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Senile Cataract Progression Studies Using the Lens Opacities Classification System II
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Purpose. To determine cataract progression rates at 6-mo intervals as evaluated using the Lens Opacities Classification System II (LOCS II).

Methods. Idiopathic age-related cataracts in both eyes of 50 cataract patients and 17 normal control subjects were graded. The lenses were reexamined at 6 and 12 mo (±2 mo) from baseline to determine rates of change. Progression or regression in patients or control subjects was considered to have occurred at the 6-mo examination if a one or more step change in the LOCS II grading was noted in at least one eye at 6 mo and maintained at the 12-mo visit.

Results. Six months from baseline, 38% of patients' conditions worsened in the nuclear area, 34% of patients' conditions worsened in the cortical region, and 8% of patients' conditions worsened in the posterior subcapsular region. Regression rates were 4% in each region. The percentages of patients progressing in the nuclear and cortical regions were significantly greater than the corresponding regression rates \( P < .001 \). Greater progression was noted in the nuclear \( P = .06 \) and posterior subcapsular \( P < .01 \) regions in patients with early opacities (LOCS + 1/+2) as compared to patients with no opacities initially in the same lenticular areas.

Conclusion. This study suggests that the LOCS II is capable of detecting changes in lens opacities in vivo. The Lens Opacities Classification System II (LOCS II) has been offered as a simple and reliable subjective method for grading lens opacities in vivo. This system had been used previously in large case-control and cross-sectional studies of cataracts, and its validity and high reproducibility have been repeatedly demonstrated. The shift toward longitudinal studies would be a test to determine whether this system, as well as others, is sensitive enough to accurately detect and monitor lens changes over time. Not only would these studies be valuable in obtaining cataract progression rates, but they would be more valuable in therapeutic and drug intervention studies. A longitudinal study using the LOCS II method of slit and retroillumination photography has been presented, but a similar study using clinical LOCS II grading has not yet been reported. Currently, there is a paucity of published data on longitudinal studies of cataracts.

We have been using the LOCS II to clinically monitor age-related cataract changes over time in our patient population. We wished to determine whether the LOCS II was capable of detecting changes in lens opacities within 6 mo among patients with early to moderate opacities. The results of our follow-up studies on nuclear, cortical, and posterior subcapsular (PSC) cataracts using clinical grading are presented.

MATERIALS AND METHODS. Subjects were patients with cataracts referred by their physicians for inclusion in an Intramural Review Board approved clinical research study at the National Eye Institute, and a control group of patients without cataracts of similar age distribution. Informed consent was obtained from all patients after the nature and possible consequences of the study were explained to them. The tenets of the Declaration of Helsinki were strictly followed.

Inclusion criteria consisted of: 1) Patients with both lenses present at the initial visit, and in whom no lens extractions were contemplated in their cataractous eyes within 10–12 mo of baseline; 2) Patients and control subjects with no history of systemic disorders or drug exposure that may predispose to cataracts (ie, diabetes, prednisone, total body irradiation). Excluded were persons with monocular aphakia, patients with secondary cataracts and congenital cataracts, and patients with mature, opaque lenses (LOCS grade > NO3C3P3) in at least one eye. There were 21 men and 29 women in the cataract group with an age range of 43–86 yr, and 10 men and 7 women in the control group with an age range of 36–66 yr.
TABLE 1. Location and Severity of Opacities Present in the Cataract Patient Population*

<table>
<thead>
<tr>
<th>Cataract Severity/LOCS II Grade</th>
<th>Location of Opacity (Worse Eye)</th>
<th>Nuclear</th>
<th>Cortical</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>18</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>31</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4-5</td>
<td></td>
<td>0</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td></td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

PSC = posterior subcapsular opacity.

* Note that both eyes of each patient were graded, and these distribution data represent the severity grade of the worse eye. Normal controls are not included in this table.

All eyes were examined at baseline, 6 mo, and 12 mo. Both eyes were maximally dilated using three doses of 1% tropicamide and 2.5% Neosynephrine eye drops (phenylephrine hydrochloride; Winthrop Pharm., New York, NY).

Clinical grading at the slit lamp using the LOCS II standards was performed by one observer masked as to each patient’s previous grading, if any. This observer (MBD) was an experienced ophthalmologist trained by the developers of the LOCS II in both photographic and clinical grading. LOCS II standards were obtained courtesy of Dr. Leo Chylack, Center for Clinical Cataract Research, Boston, MA. Progression or worsening was considered to have occurred by the 6-mo examination if a one or more step increase in the LOCS II grade was noted at 6 mo and maintained at the 12-mo visit (the validation visit). Conversely, regression or improvement was defined as a decrease by at least one step in the LOCS II grade at 6 mo and maintained at the 12-mo visit. Any change at the 6-mo visit that was not confirmed at the 12-mo visit was regarded as “no change.”

