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Solar Urticaria in 145 patients: Assessment of Action Spectra and Impact on Quality of Life in adults and children

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Abstract

Background. Solar urticaria (SU) is a rare chronic inducible urticaria triggered via uncharacterised chromophores. We detail responses of a large patient series to monochromator phototesting and broadband ultraviolet radiation (UVR); relationship to life quality is explored.

Methods. Retrospective review of all SU patients undergoing standardised diagnostic photoinvestigation at a specialist centre during 2000-2016. From 2011, patients completed dermatology life quality index (DLQI) questionnaires for the past week and year.

Results. In 145 patients (mean 35.8, range 3-69 years; 18 aged <18yrs; 100 female), combined phototesting with broadband UVR and monochromator sources successfully provoked 74.5% patients, with 65.6% provoked by broadband UVR alone and 57.9% by monochromated radiation alone. The narrow wavebands most frequently eliciting wheal and flare response were between 370-400nm, with 25% patients at 300±5nm, 53.6% at 320±10nm, 66.7% at 330±10nm, 77.4% at 350±20nm, 83.3% at 370±20nm, 86.9% at 400±20nm, 44% at 500±20nm, 17.8% at 600±20nm. In 62 patients, the DLQI revealed 56.1% had very to extremely large impact in the past week (all patients: mean score 11.1, range 0-29) rising to 69.8% for the past year (12.5, 0-30); adults and children were similarly affected. Patients with positive photoprovocation had higher DLQI score than those who were negative (DLQI for past week: mean 12.6 ± SEM 1.1 vs 4.6 ± 1.4, p<0.01).

Conclusion. SU is predominantly provoked by longer UVA-shorter visible radiation, which penetrates window-glass and where sunscreens are less effective; impact on life quality is considerable. Photoprotective agents effective against this spectrum are needed.

Introduction

Solar urticaria (SU) is a rare physical urticaria characterised by rapid onset of pruritus, erythematous flare and wheal formation following exposure to non-ionising radiation. The wavelengths triggering the reaction, i.e. the action spectrum, can include ultraviolet (UV) B, UVA and visible light (1-3).

It is hypothesised that the provoking radiation reacts with a chromophore to form a photoallergen, which triggers IgE-mediated mast cell degranulation and release of histamine, accompanied by enhanced synthesis of vasoactive and pro-inflammatory mediators including arachidonic acid metabolites, cytokines and chemokines (4, 5). Involvement of cutaneous nerves produces itch and release of neuropeptides which may assist recruitment of mast cells and induction of erythematous flare (6, 7). Despite preliminary work implicating differently sized chromophores in UVR and visible light triggered SU (8), their exact nature remains unknown (9).

Patients with SU can suffer disabling symptoms, usually occurring within a few minutes of sunlight exposure, and causing significant impact on their lives. A multicentre postal questionnaire study found that of 48 adult patients, one-third had a Dermatology Life Quality Index (DLQI) of >10, signifying a very large impact on their lives (10).

First-line management of SU comprises photoprotective measures and oral antihistamines. However, the efficacy of antihistamines is variable, with only 35% of 34 patients reported to benefit (1), while some improvement of symptoms was seen in 75% of 29 patients (2). Similarly, the efficacy of photoprotection is variable, ranging from 30% reporting a good response to “external photoprotection” (2) to 68% reporting sunscreens to be of some benefit (1). Phototherapy has been reported in limited cases, with benefit seen through UVA therapy in 3 (11) and 2 (12) patients, and in 36.2% of 47 patients (2), while PUVA (13) successfully treated 4 cases of SU, and UVB provided some benefit for 85% of 39 patients (14). Plasmapheresis, which is difficult to access, and intravenous immunoglobulins sourced from pooled human plasma, have also been used (15,16), while more

recently a good response has been reported in a proportion of SU patients treated with anti-IgE monoclonal antibody (17).

