2628±239 (unaffected eyes)
Glaucoma					
Prevalence of Glaucoma	66.66%	100%	71% of total ICE group, 18% of subtotal	50%	86.4%
Requirement of Glaucoma surgery (%)	53.33	91.66	-	33.33	65.22

studies demonstrating "small cells".[18] In the present series though the number of eyes with ICE + type of endothelial cells was relatively small to draw any definitive conclusion, this variant appeared to be associated with clinically more severe disease as compared to the ICE –cell type as reflected indirectly in the significantly younger age of the patients with ICE + type cells as compared to those with the ICE– cells, as also the greater proportion (83%) of ICE + patients suffering from a more severe grade of glaucoma (Grades 2 or 3) vis a vis those with ICE – pattern in whom nearly half (47%) had Grade 1 or no glaucoma.

The ECD overall was lower in the affected eyes as compared to the uninvolved eyes, as has also been reported by Le *et al.*[17] However, the mean ECD between affected eyes with and without corneal edema, was comparable suggesting that the cell count did not accurately reflect endothelial function in ICE eyes. Further the ICE cell type i.e. the "+" or "–" variant was also not predictive of the occurrence of corneal edema as seen by the significantly different mean ECD's but comparable occurrence of corneal edema in ICE + and – eyes. Our results appear similar to those of Liu *et al.*,[16] who in their series of 15 patients with ICE syndrome used both Hirst[2] and Sherrard,[12] classifications but did not find any distinct correlation between either ICE grading and occurrence of corneal edema or endothelial function and cell density.

To summarize we evaluated 21 patients of Indian origin having ICE syndrome and noted certain differences compared to published western literature. These include a greater overall incidence of raised IOP and/or glaucoma and more frequent occurrence of both the total ICE pattern versus the subtotal disease and ICE – cells versus the ICE + variant. An interesting, previously unreported observation was a gender predilection of the ICE cell variants, with ICE – cells being commoner in males and ICE + cells in females. The latter also appeared to manifest with clinically evident disease earlier than patients with ICE – cells, which may in part account for the common perception of ICE being predominantly a disease of women in young to middle adulthood, as the early onset of glaucoma may lead to a quicker diagnosis in these patients. This observation however needs to be validated in future studies, due to the small number of patients with ICE + patients in our series. Drawbacks of the present study include its retrospective nature, small sample size and qualitative rather than quantitative categorization of ICE cells as the "+" or "–" variant. Another limitation of the study was that the corneal edema was defined clinically and was not quantified because the study was a retrospective study and corneal edema was not a part of the three criteria required for clinical diagnosis of ICE. A comparison of salient results of the present study with the previous studies is provided in Table 2.

Conclusion

In conclusion recognizing the association (or lack thereof) of cell morphology as seen on IVCM, with clinically relevant parameters of gender, age, corneal edema, and severity of glaucoma in the clinical setting may help in better long-term prognostication of these eyes even when seen at earlier stages of the disease process.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shields MB. Progressive essential iris atrophy, Chandler's syndrome, and the Iris Nevus (Cogan-Reese) syndrome: A spectrum of disease. Surv Ophthalmol 1979;24:3-20.

2. Hirst LW, Quigley HA, Stark WJ, Shield MB. Specular microscopy of iridocorneal endothelial syndrome. Am J Ophthalmol 1980;89:11-21.

3. Alvarado JA, Murphy CG, Maglio M, Hetherington J. Pathogenesis of Chandler's syndrome, essential iris atrophy and the Cogan-Reese syndrome. I. Alterations of the corneal endothelium. Invest Ophthalmol Vis Sci 1986;27:853-72.

4. Alvarado JA, Murphy CG, Juster RP, Hetherington J. Pathogenesis of Chandler's syndrome, essential iris atrophy and the Cogan-Reese syndrome. II. Estimated age at disease onset. Invest Ophthalmol Vis Sci 1986;27:873-82.

5. Grupcheva CN, McGhee CN, Dean S, Craig JP. *In vivo* confocal microscopic characteristics of iridocorneal endothelial syndrome. Clin Exp Ophthalmol 2004;32:275-83.