Progression or regression of lens opacities was analyzed in terms of changes by persons, not eyes, such that any change (increase or decrease) in the lens opacities in at least one eye was regarded as a change for the person. We obtained rates of change in each region of the lens (nucleus, cortex, and posterior subcapsular) for each person.

Two modifications were made in the analysis of the LOCS II scores. Although nuclear color was part of the clinical grading, it was not included in the analysis. Trace cortical opacities were considered as C-0.

McNemar’s paired data chi-square was used in the statistical comparison of cataract progression rates for each lenticular region. Comparisons of progression rates between sexes employed the Pearson’s chi-square, whereas evaluation of the rates across age groups was done using the test for linear trend in proportions (z test).

RESULTS. Table 1 shows the distribution of the cataract population by persons, based on the location and severity (classified by worse eyes) of cataract.

Table 2 shows the rate of cataract change by person. We found that 38% of the cataract patients progressed in the nuclear area in at least one eye, whereas 34% and 8% of the patients worsened in the cortical and PSC regions, respectively. Regression rates were 4% for all cataract types. The percentages of patients progressing in the nuclear and cortical regions were significantly greater than the corresponding regression rates \((P < 0.001, \text{z test})\). When regression rates were computed only for those patients whose opacities had a potential to regress (Grade 1 or more), the rates were 6% (2 of 32) for nuclear, 7% (2 of 30) for cortical and 11% (2 of 18) for PSC opacities.

Rates of change for nuclear and cortical opacities in the cataract group were significantly greater than the corresponding rates in the normal control subjects.

TABLE 2. Rates of Change After 6 Months

<table>
<thead>
<tr>
<th>Baseline Status (n)</th>
<th>Nuclear</th>
<th>Cortical</th>
<th>PSC</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prog</td>
<td>Reg</td>
<td>Prog</td>
<td>Reg</td>
</tr>
<tr>
<td>All cataract (50)</td>
<td>38</td>
<td>4</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Pure* nuclear (11)</td>
<td>36</td>
<td>9</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Pure cortical (11)</td>
<td>18</td>
<td>0</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Pure PSC (4)</td>
<td>25</td>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Mixed† (24)</td>
<td>46</td>
<td>4</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>No cataract (17)</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are percentages.

Prog = progression, at least one step increase in LOCS II grade in either eye; Reg = regression, at least one step decrease in LOCS II grade in either eye.

* Single cataract type present in at least one eye. Fellow eye may be the same type or noncataractous.

† Presence of more than one cataract type in at least one eye, or different pure types in both eyes.
In no instance did a subject have one eye progress and the fellow eye regress.

If only one eye for each patient was analyzed (left eyes), progression rates would have been slightly lower: 28% for nuclear, 24% for cortical, and 6% for PSC opacities. Corresponding regression rates were 4%, 2%, and 0%, respectively. Similarly, nuclear and cortical progression rates were significantly greater than their regression rates \((P < 0.02)\). No particular pattern in the progression rates was noted among the different age groups.

Table 3 shows progression rates of cataract patients based on initial visit LOCS II grades. In the nuclear region, only 22% of patients without any nuclear opalescence initially (Group I), progressed to +1 in at least one eye at 6 mo. However, for those who already had early nuclear opacities (Groups II and III) an even greater percentage progressed by one step 6 mo later \((P = 0.06, z\) test). A more significant pattern was seen with PSC opacities \((P < 0.01)\), but cortical opacities showed no particular pattern.

**DISCUSSION.** Our results suggest that the LOCS II is capable of detecting changes in lens opacities within 6 mo among persons with early to moderate cataracts. As mentioned earlier, at 6 mo, 38% showed nuclear progression, and 34% of patients showed cataract progression in the cortical region (Table 2). These progression rates were significantly more than the regression rates of 4% for the same regions, suggesting that our changes are real and beyond the error range.

In addition, as shown in Table 3, when patients already had cataracts (Groups II and III) at the baseline examination, the amount of progression more than doubled by the subsequent visit as compared to those with no opacities in both eyes for that lens region (Group I). This suggests that once a cataract appears, the rate of change accelerates. The normal subjects had much lower progression rates compared to the subjects with cataracts. This also suggests that having an all-cataract population at baseline would result in higher progression rates than rates obtained from the general population. However, larger studies are needed to confirm these findings.