Data contributing to a better understanding of the challenges facing SU patients may assist future developments in their management. We reviewed a large cohort (n=145) of adult and child patients diagnosed with SU at a specialist photoinvestigation centre. Our principal objective was to examine the action spectrum of the condition; additionally we assessed impact of SU on quality of life in a subset (n=62) of patients and explored for a relationship to SU provocation.

Materials and Methods

Subjects

Patients underwent diagnostic photoinvestigation at a specialist unit (Photobiology Unit, Dermatology Centre, Salford Royal NHS Foundation Trust, Greater Manchester, UK) between October 2000 and December 2016. All patients had detailed clinical (history, examination) and photobiological evaluation by a specialist photodermatology team according to a standardised proforma. Clinical appraisal included duration, appearance and symptoms of the condition, triggers and timing, if it occurred through window glass, whether sunscreens helped prevent the condition, and perceptions of increased tolerance as the summer months progressed. Detailed drug, past medical and family history were taken.

Photoinvestigation

Monochromator phototesting: The skin of the mid-back was exposed to narrow wavebands of radiation to determine the wavelengths of sensitivity and thresholds for provocation of the condition, as previously described (18). In brief, patients were exposed to narrowband radiation at 300, 320, 330,

350, 370, 400, 500 and 600 nm (half-maximum bandwidth 5nm at 300nm, 10nm at 320 and 330nm; 20nm at all other wavelengths) using a xenon arc lamp (1KW short arc, Newport Spectra-Physics Ltd, Didcot, UK) coupled to a 1/4m grating monochromator (Newport Spectra-Physics Ltd). Irradiance was measured using a calibrated thermopile (Medical Physics, Dryburn Hospital, Durham, UK) and digital voltmeter (Medical Physics, Royal Liverpool University Hospital, Liverpool, UK). Patients were exposed in horizontal rows to a geometric progression of doses (common ratio = $\sqrt{2}$) at each wavelength. The lowest dose at which a flare and wheal reaction was provoked, i.e. the minimum urticarial dose (MUD), was determined for each waveband. The minimum erythematous dose, (MED) was also noted at 24 hours.

Broadband UVR provocation testing: Testing was performed on 5 x 5 cm areas of skin of the ventral forearm. All patients were given 15J/cm² broadband UVA (320-400nm) using a custom built arm exposure unit incorporating Cleo Performance™ bulbs (Phillips Healthcare UK Ltd. Guildford UK). Additionally from 2009 onwards provocation testing was performed on the contralateral forearm using 10J/cm² solar simulated radiation (SSR) (290-400nm, 1KW xenon arc plus atmospheric attenuation filter Newport Spectra-Physics Ltd).

Photopatch testing: This was carried out to examine for co-existence of photocontact allergy. From 2009 this involved 25 agents: 19 UV filters, 4 non-steroidal anti-inflammatory agents (NSAID) (Chemotechnique Diagnostics, Vellinge, Sweden) (19) and sunscreen products while prior to 2009, the photopatch series comprised 10 agents: 9 organic UV filters, and sunscreen-products. Duplicate patches were applied (day 1) to skin of the mid-back for 24 hours following which one set was irradiated (day 2) with broadband UVA (320-400nm; UVAL 801, Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany). Readings were taken at 24 and 48 hours post-UVR (days 3, 4) to examine for a crescendo response, using the International Contact Dermatitis Research Group (ICDRG) grading (20)

Laboratory tests: These included plasma and urine porphyrin scan, and serum autoantibody screen, which were performed in all patients.

Quality of Life Evaluation

The DLQI questionnaire (21) was completed by patients from January 2011 onwards to assess the impact of SU on quality of life both in the past week and past year (10). The questionnaire comprises 10 questions relating to pruritus (Q1), embarrassment (Q2) shopping/gardening (Q3), clothing (Q4), social and leisure activities (Q5), sport (Q6), working or studying (Q7), friendships (Q8), sexual difficulties (Q9) and impact of treatment (Q10). Each question is answered by 'not at all', 'a little', 'a lot' or 'very much'. The score for each question ranges from 0 to 3 making a maximum score of 30, with higher scores equating to greater impairment, i.e. score of >10 is very large impact, >20 is extremely large impact. The childhood dermatology life quality index (CDLQI) was used in those aged ≤ 18 years (text version 11-17 years (22); cartoon version ≤ 10 years (23)).