6. Campbell DG, Shields MB, Smith TR. The corneal endothelium and the spectrum of essential iris atrophy. Am J Ophthalmol 1978;86:317-24.

7. Howell DN, Damms T, Burchette JL Jr, Green WR. Endothelial metaplasia in the iridocorneal endothelial syndrome. Invest Ophthalmol Vis Sci 1997;38:1896-901.

8. Chiou AG, Kaufman SC, Beuerman RW, Ohta T, Yaylali V, Kaufman HE. Confocal microscopy in the iridocorneal endothelial syndrome. Br J Ophthalmol 1999;83:697-70.

9. Levy SG, Kirkness CM, Moss J, Ficker L, McCartney ACE. On the pathology of the Iridocorneal-endothelial syndrome: The ultrastructural appearances of 'Subtotal ICE.' Eye 1995;9:318-23.

10. Chandler PA. Atrophy of the stroma of the iris, endothelial dystrophy, corneal edema and glaucoma. Am J Ophthalmol 1956;41:607-15.

11. Cavanagh HD, Petroll WM, Alizadeh H, He YG, McCulley JP, Jester JV. Clinical and diagnostic use of *in vivo* confocal microscopy in patients with corneal disease. Ophthalmology 1993;100:1444-54.

12. Sherrard ES, Frangoulis MA, Kerr Muir MG, Buckley RJ. The posterior surface of the cornea in the irido-corneal endothelial syndrome: A specular microscopical study. Trans Ophthalmol Soc UK 1985;104:766-74.

13. Lucas-Glass TC, Baratz KH, Nelson LR, Hodge DO, Bourne WM. The contralateral corneal endothelium in the iridocorneal endothelial syndrome. Arch Ophthalmol 1997;115:40-4.

14. Kupfer C, Kaiser-Kupfer MI, Datiles M, McCain L. The contralateral eye in the iridocorneal endothelial (ICE) syndrome. Ophthalmology 1983;90:1343-50.

15. Malhotra C, Pandav SS, Gupta A, Jain AK. Phenotypic heterogeneity of the corneal endothelium in iridocorneal endothelial syndrome by *in vivo* confocal microscopy. Cornea 2014;33:634-7.

16. Liu YK, Wang IJ, Hu FR, Hung PT, Chang HW. Clinical and specular microscopic manifestations of iridocorneal endothelial syndrome. Jpn J Ophthalmol 2001;45:281-7.

17. Le QH, Sun XH, Xu JJ. In-vivo confocal microscopy of Iridocorneal endothelial syndrome. Int Ophthalmol 2009;29:11-8.

18. Sherrard ES, Frangoulis MA, Muir MG. On the morphology of cells of posterior cornea in the iridocorneal endothelial syndrome. Cornea 1991;10:233-43.

19. Laganowski HC, Kerr Muir MG, Hitchings RA. Glaucoma and the iridocorneal endothelial syndrome. Arch Ophthalmol 1992;110:346-50.

20. Niederer R L, Mcghee CN. Clinical *in vivo* confocal microscopy of the human cornea in health and disease. Prog Retin Eye Res 2010;29:30-58.

21. Laganowski HC, Sherrard ES, Muir MG, Buckley RJ. Distinguishing features of the iridocorneal endothelial syndrome and posterior polymorphous dystrophy: Value of endothelial specular microscopy. Br J Ophthalmol 1991;75:212-6.

22. Hemady RK, Patel A, Blum S, Nirankari VS. Bilateral iridocorneal endothelial syndrome: Case report and review of literature. Cornea 1994;13:368-72.

23. Keiser-Kupfer M, Kuwabara T, Kupfer C. Progressive bilateral essential iris atrophy. Am J Ophthalmol 1977;83:340-6.

24. Huna R, Barak A, Melamed S. Bilateral iridocorneal endothelial syndrome presented as Cogan-Reese and Chandler's syndrome. J Glaucoma 1996;5:60-2.

25. Teekhasaenee C, Ritch R. Iridocorneal endothelial syndrome in Thai patients. Arch Ophthalmol 2000;118:187-92.