Lens changes usually were one-step increments. Only four eyes of three patients showed a two-step progression (in nuclear and cortical regions) which, according to Bailey, should be the only eyes to be considered to show a statistically significant change (falling over the 95% confidence limits) for a four-step integer grading scale. However, we believe it would be impractical to apply the two-step change rule in this situation, because it would reduce the sensitivity of the system to detect smaller changes. In lieu of decimalization, as suggested by Bailey, we have used the two follow-up visit rule to confirm grades noted at 6 mo, thus reducing the chance for misclassification.

Misclassification on one follow-up visit was found to be 17% for nuclear, 19% for cortical, and 33% for PSC opacities, obtained by determining the proportion of eyes that changed at 6 mo but reverted back to their baseline grade at the 12-mo visit, over all the eyes that changed at 6 mo (Table 4). The two follow-up visit requirement was, therefore, found to be helpful in placing more confidence on the 6-mo change, and minimized such misclassification.

Analysis of cataract changes on a personal basis, rather than by eyes, is more appropriate in some situations.

### Table 3. Rates of Changes (One-Step Progression) Among Groups Divided According to Baseline Cataract Severity

<table>
<thead>
<tr>
<th></th>
<th>Nuclear</th>
<th>Cortical</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (grade 0)</td>
<td>4/18 (22%)</td>
<td>5/20 (25%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td>Group II (grade 1)</td>
<td>6/13 (46%)</td>
<td>3/7 (43%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Group III (grade 2)</td>
<td>9/17 (53%)</td>
<td>2/11 (18%)</td>
<td>2/8 (25%)</td>
</tr>
</tbody>
</table>

* Both eyes = grade 0 initially.
† One eye = grade 1, other eye = grade 0 or 1.
‡ One eye = grade 2; other eye = grade 0, 1, or 2.

### Table 4. Reliability of Clinical LOCS II Grading of 134 Eyes at the 6-Month Visit

<table>
<thead>
<tr>
<th></th>
<th>Nuclear</th>
<th>Cortical</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed and maintained</td>
<td>30</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Changed, not maintained</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>No change</td>
<td>98</td>
<td>102</td>
<td>122</td>
</tr>
</tbody>
</table>

* The change in LOCS II grade at the 6-month visit (at least 1 step increase or decrease from baseline) was confirmed or maintained at the 12-month visit: the 12-month LOCS II grade was the same or showed a further increase or decrease, as the 6-month visit grade.
† The change in LOCS II grade at the 6-month visit was not confirmed or maintained at the 12-month visit (counted as no change in the analysis).
‡ Six-month LOCS II grade was similar to that in the initial visit.
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dons, such as evaluating the effects of a systemically administered anti-cataract drug, because both eyes will be affected. It should be noted that there is only one event rate per person, regardless of whether one or both eyes change. Fortunately, there was no instance of one eye progressing and the fellow eye regressing. In this study, we showed the usefulness of this method of analyzing data.

Although objective methods, such as Scheimpflug photography\(^8\)\(^\text{,}\)\(^9\) and retroillumination photography\(^10\)\(^\text{,}\)\(^11\) have been shown to be reproducible, they are expensive and laborious to process as compared to a simple and inexpensive subjective system, such as the LOCS II. Therefore, the LOCS II could be very useful in natural history studies and in the clinical testing of anti-cataract drugs.

Key Words

senile cataract, cataract classification, cataract progression, cataract regression, person data

Acknowledgments

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References


Retinal Pigment Epithelial Cell Transplants in Retinal Degeneration Slow Mice Do Not Rescue Photoreceptor Cells

Linxi Li,* Harold J. Sheedlo,* and James E. Turner*++

Purpose. To determine if retinal pigment epithelial cells are in any way involved in the degeneration of photoreceptor cells in the retinal dystrophy mouse model, retinal degeneration slow (rds); to determine if normal retinal pigment epithelial cell transplants can affect outer segment development in the retina.

Methods. Retinal pigment epithelial cells of neonatal normal pigmented C57 mice were isolated and transplanted into retinas of postnatal day 33 albino rds mice. Then eyes of 4-month-old rds mice, retinal pigment epithelial cell-transplanted and sham and non-treated control mice, were processed for light and electron microscopy and the thickness of the outer nuclear layer were measured and compared.

Results. Measurements of outer nuclear layer thickness in the transplant and control groups revealed that normal retinal pigment epithelial cell transplants did not cause photoreceptor cell rescue in rds mice. In addition, outer segments were not seen in retinal pigment epithelial cell-transplanted rds retinas.