Statistical analysis

Values are expressed as mean $\pm$ SEM. Data was analysed using ANOVA and Pearson's correlation (r). Statistical significance was accepted at the $p < 0.05$ level (Stats Direct Ltd, Altrincham, UK).

Results

Subject Demographics

In total, 2318 patients underwent photoinvestigation at the Photobiology Unit over this period; of these 145 (6.2%) patients were diagnosed to have SU (100 female; mean age 35.8, range 3-69 years). Eighteen were aged under 18 years (14 female; mean age 11.1, range 3-17 years). Mean age at symptom onset was 29.8, range 0-68 years (female: 29.1, range 0-68 years; male: 31.4, range 1-59 years). The frequencies of sun reactive skin types I-VI were: 17.2%; 28.3%; 31%; 6.2%; 7.6% and 0.7% respectively; not recorded in 9%.

Clinical Features

With regards to experience in daily life, the following relate to the n=118-126 patients addressing each individual aspect: 80.1% patients reported that less than 30 minutes of sunlight exposure triggered their condition; 82.5% reported their rash was triggered through window glass; a minority of patients (21%) perceived an increase in tolerance as the summer progressed; facial involvement was reported in 78.8% of patients. Of 97 (66.8%) patients who used sunscreen 43 (44.3%) reported some benefit and 29 (29.9%) no benefit.

In terms of seasons of the year affected, of the n=145 patients: 9% were affected during 1 season, i.e. summer only; 6.2% were affected during 2 seasons; 15.9% were affected in 3 seasons; and the majority (60%) were affected all year round; this information was uncertain in 9% patients.

Phototesting

Of the 145 patients the majority (74.5%) had urticarial i.e. wheal and flare responses provoked on phototesting, while the remaining 37 (25.5%) were diagnosed from characteristic clinical features alone, showing no response to narrowband or broadband UVR provocation testing. Amongst the children, 55.6% were diagnosed from characteristic clinical features alone, reflecting the less extensive phototesting performed in younger children.

Eighty four (57.9%) patients were provoked by monochromator phototesting. Amongst the 18 children, 6 (33%) were provoked by monochromator phototesting. Of subjects responding to monochromator phototesting, 10.7% were provoked by UVA wavelengths (between 320-370nm) alone, 10.7% by visible light (400-600nm) alone, 53.6% by UVA and visible light and 25% by UVB, UVA and visible light. Figure 1a shows frequency of reactions by wavelength, with the most frequent responses occurring at 370 and 400nm.

Overall, 65.6% patients were provoked on broadband UVR testing. Broadband UVA testing (n=142 patients) provoked wheal and flare response in 85 (59.8%) patients. Of the 17 children tested to broadband UVA, 6 (35.2%) were provoked. A subset (n=63) of patients underwent additional SSR testing of whom 56 (88.9%) were provoked.

Testing using a combination of monochromator phototesting and broadband UVR sources successfully provoked urticarial responses in 108 of 145 patients; had either alone been used the response rate would have been lower (Figure 2). If the broadband UVA source alone had been used, 16 patients who were broadband UVA negative but monochromator positive would have been missed (Fig 2a). Similarly the use of the solar simulator alone would have missed 3 monochromator positive patients (Fig 2b). Of the 61 patients who were monochromator negative, 24 were provoked by broadband UVR (Figure 2c) highlighting the importance of using both narrow and broad emission sources. No SSR provocation negative patients were successfully provoked by broadband UVA, while 8 broadband UVA provocation negative patients were positively provoked by SSR (Figure 2d).

Photopatch testing

Four patients had five positive photopatch tests, while three patients had three positive responses to both the photopatch test and its control patch test, indicating a positive patch test. The positive photopatch responses were to patients own sunscreen products and, in one case, topical ketoprofen. The agent responsible in the patients' own sunscreen products was not identified although it is noted that the products contained additional UV filters that did not form part of the test series at that time. Patch positive responses were all to patients own sunscreen products.

DLQI

Sixty-two (78%) SU patients since 2011 completed the DLQI questionnaires; these gave a mean $\pm$ SEM DLQI score of 11.1 ± 1.0 (range 0-29) for the past week and 12.5 ± 1.1 (range 0-30) for the past year. The impact was similar in children and adults (children, $n=4$: 11.7 ± 4.8 (range 1-24) for past week and 13.5 ± 4.0 (range 6-25) for past year; adults, $n=58$: 11.0 ± 1.1 (range 0-29) for past week and 12.4 ± 1.1 (range 0-30) for past year).

The percentage of all patients with an impact score ≥ 10 , signifying very large impact on QoL (21), was 56.1% (past week) and 69.8% (past year) with 19.3% (week) and 30.2% (year) experiencing an extremely large impact (score > 20). No significant correlation was found between DLQI and number of months affected (past week $r = 0.2$, $p = 0.15$ and past year $r = 0.002$, $p = 0.99$) or facial involvement (past week $p = 0.83$ past year, $p = 0.94$, ANOVA).

Patients with positive photoprovocation had higher DLQI than those who were negative (week score: mean 12.6 ± 1.1 vs 4.6 ± 1.4 , $p < 0.01$; year score: 13.3 ± 1.3 vs 9.3 ± 1.5 , not statistically significant). Monochromator phototest responders ($n=41$) compared with monochromator non-responders ($n=21$) showed higher impact on QoL for the past week (DLQI 13.0 ± 1.3 versus 7.9 ± 1.5 respectively, $p=0.02$), with a similar pattern for the past year (13.5 ± 1.5 and 10.8 ± 1.2 , non-significant). Comparison of broadband provocation responders ($n=46$) with broadband non-responders ($n=15$) showed similar findings for DLQI for past week (12.5 ± 1.2 versus 6.6 ± 1.8 respectively, $p=0.02$) and past year (13.1 ± 1.3 versus 10.7 ± 1.9 , non-significant).

Responses to the individual questions of the DLQI questionnaire are shown in Figure 3. The greatest impact was on choice of clothing, with mean score 2.1 ± 0.1 and 2.2 ± 0.1 (past week and year, respectively) and the lowest impact was for sexual difficulties (0.3 ± 0.1 and 0.3 ± 0.1 , past week and year respectively).

Discussion

In this large series of patients with the orphan disorder SU, the majority, almost three-quarters (74.5%), were positively provoked by phototesting. The most frequent wavelengths provoking urticarial responses were in the UVA, and UVA plus visible light, wavebands, with few patients provoked by UVB. Our experience highlights the increased positive photoprovocation yield when using both broadband (65.6% patients provoked if used alone) and monochromator (57.9% patients provoked if used alone) sources during investigation of patients with suspected SU, with ~one-quarter patients who were broadband UVR positive found to be narrowband UVR negative, and vice-versa. Comparing broadband UVR sources, photoprovocation was notably more successful with solar simulated UVR than with broadband UVA.

Monochromator phototesting highlighted the role of longer wavelength UVA and shorter wavelength visible light in provoking urticarial responses, with the most frequent responses seen at 370 and 400nm. The key role these longer wavelengths play in SU is consistent with our review of published action spectra derived from monochromator phototesting, as summarised (Figure 1b, table 1). In their report of 87 patients in whom SU was demonstrable on phototesting, Beattie et al (1) also highlighted the involvement of 430 and 460nm. In the examination of potential chromophores responsible (24), those absorbing at the longer UVA/visible border warrant particular attention.

Longer wavelength UVA and visible light are present in substantial amounts in ambient radiation in winter as well as summer, and thus, while the severity of expression tends to be worse in the summer months, patients provoked by these wavelengths may manifest their condition in a year-round manner. This is consistent with our data showing a majority of 60% of SU patients were affected all year round while 31.1% were affected seasonally. Additionally, topical sunscreen efficacy is reduced at these longer wavelengths, with 29.9% of responding patients reporting no benefit, which may contribute to the large impact SU has on the quality of life.

Our DLQI data highlights the impact SU can have on QoL with 56.1% and 69.8% of patients (past week and year, respectively) experiencing a very large (score >10) and 19.3% and 30.2% an extremely large (score >20) impact (25). Subdomain scores highlight the impact on daily activities such as “shopping” and “clothing choices” with a mean of 1.8 (SD 1.1) when compared to chronic spontaneous urticaria (mean $\pm$ SD, 1.3 $\pm$ 0.9) (26). The impact on life quality of this rare condition has not been extensively reported. A UK multicentre study of the DLQI of n=48 adult SU patients was reported in 2008, based on questionnaires mailed to previously photoinvestigated patients (10). We found a higher median DLQI over the past week of 11 compared with 9 in the multicentre study, and DLQI over the past year of 12 compared with 10. This might reflect differences in study design, with our DLQI data consistently collected from patients at their investigation visit; patients were given explanation if required although completed the forms independently. Thus, 78% patients (2011-2016) complied with completion of the DLQI form compared with 42% in the multicentre study. Both studies highlight the value of assessing impact of SU over the past year, as the expression of this photosensitivity disorder depends on ambient UVR/visible radiation level and personal sunlight exposure behaviour, and can thus be underestimated with assessment of impact over the past week alone. We included children <18 years in our study, and found a similar impact of their SU to that in adults.

We further demonstrated an association between DLQI and a positive photoprovocation response. These respective subjective and objective measures could be used in clinical trials in the assessment of efficacy of treatments for SU. It has been noted that the chronic inducible urticarias can be particularly resistant to therapy (27) and avoidance of physical triggers is recommended by the European Academy of Allergy and Clinical Immunology/Global Asthma and Allergy Forum/European Dermatology Forum/World Allergy Organization (EAACI/GA2LEN/EDF/WAO) urticaria classification, diagnosis and management guidelines (28). However, avoidance of light is incompatible with everyday life, and thus the impact on a life spent avoiding light is very significant. Recently, promising new developments have been seen in the systemic management of SU. The melanising agent, afamelanotide (Scenesse™, Clinuvel Pharmaceuticals Ltd) has shown protection

against photoprovocation of SU including to longer wavelength UVA/visible radiation in a phase II clinical trial (18). Further, the recombinant monoclonal anti-IgE, omalizumab (Xolair[™], Novartis Pharmaceuticals UK Ltd), has shown evidence of protection in several patients with SU provoked by differing components of UVR and visible light (29).

Strengths of this study include the detailed clinical and phototesting data obtained in a large series of this rare disorder, in both adults and children. While the study is retrospective, and DLQI questionnaires were only commenced in 2011, detailed and standardised clinical and photobiological proforma were used in all patients. The impact of the disorder on QoL was assessed using a validated tool, the DLQI questionnaire; however this is validated for assessment of impact on QoL over the past week, and while it has been applied to assessing impact over the past year including in a multicentre study (10), its use in this manner awaits validation.

In conclusion, this largest reported study of monochromator phototesting in SU has confirmed the variable action spectrum of this disorder but with peak frequencies in the longer UVA and visible waveband; demonstrated that a combination of narrowband and broadband (solar simulated UVR) testing is most effective in eliciting photoprovocation; shown the very high impact on the lives of adults and children; and demonstrated higher impact in those with positive photoprovocation. Awareness of the particular challenges of SU should be raised amongst the medical, scientific and regulatory communities, to promote further development with randomised controlled trials of effective preventive and treatment measures protecting across the SU action spectrum.

Acknowledgement

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Table 1. Demographic data corresponding to action spectra in figure 1(b)

	No. of patients	Female: male ratio	Age at onset (years)
Haylett et al 2018	145	2.2 : 1	29.8
Beattie et al 2003	87	2.3 : 1	35
Ng et al 2002	12	3 : 1	n/a
Rykaert et al 1998	25	n/a	n/a
Cripps 1981	4	3 : 1	30.5

Figure Legends

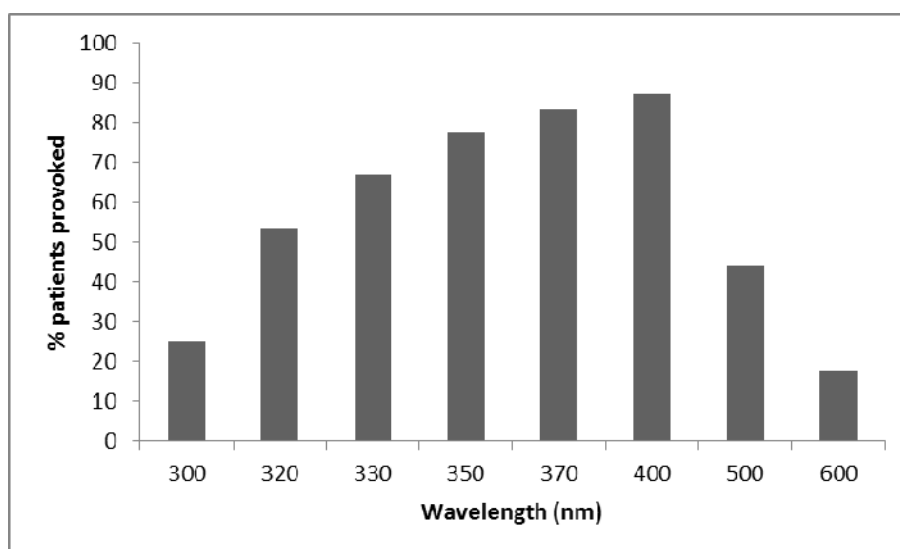
Figure 1. Wavelengths at which urticarial responses were observed in SU patients provoked by monochromator phototesting, shown for (a) the current study, n=145 (b) the collation of SU patient series reported in the literature, as detailed in table 1. Data shown are % patients responding to a given waveband.

Figure 2. Comparison of provocation responses to broadband and monochromator phototest sources. Numbers of patients with positive monochromator response who a) tested negative to broadband UVA and vice versa and b) tested negative to SSR and vice versa. c) tested negative to any broadband UVR source d) solar simulator positive patients testing negative to broadband UVA and vice versa.

Figure 3. Responses to individual questions of the DLQI questionnaire, assessing impact over the past week and past year. Data are mean $\pm$ SEM.

Figure 1

(a)



(b).

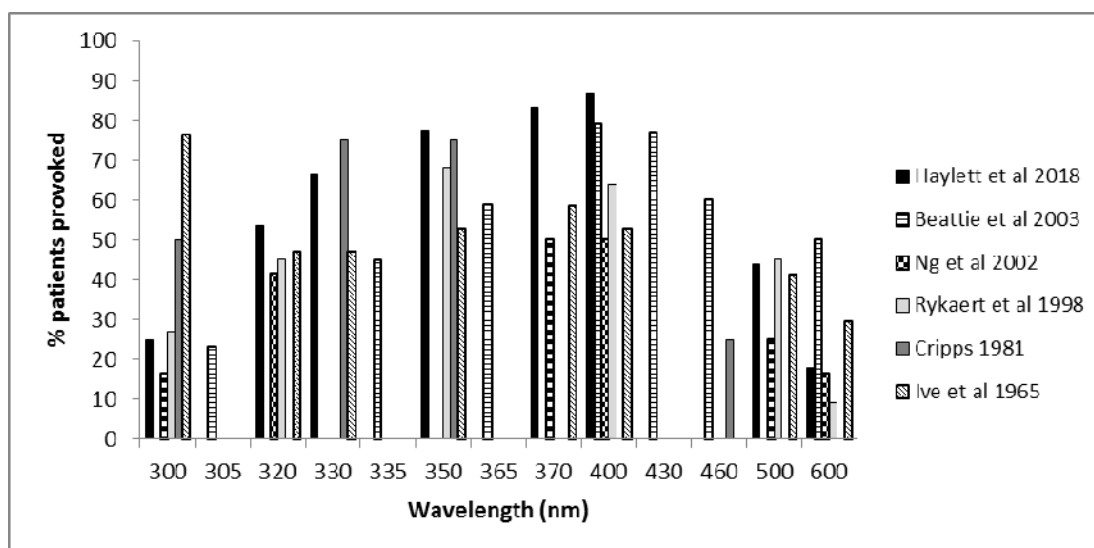
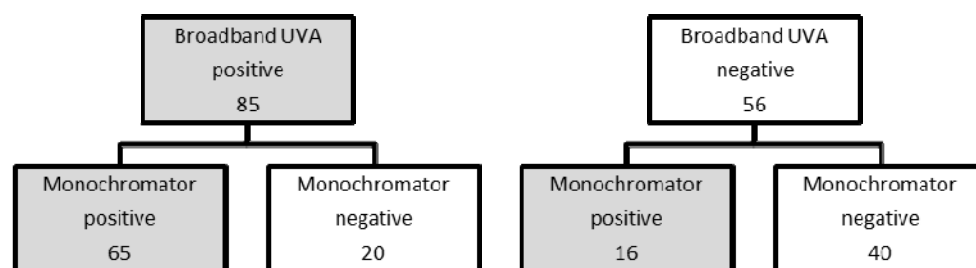
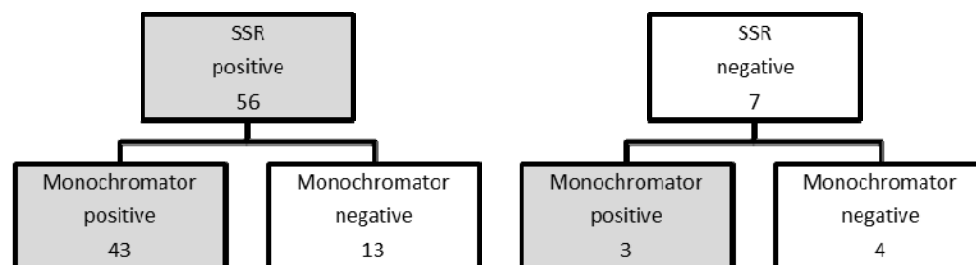


Figure 2

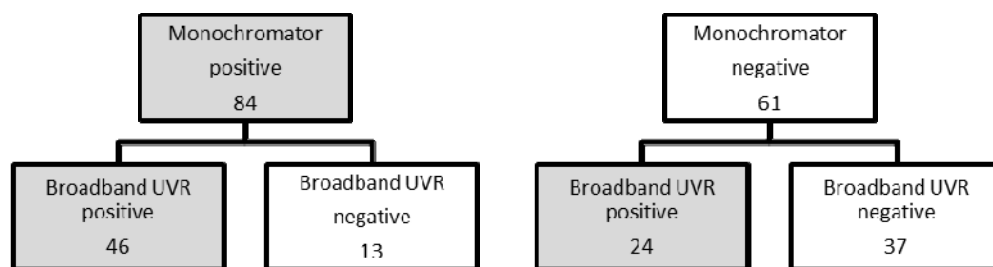
a)



b)



c)



d)

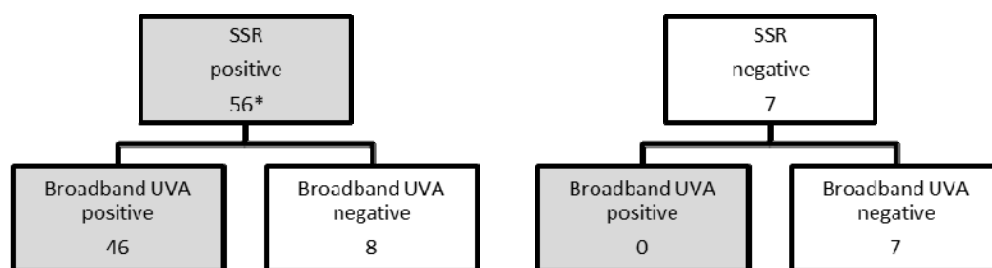


Figure 3

